ISSN en trámite

Cardiovascular and Metabolic Science

Continuation of the Revista Mexicana de Cardiología

2021

Dyslipidemias, the deadly flagellum that harms the vessels and the heart

VOLUME 32, SUPPLEMENT 3
JULY-SEPTEMBER 2021

Indexed under CUIDEN data base (Granada España)
Complete version on internet (indexed and compiled):
Medigraphic, Literatura Biomédica: www.medigraphic.org.mx

Cardiovascular and Metabolic Science

Continuation of the Revista Mexicana de Cardiología

Official communication organ of:

- Asociación Nacional de Cardiólogos de México
- Sociedad de Cardiología Intervencionista de México
- Asociación Nacional de Cardiólogos del Centro Médico La Raza
- Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado
- Asociación Mexicana para la Prevención de la Aterosclerosis y sus Complicaciones
- Alianza por un Corazón Saludable
- Sociedad Mexicana de Cardiología Preventiva
- Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca
- Asociación Médica del Hospital de Cardiología Centro Médico Nacional Siglo XXI
- Fundación InterAmericana del Corazón México

PREVENIR ES NUESTRA META

Asociación Nacional de Cardiólogos de México

Board of Directors 2020-2022

President: Dra. Gabriela Borrayo Sánchez
Vice President: Dr. Arturo Guerra López
Secretary: Dr. Rodolfo Herrera Franco
Assistant Secretary and Social Communication: Dr. Ernesto Díaz Domínguez
Treasure: Dra. Ana Elena Ancona Vadillo
Scientific Committee: Dr. Eduardo Almeida Gutiérrez

Founder President: Dr. Guillermo González Ramírez

Sociedad de Cardiología Intervencionista de México

Board of Directors 2020-2021

President: Dr. Yigal Piña Reyna
Vice President: Dr. Andrés García Rincón
Secretary: Dr. Alejandro Ricalde Alcocer
Assistant Secretary: Dr. José Luis Leiva Pons
Treasurer: Dr. Manuel Gaxiola Macías
Myocardial Infarction Program: Dr. Patricio H. Ortiz Fernández

Asociación Nacional de Cardiólogos del Centro Médico La Raza

Board of Directors 2019-2021

President: Dr. Jaime Eduardo Cruz Alvarado
Vice President: Dr. Carlos Obeth Ferreyra
Secretary: Dr. Salvador Ocampo Peña
Treasurer: Dr. Salvador Facundo Bazaldua
Founder President: Dr. Marco Antonio Ramos Corrales

Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado

Board of Directors 2018-2020

President: Dr. Francisco Valadez Molina
Vice President: Dr. José Alfredo Merino Rajme
Secretary: Dra. Julieta Morales Portano
Treasurer: Dr. Alejandro Alcocer Chauvet
Assistant Secretary: Dr. Roberto Muratalla González

Cardiovascular and Metabolic Science (continuation of Revista Mexicana de Cardiología), is the official organ of following medical societies and associations: Asociación Nacional de Cardiólogos de México (ANCAM), Sociedad de Cardiología Intervencionista de México (SOCIME), Asociación Nacional de Cardiólogos del Centro Médico La Raza (ANCCMR), Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado (ANCISSSTE), Asociación Mexicana para la Prevención de la Aterosclerosis y sus Complicaciones (AMPAC), Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca (SOMEEC), Asociación Médica del Hospital de Cardiología del Centro Médico Nacional Siglo XXI, Sociedad Mexicana de Cardiología Preventiva, and Alianza por un Corazón Saludable. Address: Magdalena 135, Col. del Valle Norte, Benito Juárez, CP 03103. revistamexicanadecardiologia@medigraphic.com, revmexcardiol@gmail.com.
Cardiovascular and Metabolic Science publishes quarterly, one volume per year. Copyright reservation 04-2019-022717130200-102. Freely distributed with title Certificate No. 3575 and Content Certificate No. 3875. Print run: 2,000 copies. Postage paid, periodic publication permit authorized by SEPOMEX, number PP09-1877. Characteristics 220441116. The partial or total reproduction of the content of this number can be done with prior authorization of the publisher and mention of the source. **The concepts published in the articles are the entire responsibility of the authors.**
Cardiovascular and Metabolic Science is registered in the following indexes: Medigraphic, Literatura Biomédica, Sistema Regional de Información en Línea para Revistas Científicas de América Latina, El Caribe, España y Portugal (LATINDEX, by its Spanish abbreviation), Literatura Latinoamericana en Ciencias de la Salud (LILACS), Periódica-UNAM, Biblioteca Virtual en Salud, Brasil (BVS), and University of Salamanca Library, Spain.
Electronic address: **www.medigraphic.com/cms/** E-mail addresses: **revmexcardiol@gmail.com**
Editorial coordination: Dr. José Rosales Jiménez and Marco Antonio Espinoza Lorenzana. Editorial design: Diego Lozano Saavedra.
Art, design, typesetting, pre-press and printing by **Graphimedic, SA de CV.** Tel: 55-8589-8527 to 32. E-mail: emyc@medigraphic.com. ***Printed in Mexico.***

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

CONTENTS

Dyslipidemias, the deadly flagellum that harms the vessels and the heart

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 32 Supl. 3
Julio-Septiembre 2021

CONTENIDO

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100784

Introductory remarks

Notas introductorias

Eduardo Meaney, MD, PhD* Nayelli Nájera, PhD* Guillermo Ceballos, MD, PhD*

This text, named «Dyslipidemia, the deadly epidemic flagellum that harms the vessels and the heart» is the final product of the efforts of Dr. Edith Ruiz-Gastélum, Coordinator of the Dyslipidemias and Atherosclerosis Chapter of our Association, who led a group of hard-working academic-oriented cardiologists, endocrinologists, geneticists, basic scientists, and nutritionists, to review extensively and in depth, many basic, clinical, therapeutic and preventive aspects of lipid disorders, and their relationship with atherosclerotic cardiovascular diseases (ASCVD).

Once the infamous pandemic of COVID-19 finally fades away due to an extensive vaccination, the panendemic of some cardio-metabolic chronic degenerative diseases or conditions, as dyslipidemias, high blood pressure, obesity, diabetes, heart failure, and ASCVD, among others, still be there, attempting against the well-being, the health, the economy, and the happiness of humans. Very unfortunately, for these pathological conditions there is not the relatively simple preventive resource of a vaccine. Their control demands multiple actions from different actors, all united in a bundle of wills and coordinated efforts. What the human genre needs to knock-out these scourges are wise and brave public health policies from the executive branch of our governments, the legal support from the legislative branches and the judiciary power, the understanding and collaboration of food enterprises, the everlasting and fruitful alliance with the pharmaceutical and medical supplies industries, the collaboration from the mass media, the acceptance of the whole civil society, and the therapeutic and preventive attitudes from all physicians and other estimable members of the health team (basic scientists, nurses, medical technicians, clinical chemists, nutritionists, geneticists, psychologists, etc.).

Lipidology is riding on the crest of a wave of constant renovation and innovation. Every day there are new discoveries about the molecular and pathophysiological bases of dyslipidemias and atherosclerosis, and new diagnostic and pharmacological tools. That spiral of progress forces the practitioner to be up to date, to provide patients with the best and most modern and scientific medicine. This is the intention of the courses about dyslipidemias organized by Dr. Ruiz-Gastélum, and that is indeed the purpose of this text. The more theoretical preparation that general practitioners and specialists should acquire, the greater the detection of patients with dyslipidemia and the better their clinical care and prognosis.

We wish to thank Dr. Ruiz-Gastélum for the trust she placed in us to carry out the technical and editing review of this text. Considering that in this field of medicine, as in others of human knowledge, there are no absolute truths, nor holders of supreme and irrefutable authority, and accepting naturally that there are areas of conflict and controversy, these editors always respected the central ideas of the authors. In consequence, each author is responsible for the concepts expressed freely in her or his text.

We would like to manifest our gratitude to the two Presidents of the Association under whose auspices the lipid courses were held, and this text was written: Dr. Gabriela Borrayo-

* Editing Committee.

How to cite: Meaney E, Nájera N, Ceballos G. Introductory remarks. Cardiovasc Metab Sci. 2021; 32 (s3): s141-s142. https://dx.doi.org/10.35366/100784

Sánchez, current President of ANCAM and Dr. Pedro Gutiérrez Fajardo, immediate past President. Both generously and in solidarity supported the efforts of this group.

Finally, last but not least, as the classics use to say, we want to express our appreciation to all authors for their exemplary performance and dedication, and to our Medigraphic editors for their patience and collaborative spirit.

Correspondence:
Eduardo Meaney, MD, PhD
E-mail: lalitomini1@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100785

Epidemiology and burden of morbidity and mortality in dyslipidemias and atherosclerosis

Epidemiología y carga de morbilidad y mortalidad en dislipidemias y aterosclerosis

Gabriela Borrayo-Sánchez, MD, PhD*

THE EPIDEMIOLOGICAL SCOPE OF DYSLIPIDEMIAS

Since the discovery of low-density lipoproteins (LDL-c) by John Gofman in 1955, the contribution of this knowledge to the development of the Framingham study (focused on cardiovascular risk), the meritorious scientific studies in this topic of eleven scientists awarded with the Nobel Prize, and the introduction of statins, the importance of dyslipidemias and their impact on the burden of cardiovascular morbidity and mortality associated with atherosclerosis have been widely recognized.[1] Dyslipidemias have become an important public health challenge around the world, as they are considered one of the paramount risk factors of the two main causes of mortality in the world according to the World Health Organization: ischemic heart disease and stroke.[2] In the United States MESA multi-ethnic trial population, that included persons without evident cardiovascular disease (CVD), close to one third of the study participants had elevated concentrations of cholesterol linked to low-density lipoprotein (LDL-c) and about two thirds had hypertriglyceridemia.[3] The proportions of elevated LDL-c and decreased concentrations of the cholesterol linked to high-density lipoprotein (HDL-c), are higher in urban than in rural areas.[4] In Canada, the prevalence of dyslipidemia is 45% in persons aged 18 to 79 years, 57% of respondents of a national survey were not aware of their condition, and only 19% of persons with dyslipidemias had their lipid concentrations, below the recommended levels. Of those taking medications, only 41% reached the recommended Canadian target of LDL-c < 77 mg/dL or an Apo B concentration < 0.8 g/L.[5] In France, the prevalence of hypercholesterolemia was 23.3% (27.8% men and 19.0% women) and only 7.2% were treated (8.5% men and 5.8% women), Only 29.7% of adults on secondary prevention medications attained a reduction in lipids within 6 months.[6]

Although the elevation of cholesterol is considered more frequent among the western rich countries, the diet and some other environmental determinants have extended this disorder worldwide. Overall, the measurement of blood lipids in 102.6 million individuals aged 18 years and over to estimate trends in a period between 1980 to 2018 in 200 countries did not show remarkable differences in total and non-HDL cholesterol (HDL-c) in that lapse. However, those lipids increased in both, low- and middle-income nations (mainly some Asians populations). Contrarywise, the two cholesterols decreased in some high-income western European, North American nations and Australia, phenomenon that shifted the epicenter of the dyslipidemia epidemic from Europe and North America to Asia and the Pacific area. While cardiovascular mortality decreased in most of the industrialized western nations, in 2017, high non-HDL cholesterol caused about 3.9 million of deaths worldwide,

* President, National Association of Mexican Cardiologists (ANCAM).

Received:
05/07/2021
Accepted:
13/07/2021

How to cite: Borrayo-Sánchez G. Epidemiology and burden of morbidity and mortality in dyslipidemias and atherosclerosis. Cardiovasc Metab Sci. 2021; 32 (s3): s143-s146. https://dx.doi.org/10.35366/100785

half of which happened in East, Southeast, and South Asia. These facts clearly indicate the cost of acculturation secondary to the rapid industrialization and the abandonment of the traditional lifestyles of many populations, for the sake of globalization.[7]

In Mexico, we are having a similar situation, due to a rapid epidemiological, nutritional, and anthropometric transition, that affects in a non-homogeneous way several regions of the country. The last national health survey in which lipids were measured (ENSANUT 2012), revealed that more than half of the surveyed population had low levels of HDL-c (hypoalphalipoproteinemia) and LDL hypercholesterolemia. Almost half of the respondents had hypertriglyceridemia. The disappointing rates of patient's awareness, treatment and control of the lipid disorders were, respectively, 12.6, 3.7 and 3.1%.[8] An ENSANUT 2012 contemporary multiple primary intervention trial carried out in Mexico City, the Lindavista study, showed that more than two thirds of the studied sample of a middle-class urban population had hypoalphalipoproteinemia, one third had total cholesterol values ≥ 240 mg/dL, 35% of the participants had values of LDL-c ≥ 130 mg/dL, and about half of them had triglycerides concentrations ≥ 150 mg/dL.[9]

The impact of a theoretical minimum risk exposure level (TMREL) of LDL-c (about 27-50.2 mg/dL) on DALYs (Disability-Adjusted Life Years, a measure of the disease burden composed by the number of years lost, plus disability and premature deaths due to a specific disease), is impressively significant. Secondary to ischemic heart disease in 2019 the number of DALYs rose to 182 million and to 9.14 million of deaths.[10] Concurrently with a slowing progress to lower the disease burden related to LDL-c levels, DALYs increased rapidly in men from 30 years of age. In comparison, men between 40 to 44 years old had the same DALYs than women aged 60 to 64 years. Anyhow, menopause lessen in the latter this gender advantage. All this problematic situation requires the implementation of solid public health policies. Of course, every country or ecological region has its own characteristics that determine the magnitude of the epidemiological scourge of dyslipidemia and its atherosclerotic consequences. The prevalence of obesity, the type of diet and the patterns of tobacco consumption, among other lifestyle traits, must be recognized and considered for every national health system, to generate the appropriate control preventive mechanisms since childhood and adolescence, as the promotion of a healthy nutrition, the attain of a low body mass index, the practice of physical exercise, and the abhorrence of tobacco consumption.[7]

THE IMPACT OF DYSLIPIDEMIAS ON MORBIDITY AND MORTALITY

Dyslipidemia increases cardiovascular risk, by raising the incidence of both, coronary and cerebrovascular diseases. Among Latin American population, a higher risk has been attributed to the increase of the ratio apo B100/apo A-1 (relative risk 2.31) for acute myocardial infarction (AMI). As it is known, the main cardiovascular risk factors are high blood pressure, diabetes mellitus (DM), dyslipidemia, smoking, obesity, and family history of atherosclerotic cardiovascular disease (ASCVD). If they are associated with poor eating habits, lack of regular physical activity, excessive alcohol consumption, and psychosocial stress, they can foster the formation of atheroma plaques.[11] Most of patients with a first AMI have at least one of the main risk factors. The greater the accumulation of risk factors, the higher the risk of in-hospital mortality during the first myocardial infarction. This direct correlation is clearer among patients with 0 versus patients with five risk factors.[12] On the other hand, people with healthy lifestyles and cholesterol concentration within physiological limits hold a lower incidence of major cardiovascular events. This fact underlines the importance of early recognition of ASCVD risk factors and their therapeutic control.[13]

Dyslipidemia is common among patients with type 2 DM (prevalence > 75%). It is called atherogenic dyslipidemia or lipid triad, composed by hypertriglyceridemia, hypoalphalipoproteinemia (low HDL-c concentrations), and the increase of small and dense LDL particles, with greater atherogenic power than large buoyant particles. In Mexico,

with a high prevalence of abdominal obesity or overweight, and diabetes, atherogenic dyslipidemia is very common, and a frequent lipid abnormality behind the occurrence of AMI in our country.[14] In this regard, our mestizo population, whose most important ethnic component comes from our Amerindian ancestors, had a genetic predisposition to have peculiar metabolic abnormalities, as abdominal obesity/overweight, insulin resistance syndrome, DM2, and atherogenic dyslipidemia. In addition, as in Mexico the underdiagnosis and under-treatment of dyslipidemia are relevant and rather frequent problems,[15] public health policies focused on the prevention of CVD through better control of the lipid profile are mandatory.

The most recent lipid guidelines are directed to the reduction of LDL-c and other cholesterol-rich lipoproteins containing apolipoprotein B (apo B), to lessen ASCVD and cardiovascular risk.[16] The use of higher potency statins in combination with ezetimibe and/or IPCSK9, allows a remarkable reduction of LDL-C concentrations. Several clinical trials have established the fact that the lower the LDL-c concentration, the lesser the rate of future cardiovascular events. The proportional reduction of LDL-c ranges from 30 to 50% with moderate or high-intensity statins, respectively, and this abatement rises to 65% when combined with ezetimibe. PCSK9 inhibitors achieve 60% of LDL-c reduction, 75% when combined with high intensity statins, and up to 85%, when ezetimibe is added.[17]

More recently has been doubtlessly established that Lipoprotein (a) is a strong cardiovascular risk predictor. Lp (a) is a small lipoprotein containing Apo B and apolipoprotein a, whose functions have not been fully elucidated. Normally, it has a crucial function as a wall vascular and endothelium tissue-repair agent, although its structure can be modified by oxidation and be transformed in a pro-inflammatory, pro-atherogenic and prothrombotic substance.[18] The relative risk for ASCVD rises between 10-12% for each increment of 50 nmol/L. Although a cut-off value has not been clearly determined, cardiovascular risk is more pronounced with Lp(a) values ≥ 150 nmol/L, equivalent to 70 mg/dL.[19] It seems that high levels of Lp(a) in women confer a higher risk of ASCVD, even in the absence of elevated LDL-c. This parameter could identify a group that can be benefited from intensive pharmacological therapy, even with normal values of LDL-c.[20] Elevation of Lp (a) (specially at concentrations greater than 30-50 mg/dL) is a hereditary condition associated to an increase of atherogenic, inflammation and prothrombotic risk, for what should be considered an independent ASCVD risk factor. Recent international guidelines recommend the measurement of Lp(a) to reassess cardiovascular risk. There are established treatments for this condition, particularly PCSK9 inhibitors, that it seems can provide a promising and innovative therapeutic approach to control this lipid abnormality.[21]

CONCLUSIVE REMARKS

Dyslipidemia is recognized as one the main atherogenic risk for ASCVD, not only LDL-c hypercholesterolemia, but the entire spectrum of lipid abnormalities; hypertriglyceridemia, hypoalphalipoproteinemia, mixed or atherogenic dyslipidemia, and increases of Lp(a). We have already the diagnostic and therapeutic tools for unveil these abnormalities and reduce them to decrease cardiovascular risk. What is needed is to raise the social conscience about this matter, expand the clinical, therapeutic, and prevalent strengths of the medical community, and encourage our governments to deploy a set of public health policies focused to control these fearsome epidemic scourges.

REFERENCES

1. Kuijpers PMJC. History in medicine: the story of cholesterol, lipids and cardiology. E-Journal-of-Cardiology-Practice [On Line]. 2021 [Available in: https://www.escardio.org]; 19: 9.
2. World Health Organization. Mortality and global health estimates. The top 10 causes of death. 2019. Available in: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. Goff Jr DC, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY et al. Dyslipidemia prevalence, treatment, and control in the multi-ethnic study of atherosclerosis (MESA). Gender, ethnicity, and coronary artery calcium. Circulation. 2006; 113: 647-656.

4. Xing L, Jing L, Tian Y, Yan H, Zhang B, Sun Q et al. Epidemiology of dyslipidemia and associated cardiovascular risk factors in northeast China: a cross-sectional study. Nutr Metab Cardiovasc Dis. 2020; 30: 2262-2270.
5. Joffres M, Shileds M, Trembal MS, Gorber SC. Dyslipidemia prevalence, treatment, control, and awareness in the Canadian Health Measures Survey. Can J Public Health. 2013; 104: e252-e257.
6. Blacher J, Gabet A, Vallée A, Ferrières J, Bruckert E, Farnier M et al. Prevalence and management of hypercholesterolemia in France, the Esteban observational study. Medicine (Baltimore). 2020; 99: e23445.
7. NCD Risk Factor Collaboration (NCD-RisC). Repositioning of the global epicentre of non-optimal cholesterol. Nature. 2020; 582: 73-77.
8. Hernández-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, Pedroza-Tobías A, Villalpando S, Shamah-Levy T et al. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. Salud Publica Mex. 2020; 62: 137-146.
9. Meaney A, Ceballos-Reyes G, Gutiérrez-Salmeán G, Samaniego-Méndez V, Vela-Huerta A, Alcocer L et al. Cardiovascular risk factors in a Mexican middle-class urban population. The Lindavista Study. Baseline data. Arch Cardiol Mex. 2013; 83: 249-256.
10. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM et al. Global burden of cardiovascular diseases and risk factors, 1990-2019. Update from the GBD 2019 Study. J Am Cardiol Coll. 2020; 76: 2982-3021.
11. Lanas F, Avezum A, Bautista L, Diaz R, Luna M, Islam S et al. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. Circulation. 2007; 115: 1067-1074.
12. Canto JG, Kiefe CI, Rogers WJ, Peterson ED, Frederick PD, French WJ et al. Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction. JAMA. 2011; 306: 2120-2127.
13. Kopin L, Lowenstein C. Dyslipidemia. Ann Intern Med. 2017; 167: ITC81-ITC96.
14. Estrada García T, Meaney A, López-Hernández D, Meaney E, Sánchez-Hernández O, Rodríguez-Arellano E et al. Hypertension and lipid triad are the most important attributable risks for myocardial infarction in a middle class urban Mexican population. Nutr & Metabol. 2013; 63: 1343.
15. Rivas-Gomez B, Almeda-Valdés P, Tussié-Luna M, Aguilar-Salinas C. Dyslipidemia in Mexico, a call for action. Rev Invest Clin. 2018; 70: 211-216.
16. Mach F, Baigent C, Catapano A, Koskinas K, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019; 41: 111-188.
17. Estruch R, Ruilope L, Cosentino F. The year in cardiovascular medicine 2020: epidemiology and prevention. Eur Heart J. 2021; 42: 813-821.
18. Orsó E, Schmitz G. Lipoprotein(a) and its role in inflammation, atherosclerosis and malignancies. Clin Res Cardiol Suppl. 2017; 2 (Suppl 1): 31-37.
19. Patel AP, Wang M, Pirruccello JP, Ellinor PT, NG K, Kathiresan S et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease. New insights from a large national Biobank. Arterioscler Thromb Vasc Biol. 2021; 41: 465-474.
20. Costello B, Silverman E, Doukky R, Braun L, Aggarwal N, Deng Y et al. Lipoprotein (a) and increased cardiovascular risk in women. Clin Cardiol. 2016; 39: 96-102.
21. Wu MF, Xu KZ, Guo YG, Yu J, Wu Y, Lin LM. Lipoprotein(a) and atherosclerotic cardiovascular disease: current understanding and future perspectives. Cardiovasc Drugs Ther. 2019; 33: 739-748.

Correspondence:
Gabriela Borrayo-Sánchez, MD, PhD
E-mail: gborrayosa@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100786

Knowing the basic mechanisms of lipid metabolism

Conociendo los mecanismos básicos del metabolismo de los lípidos

Alejo Díaz-Aragón, MD* Edith Ruiz-Gastélum, MD‡ Humberto Álvarez-López, MD§

INTRODUCTION

Lipids are biomolecules that are only found in living beings. The way and degree of interaction of these biomolecules with water determine important aspects in some biological processes. For example, the amphipathic character of phospholipids favors the efficient formation of micelles and bilayers. On the other hand, the nonpolar characteristic of fatty acids and triglycerides requires specific transport mechanisms in the blood, through plasma lipoproteins.

Lipoproteins are complex macromolecular structures which are formed by a shell and a core. The shell is composed by phospholipids and free cholesterol, whose polar portions (electrically charged) are oriented outwards, making them soluble in water and therefore transportable. On the other hand, the hydrophobic lipid core (insoluble in water) contains esterified CHOL and TG *(Figure 1)*. The outer shell contains proteins called apolipoproteins,[1] which are characterized by having both hydrophobic and hydrophilic regions, allowing them to maintain at the same time, physical relationships with both, the lipid components, and the aqueous environment.

Based on their density (amount of mass in relation to volume), lipoproteins can be classified and separated by ultracentrifugation in larger lipoproteins with lower density, with a high lipid content and other, smaller, and denser, with a higher content of proteins. Ranging from larger to smaller, there are chylomicrons (CHY), VLDL (very low-density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins), and HDL (high density lipoproteins).[2] Different sizes and densities of several subspecies of VLDL, LDL, IDL, and HDL have been defined, and in turn subdivided in several classes, which have relevance from the clinical point of view.

Apolipoproteins are designated by letters and numbers: A-I, A-II, A-IV, A-V, B48, B100, C-I, C-II, C-III, D, E, among others, whose role is less known.[3] Apolipoproteins have four important functions, through which they regulate lipoprotein metabolism.

1. Production and secretion of lipoproteins (Apo A-I, B48, and B100).
2. Structural integrity and rigidity of the lipoprotein shell (Apo B, E, A-I, and A-II).
3. Activation or inhibition of enzymatic activity (A-I, A-V, C-I, C-II, and C-III).
4. Function as ligands for specific receptors (Apo A-I, B100, and E).

The functions of many lipoproteins are well established. In the first place, they yield to an efficient transport of TG from the intestine (exogenous triglycerides) and liver (endogenous triglycerides) to the tissues for their storage and obtention of energy, as occurs in adipose tissue or skeletal muscle. Secondly, the transport of CHOL to peripheral tissues, serves to the renewal of cell membranes and the synthesis of vitamin D, steroid hormones, or hepatic bile acids. Finally, the reverse CHOL transport from the peripheral tissues to the liver, through which it is eliminated by the bile to the intestine, is an important homeostatic mechanism.

* Facultad de Medicina de la Universidad Autónoma Benito Juárez de Oaxaca.
‡ Clínica de Hipertensión y Riesgo Cardiovascular. ISSSTESON. Hermosillo, Sonora, México.
§ Hospital de Especialidades Puerta de Hierro Andares. Guadalajara, Jalisco, México.

Received:
25/06/2021
Accepted:
02/07/2021

How to cite: Díaz-Aragón A, Ruiz-Gastélum E, Álvarez-López H. Knowing the basic mechanisms of lipid metabolism. Cardiovasc Metab Sci. 2021; 32 (s3): s147-s152. https://dx.doi.org/10.35366/100786

For a better understanding, lipid metabolism is divided into three stages: the exogenous pathway and endogenous pathways, and reverse CHOL transport.

EXOGENOUS PATHWAY

This pathway involves the transport of lipids from the intestine to the liver and other tissues. In the small intestine, bile salts, phospholipids, free CHOL, free fatty acids (FFA), and monoglycerides are assembled forming mixed micelles that permit their absorption in the intestinal mucosa.[4] The absorption of CHOL, plant sterols, and stanols is mediated by the Niemann-Pick C1-like 1 transporter (NPC1L1), located at the border of the jejunal enterocyte membrane and in the apical membrane of hepatocytes.[5] The enterocytes as all cells have a CHOL extrusion mechanism in which are involved several proteins of the superfamily called ABC (ATP bound cassettes), ABCA1, and G5 and G8. These ABCG5 and ABCG8 membrane transporters act as heterodimers, responsible for returning absorbed sterols to the intestinal lumen.[5]

Approximately half of the amount of cholesterol that has been taken up by the enterocytes and has not been returned to the intestinal lumen via the ABCG5/8 process is diffused to the endoplasmic reticulum, where it is resterified by the acetyl cholesterol acyltransferase-2 enzyme (ACAT2) present in the intestinal cells. The esterified CHOL, along with other molecules (TG, phospholipids, and FFA) are packaged by a protein called microsomal triglyceride transfer protein (MTP) to form the first lipoproteins named chylomicrons (CHY), whose function is to carry absorbed lipids inside the body. CHY have a diameter of 80 to 1000 nm, and are conformed of 90% triglycerides and 5% cholesterol, also containing several lipoproteins such as Apo B48, which is a truncated form of Apo B100, because the enterocyte has the Apo B editing enzyme.[6]

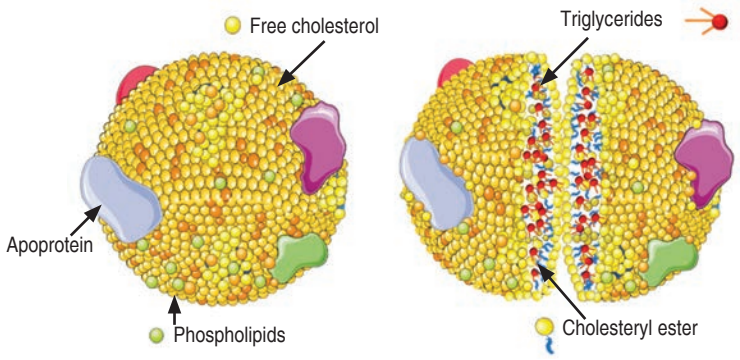


Figure 1: Characteristics and structure of lipoproteins. The cover is made up of free cholesterol, phospholipids and apoproteins, the central part or core contains esterified cholesterol and triglycerides.

CHY are transported to the lymphatic system and through the thoracic duct they reach the systemic circulation. Later, in the blood, they acquire Apo E and Apo C-II, transferred by HDL. They circulate in normal conditions and fasting no longer than 12 hours. Lipoprotein lipase enzyme (LPL) hydrolyzes most of its TG content (about 70%), turning the CHY into a smaller particle named chylomicron remnant, which is characterized by having Apo E. The FFA released are taken up by muscle cells and adipocytes. LPL activity, therefore, is the determining step in the rate of removal of dietary fat from the circulation and is highly regulated in the body.[7] Apo E and Apo C-II activate LPL, while Apo C-III and the angiopoietin 3 (ANGPTL3). and angiopoietin 4 (ANGPTL4) -like proteins inhibit its activity.[8] The presence of Apo E in the remnant is very important since through this apolipoprotein it can be recognized by the hepatic Apo E receptor, also called RRP (receptor-related protein), that traps the remnant, internalizes, and destroys it, using its lipid content for many purposes.

ENDOGENOUS PATHWAY

Endogenous lipid metabolism begins with the synthesis of VLDL, which is produced by the endoplasmic reticulum in the liver, assembling apolipoproteins and triglycerides. MTP is necessary for the secretion of VLDL. Genetic deficiency or chemical inhibition of MTP prevents the secretion of VLDL into the circulation.[9]

VLDLs have a variable diameter from 30 to 80 nm. They can be separated employing ultracentrifugation, in the range of densities

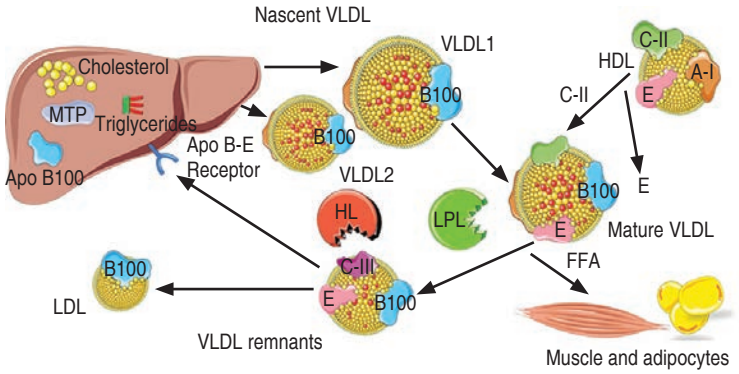


Figure 2: Endogenous pathway. VLDL is synthesized in the liver, which contains Apo B100, matures in the circulation upon receiving Apo E and Apo C-II from HDL. Lipoprotein lipase (LPL) hydrolyzes its triglycerides, releasing free fatty acids (FFA) that will be distributed to skeletal muscle and adipose tissue. As the remodeled VLDL particle lose triglycerides, it become IDL, which are eliminated by the liver or under the action of hepatic lipase (HL) giving rise to LDL.

from 0.95 to 1.006 g/mL. The lipid proportion of these lipoproteins is 60% TG 20% CHOL and the rest, phospholipids. VLDLs vary in size and composition but can be classified into two main classes: VLDL1, large and floating particles with a higher content of triglycerides, and VLDL2, which are smaller and denser.[10] The lipoprotein composition is similar to that of CHY except in two relevant aspects: they do not have Apo A-I and have the complete form of Apo B (Apo B100) since the liver does not express the Apo B-editing enzyme.

Apo B100 is the major structural protein of VLDL and derived catabolic lipoproteins. Other apolipoproteins that are minor components of VLDL are CI, C-II, C-III, and E. Immature VLDL are secreted into the circulation by the Golgi apparatus and once in plasma, VLDL mature acquiring more Apo C-II and Apo E from HDL. VLDLs serve as CHOL acceptors which are transferred from HDL, this transfer process is mediated by the enzyme cholesteryl ester transfer protein (CETP).

The content of TG in VLDL is a suitable substrate for the action of the enzyme LPL, which hydrolyzes the former in a similar process to that which occurs in CHY, releasing FFA, to be used as fuel in the muscle or to be stored in the adipocytes *(Figure 2)*. Because of the hydrolysis, the remnants of VLDL are smaller molecules named intermediate density lipoproteins (IDL). Likewise, to the catabolism of CHY, lipids and apolipoproteins are also released and incorporated into the HDL fraction.[11]

IDLs have a density of 1.006 to 1.019 g/mL with a dimension of 25 to 30 nm and constitute a reduced group of lipoproteins. Smaller in size have fewer TG and phospholipids with a greater amount of esterified CHOL. Their apolipoprotein content consists of Apo B100 and E. It is considered that approximately half of the IDL particles are captured in the liver by B/E receptors, through which they are internalized and degraded in the hepatocyte, while the other half is converted into LDL through a complex process in which hepatic lipase (HL) intervenes.

HL, originated in the liver and regulated mainly by insulin, modulates the lipolysis of TG in IDL and, unlike LPL, it does not require Apo C-II as an activator.[12] This enzyme is also involved in the metabolism of HDL, having a phospholipase activity.

Low-density lipoproteins or LDLs are the product of IDL catabolism. They have a density of 1.063 to 1.019 g/mL, with a diameter of 22 nm and a mass of ~3,000 kDa. Each particle has up to ~1,500 molecules of esters of cholesterol in the hydrophobic core that also contains TG, while the hydrophilic shell is composed by ~800 phospholipid molecules, ~600 free CHOL molecules, and a 500 kDa protein. Its apolipoprotein B-100 also acts as a ligand with cell membrane receptors, having a half-life of 2 to 3 days.[13] The role of LDL is the transport and delivery of CHOL to cells, including peripheral tissues and the liver.

The LDL receptor is a transmembrane glycoprotein that has an approximate molecular weight of 160 kDa and is made up of 839 amino acids with five well-defined regions.[14] The LDL receptor is synthesized by multiple cell lines (fibroblasts, hepatocytes, smooth muscle, adrenal cortex, ovary, and testes cells) and is translocated to the plasma membrane, where is fixed by a protein called clathrin in specific membrane areas called coated pits.[15] Approximately every 10 to 15 minutes, whether or not these coated pits have bounded LDL, they undergo endocytosis and are transported to the cytoplasm in the form of

endosomes. If they contain LDL bounded to the receptor, the latter dissociates and returns to the hepatocyte membrane, while lipoprotein content fuses with lysosomes, which through their enzymes (acid hydrolases), hydrolyze the lipoprotein components, forming amino acids and free CHOL. The pool of free CHOL created regulates different fundamental processes for cellular homeostasis:

1. Inhibition of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), a key enzyme in the intracellular synthesis of CHOL.
2. Stimulation of acyl-coenzyme A cholesterol acyltransferase (ACAT-1) that promotes the esterification of free CHOL that will be deposited in the cytoplasm in its esterified form, which is partly eliminated in the bile canaliculus and partly used to synthesize bile acids.
3. Inhibition of the synthesis of more LDL receptors.

Unlike macrophages, the liver can regulate the concentration of CHOL, its synthesis, and receptors. The synthesis depends on the amounts of the sterol in the endoplasmic reticulum. Liver cell senses its concentration through a family of proteins called SREBPs (sterol regulatory element binding proteins 1 & 2) that regulate several genes involved in the biosynthesis and capture of CHOL.[16] If hepatic CHOL concentrations are low, the SREBPs, which are transcription factors, are activated and decode genes that increase the synthesis of LDL and CHOL receptors. On the contrary, if the concentration of CHOL is high in the hepatocyte, the SREBPs are not activated.

HDL AND REVERSE CHOLESTEROL TRANSPORT

High-density lipoproteins or HDL are characterized by having mainly Apo A-I, although it also contains Apo A-II, C-I, C-II, C-III, and E. HDLs have a density of 1.21 g/mL to 1.063 g/mL, with a diameter of 8 to 12 nm. Approximately 20% of its content is CHOL, 60% are phospholipids, and TG in a smaller proportion. Their origin come in a greater proportion from hepatic synthesis, and to a lesser degree from intestinal synthesis.[17]

The most important function of HDLs is to transport cholesterol from peripheral tissues to the liver, where it is recycled, used in the production of bile acids, or eliminated in the bile, to the gut. Here, CHOL and bile acids enter in the enterohepatic cycle through which around half of the intestinal sterol, and 95% of bile acids return to the liver to be reprocessed.[18] In addition, HDLs has other athero-protective properties, e. g.:

1. Inhibition of LDL oxidation, where the enzyme paraoxonase plays a relevant role.
2. Anti-inflammatory capacity through the inhibition of the synthesis and expression of endothelial adhesion molecules.
3. Cytoprotective action by inhibiting endothelial cell apoptosis.
4. Vasodilator action by stimulating the synthesis of cellular nitric oxide and prostacyclins.
5. Antithrombotic action by inhibiting platelet aggregation.

The role in the reverse transport of HDL depends largely on its content of Apo A-I, which captures phospholipids and free CHOL through the ABCA1 protein from the liver and extrahepatic cells, resulting in lipid poor-Apo A-I with a discoidal shape, called preβ-HDL or nascent HDL, which facilitates the release of intracellular cholesterol through specific mechanisms that require energy consumption. The release or efflux of free CHOL is determined by the interaction of nascent HDL with transporters of the ATP-binding cassette A1 and G1 (ABCA1 and ABCG1) but also with scavenger receptor class B type I (SR-BI receptors).[19] Once free CHOL reaches the nascent HDL, it is esterified by the enzyme lecithin cholesterol acyltransferase (LCAT) and is sent to the core, with which the HDL increases in size and change its form from a discoid shape to a spherical one.

The newly formed HDLs are known as HDL-3 (density 1.12-1.21 g/mL). In turn, they are classified as HDL-3a, 3b, and 3c. Mature HDL is known as HDL-2 (density 1.063-1.12 g/mL), which is classified in two sub-varieties

(HDL-2a and 2b), containing a greater amount of esterified CHOL than HDL-3. The conversion of HDL-3 to HDL-2 comprises an increase in the content of esterified CHOL and therefore an increase in size, requiring the transfer of phospholipids through the enzyme phospholipid transfer protein (PLTP), which contributes to the formation of HDL and VLDL remnants.

HDL catabolism occurs in the liver, kidney, and steroidogenic tissues (adrenal gland, ovaries, or testes). Elimination can be carried out by endocytosis and lysosomal degradation of the entire HDL particle or by its interaction with the SR-BI receptor, which can endocytose the entire particle or transfer CHOL to the interior of the cell, selectively releasing the lipoprotein back to circulation in the form of a nascent HDL. In the liver, the CHOL captured can be converted into bile acids, these being eliminated by the biliary and fecal routes if it is not absorbed beforehand at the intestinal level. Considering that CHOL cannot be degraded by the body, reverse cholesterol transport is the only straight way to eliminate cholesterol from our body.

Cholesteryl ester transfer protein (CETP) is expressed in various tissues, although its main source is the liver. It is an enzyme that participates in the metabolism of HDL and influences its concentration. CETP catalyzes the transfer of TG from VLDL and LDL to HDL, while passing on CHOL esters from HDL to VLDL and LDL.[20] Under normal conditions, CETP exchanges small amounts of HDL esterified CHOL for VLDL TG, resulting in a slight increase of TG content in HDL and minimal effects on VLDL. In contrast, in hypertriglyceridemia, CETP can significantly alter the lipoprotein profile and its catabolism. The accumulation of VLDL in the plasma provides a greater number of TG to exchange with HDL and LDL CHOL. HDLs with higher TG content are less efficient in generating CHOL efflux, while large LDL rich in TG, are more atherogenic. All these changes derived from the active participation of CETP, especially in hypertriglyceridemia, explain its proatherogenic nature.

CONCLUSION

Lipid metabolism is a rather complex process, but it is necessary and important to have basic knowledge of it since this allows to understand the pathophysiology of atherosclerosis and the mechanism of action of the several drugs used in the treatment of dyslipidemia, aimed to influence the different metabolic and enzymatic pathways intervening in the absorption, transport, and synthesis of lipids and lipoproteins, to reduce the serum concentrations of atherogenic CHOL and TG, and also increase those of HDL, and in this way reduce the risk of atherosclerotic cardiovascular diseases.

REFERENCES

1. Daniels TF, Killinger KM, Michal JJ, Wright RW, Jiang Z. Lipoproteins, cholesterol homeostasis and cardiac health. Int J Biol Sci. 2009; 5: 474-488.
2. Ballantyne CM. Clinical lipidology: companion to Braunwald's heart disease. Philadelphia, PA: Elsevier; 2008.
3. Feingold KR. Introduction to lipids and lipoproteins [Updated 2021 Jan 19]. In: Feingold KR, Anawalt B, Boyce A et al, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available in: https://www.ncbi.nlm.nih.gov/books/NBK305896/
4. Green PH, Glickman RM. Intestinal lipoprotein metabolism. J Lipid Res. 1981; 22: 1153-1173.
5. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G et al. Niemann-Pick C1 Like1 protein is critical for intestinal cholesterol absorption. Science. 2004; 303: 1201-1204.
6. Temel RE, Gebre AK, Parks JS, Rudel LL. Compared with Acyl-CoA: cholesterol O-acyltransferase (ACAT) 1 and lecithin: cholesterol acyltransferase, ACAT2 displays the greatest capacity to differentiate cholesterol from sitosterol. J Biol Chem. 2003; 278: 47594-47601.
7. Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. J Lipid Res. 2002; 43: 1997-2006.
8. Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med. 2002; 80: 753-769.
9. Shelness GS, Sellers JA. Very-low-density lipoprotein assembly and secretion. Curr Opin Lipidol. 2001; 12: 151-157.
10. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014; 384: 626-635.
11. Valdemarsson S, Hansson P, Hedner P, Nilsson-Ehle P. Relations between thyroid function, hepatic and lipoprotein lipase activities, and plasma lipoprotein concentrations. Acta Endocrinol. 1983; 104: 50-56.
12. Kobayashi J, Miyashita K, Nakajima K, Mabuchi H. Hepatic lipase: a comprehensive view of its role on plasma lipid and lipoprotein metabolism. J Atheroscler Thromb. 2015; 22: 1001-1011.
13. Goldstein JL, Brown MS. A century of cholesterol and coronaries: From plaques to genes to statins. Cell. 2015; 161: 161-172.

14. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B (eds.). Metabolic and molecular bases of inherited disease. Vol II. Chapter 120. New York: McGraw-Hill Publishing Company; 2001. pp. 2863-2913.
15. Anderson RGW, Brown MS, Goldstein JL. Role of the coated endocytic vesicle in the uptake of receptor-bound low-density lipoprotein in human fibroblasts. Cell. 1977; 10: 351-364.
16. Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell. 1997; 89 (3): 331-340.
17. Fielding CJ. High-density lipoproteins. From basic biology to clinical aspects. Weinheim: Wiley VCH; 2007.
18. Li T, Chiang JY. Regulation of bile acid and cholesterol metabolism by PPARs. PPAR Res. 2009; 2009: 501739.
19. Wang X, Collins HL, Ranalletta M, Fuki IV, Billheimer JT, Rothblat GH et al. Macrophage ABCA1 and ABCG1, but not SR-BI, promote macrophage reverse cholesterol transport *in vivo*. J Clin Invest. 2007; 117: 2216-2224.
20. Paromov VM, Morton RE. Lipid transfer inhibitor protein defines the participation of high-density lipoprotein subfractions in lipid transfer reactions mediated by cholesterol ester transfer protein (CETP). J Biol Chem. 2003; 278: 40859-40866.

Correspondence:
Alejo Díaz-Aragón, MD
E-mail: adacardiologia@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100787

Primary hypercholesterolemia
Familial hypercholesterolemia

Hipercolesterolemia primaria
Hipercolesterolemia familiar

Norma Alejandra Vázquez-Cárdenas, PhD*

INTRODUCTION

Cardiovascular diseases (CVD) represent the main cause of death in the world. An estimated 17.9 million people die each year from these diseases worldwide. One of the main cardiovascular risk factors is hypercholesterolemia.[1] Basically, the causes of this dyslipidemia are divided into two large groups: primary and secondary. The primary causes are those that have a genetic origin; while hypercholesterolemia due to secondary causes is one that occurs because of another diseases or causes, such as diabetes, liver disease, kidney failure, nephrotic syndrome, hypothyroidism, the consumption of certain drugs (antiretrovirals, corticosteroids, etc.), autoimmune diseases, or a high-fat diet, among others.[2]

Of the primary, due to pure or predominant genetic causes, the most common is familial hypercholesterolemia (FH) (OMIM 143890), a disease with an autosomal dominant inheritance pattern, characterized by the fact that affected patients have very high blood cholesterol levels from birth, accelerated atherosclerosis, and thus a very high risk of premature death from CVD.[3]

Based on recent meta-analyzes and what has been published on populations for which data are available, a prevalence of 1 in 310 individuals in the general population has been estimated. Therefore, this disease represents the first cause of premature CV death of genetic cause.[4] Due to the high frequency and seriousness of its consequences, since 1998 the World Health Organization (WHO) classified it as a World Public Health Problem, that should be integrated into the screening programs of all populations, for a detection and timely treatment.[5]

FAMILIAL HYPERCHOLESTEROLEMIA

FH is caused by mutations in the LDLR (19p13.2), APOB (2p24.1) and/or PCSK9 (1p32.3) genes. These genes code for proteins that participate in the metabolism of low-density lipoprotein cholesterol (LDL-c), for which mutations in any of the three alter their homeostasis, causing an increase in serum concentration, a rise in cholesterol deposits in some tissues, and the development of atherosclerotic lesions, in turn responsible for cardiovascular syndromes.[6]

The main cause of FH is due to mutations in the LDLR gene, which codes for the LDL-c receptor, which is located on the plasma membrane of all cells, mainly that of hepatocytes. To date, more than 2000 variants distributed throughout the entire gene have been described, which could cause an alteration in the function or a decrease in the number of receptors to internalize LDL-c, what in turn causes raises in its serum concentration.[7] The APOB gene encodes apolipoprotein B, which serves as a ligand between LDL-c and its receptor, which allows to internalize the lipoprotein inside the cell, to be metabolized.

* Facultad de Medicina, Universidad Autónoma de Guadalajara. México.

Received:
16/06/2021
Accepted:
25/06/2021

How to cite: Vázquez-Cárdenas NA. Primary hypercholesterolemia. Cardiovasc Metab Sci. 2021; 32 (s3): s153-s156. https://dx.doi.org/10.35366/100787

Therefore, mutations in this gene, even without defects in the receptors, also cause hypercholesterolemia. Unlike the large number of mutations found in the LDLR gene, only very few have been reported in the APOB gene, which are generally found in exon 26 and 29, which is the coding part for receptor binding. The PCSK9 gene encodes a protein that when it binds to the LDL receptor allows lysosomes to degrade it, so mutations that cause a «gain of function» generate an excessive production of the protein, decreasing in this way the number of receptors for LDL-c and consequently provoking hypercholesterolemia.[7,8]

HETEROZYGOTE AND HOMOZYGOTE FH

In addition to severe hypercholesterolemia from birth and premature atherosclerosis, some patients with FH may have accumulation of cholesterol in other parts of the body, such as eyelids, eyes, and tendons, causing additional clinical manifestations such as xanthelasma, corneal arch and xanthomas, respectively *(Figure 1)*. Based on the clinical and biochemical characteristics, classically, patients have been classified into two large groups: heterozygous and homozygous. Heterozygous patients have 2 to 3 times the normal levels of LDL-c, and without adequate treatment, most will suffer CVD between 30-50 years old. Xanthelasma, corneal arch and xanthomas, usually appear from the second decade of life. Unfortunately, only a low percentage of patients have these extravascular manifestations, which makes early detection of the disease difficult.[9] The clinical and biochemical characteristics of homozygous patients are much more serious. LDL-c levels are 5 to 10 times above normal values, causing signs and symptoms of CVD at early ages, even since childhood. Most of these patients without treatment, die before the age of 30. Unlike heterozygotes, most homozygous patients present xanthelasma, corneal arch and xanthomas from the first decade of life, thus favoring detection. Fortunately, the prevalence of homozygous patients is much lower, ranging from 1 in 250,000 to 1 in 1,000,000.[10]

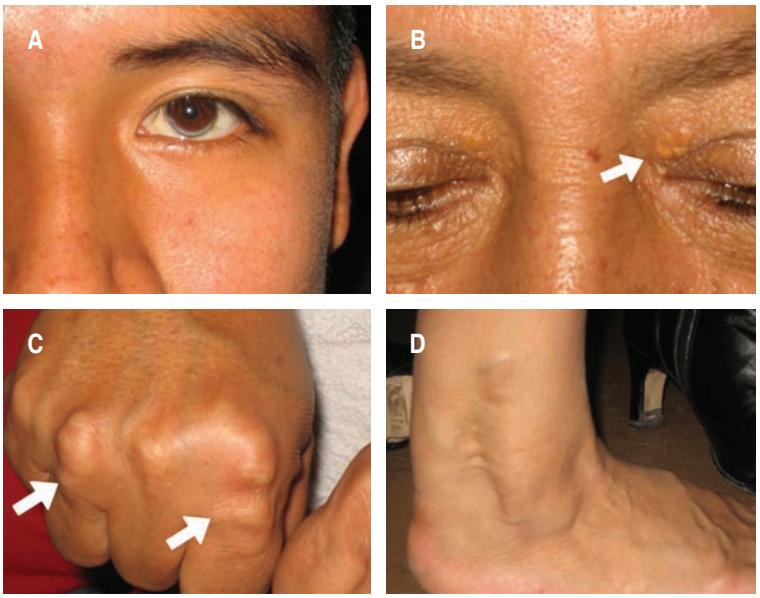


Figure 1: Clinical characteristics of familial hypercholesterolemia: **A)** Corneal arch. **B)** Xanthelasma. **C)** Xanthomas in tendons of the fingers of the hands. **D)** Xanthoma in the Achilles tendon.

Thanks to advances in the knowledge of the molecular bases of FH, patients with clinical and biochemical characteristics of homozygous variety are classified into three groups: true homozygous, compound heterozygous, and double heterozygous. True homozygotes are those that present the same mutation in each of the two alleles of the same gene, either in the LDLR, APOB or PCSK9 gene. Compound heterozygotes show different mutations in each of the two alleles of the same gene. Finally, double heterozygotes are those that have one of the two mutated alleles in a gene and another of the two mutated alleles of another gene.[9]

CLINICAL, BIOCHEMICAL, AND MOLECULAR DIAGNOSIS

In most cases, the diagnosis is established based on clinical and biochemical criteria and through family study. However, for some patients, especially in those who do not have a family history or who do not meet sufficient criteria, a molecular study will be required to identify the genetic cause and thus diagnostic confirmation.[6,11] The diagnostic criteria based on scores help to establish the diagnosis in the index case. The most used are those of the Dutch Lipid Clinic Network Diagnostic Criteria and those of the English Simon Broome Registry.

FH should be suspected in all those adults who have total cholesterol levels above 300 mg/dL and/or LDL cholesterol levels above 190 mg/dL; in patients who have CVD manifestations before the age of 60 and/or clinical signs of hypercholesterolemia, such as xanthomas, xanthelasma and/or corneal arch. The cut-off point for LDL-c level for suspected FH in children and adolescents is ≥ 160 mg/dL.[3,9]

Therefore, the diagnostic criteria for FH can be summarized in three points: 1. Severe hypercholesterolemia at the expense of LDL-c, once secondary causes such as hypothyroidism, kidney and liver damage, consumption of certain drugs, among others, have been ruled out.[2] 2. Presence of premature CVD, xanthomas, xanthelasma and/or corneal arch and 3. History of relatives with severe hypercholesterolemia and premature CVD. The study of relatives is extremely important, since it allows to corroborate the vertical transmission of the disease (autosomal dominant inheritance) and also the detection of other members of the family, that is, the diagnosis through the cascade screen.[3,12,13]

GENETIC COUNSELING

Being a disease with an autosomal dominant inheritance pattern, the theoretical risk for the offspring of a heterozygous index case is 50% and 100% for a homozygous index case. Given that it is a disease whose fatal consequences can be prevented with timely and adequate treatment, when identifying an index case, it is required to do the «cascade screening», that means that all first-degree relatives must be studied as far as possible, and once another affected individual has been identified, his or her offspring must be screened, and so on. Screening for FH is not recommended in children under two years of age, as to date, there is no treatment approved for such age. The cascade sieve is more effective, when the molecular study is available.[14] It should be noted that there is a form of autosomal recessive inherited hypercholesterolemia (ARH), which is caused by mutations in the LDLRAP1 gene, which encodes for a protein that participates in the internalization of the LDL-LDL receptor complex. It is important to suspect this type of hypercholesterolemia in those patients who have a healthy parents or when consanguinity and inbreeding are documented. The risk of recurrence for this type of hypercholesterolemia is 25%.[15]

TREATMENT

The goal of treatment is to lower cholesterol levels to normal levels, in order to reduce cardiovascular risk, indefinitely. Diet and lifestyle modifications are important, but not sufficient to achieve a significant decrease in cholesterol in these patients, which in consequence require lipid-lowering drugs. In heterozygous patients, the drugs of choice are potent high-dose statins, alone or in combination with other oral lipid-lowering drugs, as ezetimibe. The dose will depend on the baseline values of LDL-c and the response to treatment of everyone, requiring indefinitely monitoring by a multidisciplinary team. The therapeutic goal for adults is 100 mg/dL of LDL-c, but if the patient has additional cardiovascular risk factors, treatment must be more stringent to reach < 70 mg/dL or less. Many heterozygous patients achieve these figures with conventional drugs, as statins and PCSK9 inhibitors. However, as most of homozygotes do not have any LDLR activity or it is greatly reduced, drugs that upregulate LDL receptor expression have less or null efficacy. Also, homozygous patients frequently have LDL-c levels above 600 mg/dL, so it is more difficult to achieve the therapeutic goals. These patients require other therapeutic measures, some of them invasive, such as LDL-c apheresis. In recent years, new drugs have been developed for the treatment of FH, designed especially for those patients who do not respond to traditional drugs, alongside monoclonal antibodies for PCSK9, there are antisense oligonucleotides for apolipoprotein B and finally MTP protein (microsomal triglyceride transfer protein) inhibitors, among others.[3,9,10,12]

REFERENCES

1. Cardiovascular Diseases [Internet]. Who.int. [cited March 3, 2021]. Available in: https://www.who.int/health-topics/cardiovascular-diseases
2. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis,

management, and emerging therapies. J Am Coll Cardiol. 2014; 63: 1935-1947.
3. Alonso R, Perez de Isla L, Muñiz-Grijalvo O, Mata P. Bariers to early diagnosis and treatment of familial hypercholesterolemia: current perspectives on improving patient care. Vasc Health Risk Manag. 2020; 16: 11-25.
4. Hu P, Dharmayat KI, Stevens CAT, Sharabiani MTA, Jones RS, Watts GF et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: A systematic review and meta-analysis: a systematic review and meta-analysis. Circulation. 2020; 141: 1742-1759.
5. World Health Organization. Familial hyperchcolesterolemia [FH]: report of a WHO consultation. Geneva, Switzerland: World Health Organization; 1998.
6. Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM et al. Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. J Am Coll Cardiol. 2018; 72 (6): 662-680.
7. Leigh S, Futema M, Whittall R, Taylor-Beadling A, Williams M, den Dunnen JT et al. The UCL low-density lipoprotein receptor gene variant database: pathogenicity update. J Med Genet. 2017; 54 (4): 217-223.
8. Chora JR, Medeiros AM, Alves AC, Bourbon M. Analysis of publicly available LDLR, APOB, and PCSK9 variants associated with familial hypercholesterolemia: application of ACMG guidelines and implications for familial hypercholesterolemia diagnosis. Genet Med. 2018; 20: 591-598.
9. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol. 2016; 4 (10): 850-861.
10. Gidding SS. Managing patients with homozygous familial hypercholesterolemia. J Am Coll Cardiol. 2017; 70: 1171-1172.
11. Watts GF, Gidding SS, Mata P, Pang J, Sullivan DR, Yamashita S et al. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. Nat Rev Cardiol. 2020; 17: 360-377.
12. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. Atherosclerosis. 2018; 277: 483-492.
13. Haralambos K, Ashfield-Watt P, McDowell IFW. Diagnostic scoring for familial hypercholesterolaemia in practice. Curr Opin Lipidol. 2016; 27: 367-374.
14. Tada H, Okada H, Nomura A, Nohara A, Yamagishi M, Takamura M et al. Prognostic impact of cascade screening for familial hypercholesterolemia on cardiovascular events. J Clin Lipidol. 2021; 15: 358-365.
15. Garcia CK, Wilund K, Arca M, Zuliani G, Fellin R, Maioli M et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001; 292: 1394-1398.

Correspondence:
Norma Alejandra Vázquez-Cárdenas, PhD
E-mail: alejandra.vazquez@edu.uag.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100788

Other forms of primary hypercholesterolemia. Familial combined hyperlipidemia and polygenic or common hypercholesterolemia

Otras formas de hipercolesterolemia primaria. Hiperlipidemia familiar combinada e hipercolesterolemia poligénica o común

Alejo Díaz-Aragón, MD* Humberto Álvarez-López, MD‡ Edith Ruiz-Gastélum, MD§

Familial combined hyperlipidemia (FCHL) is a primary dyslipidemia whose prevalence ranges between 1 and 3%, although it is more frequent in patients with coronary artery disease. FCHL is found, for example, in 20% of those under 60 years old who survived an acute myocardial infarction and up to 38% in those survivors under 40 years.[1,2] Due to the lack of robust diagnostic markers, in many patients at high risk of some type of atherosclerotic cardiovascular disease (ASCVD), the diagnosis of FCHL is not established. This dyslipidemia has been characterized as a hereditary disorder (oligogenic, i.e., caused by just a few genes), autosomal, with variable penetrance. Several genetic abnormalities have been signaled as responsible for FCHL, encompassing various clinical lipoprotein phenotypes. The lipid profile of FCH is rather heterogeneous, which suggests a multifactorial origin in which a variety of genetic abnormalities lead to various pathogenic alterations of lipoproteins and their metabolism. It has been identified the gene that encode the upstream transcription factor 1 (USF1) as one of the principal contributors to this pathology.[3] USF1 regulates the expression of multiple genes involved in glucide and lipid metabolism. When it is inactivated in mice, brown adipose tissue is activated, enhancing thermogenesis, decreasing triglyceridemia, and reducing insulin resistance and its manifestations, as lipid pathology and fatty liver disease.[4] Mexican population, with a high rate of abdominal obesity and insulin resistance, is prone to suffer combined dyslipidemia and the lipid triad. In fact, several Mexican families have been found affected with FCHL.[5,6]

The genetic disorder helped by unhealthy lifestyle (high fat diet and sedentarism) increase the hepatic formation of VLDL, small and dense LDL particles, and apo B100. Frequently, FCHL is associated to low concentrations of the protective lipoprotein HDL, combination that is known as atherogenic dyslipidemia or lipid triad. This combination can be also secondary to obesity/diabetes phenotypes, and whose atherogenic power has been unveiled many years ago.[7-9]

As a heterogeneous, highly pleiomorphic dyslipidemia, and still without well-defined genetic alterations, universally accepted diagnostic criteria are lacking.[2] Therefore, the clinical approach demands the exclusion of secondary causes of combined dyslipidemia. As the phenotypic expression differs from patient to patient, the concentrations of total cholesterol (TC) and triglycerides (TG) in members of the same affected family show a great variability.[8] The following could be valuable diagnostic clues, although none of them is indispensable or specific: 1) Familial history of premature ASCVD (atherosclerotic events occurring in men

* Cardiologist.
‡ Hospital de Especialidades Puerta de Hierro Andares. Guadalajara, Jalisco, México.
§ Clínica de Hipertensión y Riesgo Cardiovascular. ISSSTESON. Hermosillo, Sonora, México.

Received:
30/06/2021
Accepted:
06/07/2021

How to cite: Díaz-Aragón A, Álvarez-López H, Ruiz-Gastélum E. Other forms of primary hypercholesterolemia. Familial combined hyperlipidemia and polygenic or common hypercholesterolemia. Cardiovasc Metab Sci. 2021; 32 (s3): s157-s159. https://dx.doi.org/10.35366/100788

under 55 years old, or in women under 65 years). 2) Familial history of dyslipidemia (two or more first degree relatives with some type of dyslipidemia). 3) Combined total and LDL hypercholesterolemia (> 240 and > 160 mg/dL, respectively) plus hypertriglyceridemia (> 200 mg/dL). In general, concentrations of TC and LDL are not strikingly elevated, as in familial hypercholesterolemia. Concomitant hypoalphalipoproteinemia (HDL-c less than 40 mg/dL) is common. Hypertriglyceridemia stimulates the production of small and dense LDL particles, highly oxidizable and atherogenic. 4) Apolipoprotein B100 elevated (> 120 mg/dL). 5) Absence of clinical or biochemical data signaling secondary causes of combined dyslipidemia as hypothyroidism, nephrotic syndrome, chronic kidney disease, pheochromocytoma, Cushing syndrome or steroids consumption, and use of drugs like retinoids, and some antiretroviral agents, among many others. 6) Absence of tendinous xanthomas. 7) Genetic studies: gene encoding USF1, and members of the gene cluster APOA1/C3/A4/A5, that influence lipid metabolism, among others under scrutiny.[1,2,9-11]

The relationship between this hereditary dyslipidemia and the physiopathological clinical complex composed by obesity/overweight, insulin resistance, and diabetes mellitus, is unclear. Very probably there is a bilateral and complementary connection, in which the lipid pathology caused by defective genes is magnified by the metabolic abnormalities secondary to the insulin resistance/hyperinsulinism binomial and diabetes syndromes. Contrariwise, persons with FCHL also have the propensity to develop abdominal dysmetabolic adiposity, insulin resistance and diabetes. Modest increases in weight and insulin resistance were associated with significantly higher probability of FCHL in a multi-ethnic US population. The multi-ethnic study of atherosclerosis (MESA) showed that in various ethnic groups, a modest increment of weight has different consequences in the development of combined dyslipidemia,[12] what seems indicate again the intricate binomial interaction between genes and environment.[13] The therapeutic management of this dyslipidemia follows the same general principles of the treatment of hypercholesterolemia and hypertriglyceridemia, reviewed in other sections of this text.

POLYGENIC OR COMMON HYPERCHOLESTEROLEMIA

Polygenic hypercholesterolemia is a frequent cause of elevated blood cholesterol secondary to multiple gene mutations, expressed as single nucleotide polymorphisms (SNPs), powerfully influenced by environmental factors, mainly diet rich in animal fat. Although they had already been identified 95 loci significantly associated to lipid anomalies,[14] more recently, the Global Lipids Genetics Consortium (GLGC) found 62 more for a total of 157.[15] Studies aimed to distinguish between polygenic and familial hypercholesterolemia (FH), have shown that only in 40-60% of patients with clinical FH can be demonstrated a monogenic defect, which involves the LDLR, Apo B or PCSK9 genes.[16] A major discovery was the finding that in many patients with FH the genetic disturbance was not monogenic but in essence polygenic.[16-18]

The genetic participation in common hypercholesterolemia, does not lessen the crucial role of lifestyle, environmental, and other metabolic factors, that greatly contribute to rise LDL-c concentrations, especially in the later stages of life. But due to genetic influence, the frequency of this type of dyslipidemia is higher in subjects with familial history of ASCVD. By having LDL concentrations lower than monogenic hypercholesterolemia, and because in the polygenic form, the lipid disorder appears late in life, the ASCVD episodes are also later (> 50 years of age), being, in general, less lethal that FHC. However, for being much more frequent the polygenic than the monogenic form, the epidemiologic impact of the former in the genesis of ASCVD is more important. A fact worth noting is the best therapeutic and dietary response of the polygenic form.[19]

REFERENCES

1. Brouwers MCGJ, van Greevenbroek MMJ, Stehouwer CDA, de Graaf J, Stalenhoef AFH. The genetics of familial combined hyperlipidaemia. Nat Rev Endocrinol. 2012; 8: 352-362.
2. Mata P, Alonso R, Ruíz-Gracia A, Díaz-Díaz JL. González N, Gijón-Conde T et al. Hiperlipidemia

familiar combinada: documento de consenso. Aten Primaria. 2014; 46: 440-446.
3. Pajukanta P, Lilja HE, Sinsheimer JS, Cantor RM, Lusis AJ et al. Familial combined hyperlipidemia is associated with upstream transcription factor 1 (USF1). Nat Genet. 2004; 36: 371-376.
4. Laurila PP, Soronen J, Kooijman S, Forsstrom S, Boon MR, Surakka I et al. USF1 deficiency activates brown adipose tissue and improves cardiometabolic health. Sci Transl Med. 2016; 8: 22-41.
5. Aguilar-Salinas CA, Olaiz G, Valles V, Torres JM, Gomez Perez FJ, Rull JA et al. High prevalence of low HDL cholesterol concentrations and mixed hyperlipidemia in a Mexican nationwide survey. J Lipid Res. 2001; 42: 1298-1307.
6. Huertas-Vazquez A, Aguilar-Salinas C, Lusis AJ, Cantor RM, Canizales-Quinteros S, Lee JC et al. Familial combined hyperlipidemia in Mexicans: association with upstream transcription factor 1 and linkage on chromosome 16q24.1. Arterioscler Thromb Vasc Biol. 2005; 25: 1985-1991.
7. Ayyobi AF, McGladdery SH, McNeely MJ, Austin MA, Motulsky AG, Brunzell JD. Small, dense LDL and elevated apolipoprotein B are the common characteristics for the three major lipid phenotypes of familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 2003; 23: 1289-1294.
8. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience). Prospective Cardiovascular Münster study. Am J Cardiol. 1992; 70: 733-737.
9. Veerkamp MJ, de Graaf J, Bredie SJH, Hendricks JCM, Demacker PNM, Stalenhoef AFH. Diagnosis of familial combined hyperlipidemia based on lipid phenotype expression in 32 families. Arterioscler Thromb Vasc Biol. 2002; 22: 274-282.
10. Shoulders CC, Jones EL, Naoumova RP. Genetics of familial combined hyperlipidemia and risk of coronary heart disease. Hum Mol Genet. 2004; 13 Spec No 1: R149-R160.
11. Naukkarinen J, Ehnholm C, Peltonen L. Genetics of familial combined hyperlipidemia. Curr Opin Lipidol. 2006; 17: 285-290.
12. Paramsothy P, Knopp R, Bertoni AG, Tsai MY, Rue T, Keckbert SR. Combined hyperlipidemia in relation to race/ethnicity, obesity, and insulin resistance in the Multi-Ethnic Study of Atherosclerosis (MESA). Metabolism. 2009; 58: 212-219.
13. Veerkamp MJ, de Graaf J, Stalenhoef AFH. Role of insulin resistance in familial combined hyperlipidemia. Arterioscler Thromb Vasc Biol. 2005; 25: 1026-1031.
14. Teslovich TM, Musumuru K, Smith AV, Edmonson AC, Stylianou IM, Koseki M et al. Biological, clinical, and population relevance of 95 loci for blood lipids. Nature. 20105; 466: 707-713.
15. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013; 45 (11): 1274-1283.
16. Sharifi M, Futema M, Nair D, Humphries SE. Polygenic hypercholesterolemia and cardiovascular disease risk. Curr Cardiol Rep. 2019; 21 (6): 43.
17. Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet. 2013; 381: 1293-1301.
18. Futema M, Bourbon M, Williams M, Humphries SE. Clinical utility of the polygenic LDL-C SNP score in familial hypercholesterolemia. Atherosclerosis. 2018; 277: 457-463.
19. Mickiewicz A, Futema M, Cwiklinska A, Kuchta A, Jankowski M, Kaszubowski M et al. Higher responsiveness to rosuvastatin in polygenic versus monogenic hypercholesterolaemia: a propensity score analysis. Life (Basel). 2020; 10 (5): 73.

Correspondence:
Alejo Díaz-Aragón, MD
E-mail: adacardiologia@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100789

From endothelial dysfunction to complicated atherosclerotic plaque -the long journey of the more lethal disease of our times-

De la disfunción endotelial a la placa aterosclerótica complicada -el largo viaje de la enfermedad más letal de nuestro tiempo-

Eduardo Meaney, MD, PhD*

INTRODUCTION

Atherosclerosis is a pathological process extremely intricate and complex, in which factors of genetic, dietary, metabolic, hemodynamic, thrombogenic, rheological, inflammatory, oxidative, immune, psychosocial, and environmental nature, concur concomitantly. Nevertheless, dyslipidemia is, doubtlessly, the major risk factor for atherogenesis. In this brief review we will summarize the essential points of the long journey that goes from endothelial dysfunction to the building-up of atherosclerotic lesions, and its eventual complications, including plaque fracture and athero-thrombotic occlusion.

Definition of atherosclerosis. Atherosclerosis is a lesion composed by two processes termed atherosis and sclerosis. The former is defined as *the intracellular and extracellular accumulation of lipid in the subendothelial space, with foam cell formation and the triggering of a state of chronic inflammation,* while the latter, sclerosis, indicates *a fibrotic, tentatively scaring process, characterized by hyperplasia of vascular myocytes and dystrophy of extracellular matrix, with hardening of the vascular wall.* Atherosclerosis affects at the beginning the subendothelium, but then it spreads to the rest of the arterial wall, affecting only large and medium-caliber arteries.

First step: accumulation of lipids in the subendothelium. Normally there is an active trans-endothelial traffic of lipoproteins between the vessel lumen and the subendothelium, mainly through pinocytic vesicles hatching on the luminal surface of the endothelial cell and trapping lipoproteins containing apolipoprotein B100, internalizing them in the cytoplasm, and later, opening in the abluminal side, depositing their lipid load in the subendothelial space. Vesicles can coalesce forming real tunnels that cross the entire endothelial cell. Furthermore, sometimes the firm intercellular junctions, composed by union proteins, are broken, increasing endothelial permeability, and easily giving way to large protein molecules (paracellular traffic).

Second step: the entrapment of lipoproteins in the subendothelial space. Subendothelial extracellular vascular matrix (ECM) is composed by numerous substances, as elastin, collagen, and proteoglycans (chondroitin sulfate, dermatan, aggrecan, and heparan, among others). Low density lipoproteins (LDL), principally those small and dense particles, have a great affinity for some of the proteoglycans, and are trapped in fibrous network during a long period.

* Laboratorio de Investigación Integral Cardiometabólica. Escuela Superior de Medicina. Instituto Politécnico Nacional. Ciudad de México, México.

Received:
21/06/2021
Accepted:
30/06/2021

How to cite: Meaney E. From endothelial dysfunction to complicated atherosclerotic plaque -the long journey of the more lethal disease of our times-. Cardiovasc Metab Sci. 2021; 32 (s3): s160-s163. https://dx.doi.org/10.35366/100789

Third step: oxidation modification of the trapped lipoproteins and inflammation. Reactive oxygen substances (ROS) are generated constantly during metabolism. Small and dense LDL particles are particularly prone to oxidative modifications. If just a few of the polyunsaturated fatty acids that are part of phospholipids, the most numerous components of the lipoprotein coating, undergo a process of oxidation, the entire particle is no longer recognized as a native substance, and in consequence unleashes a complex inflammatory and immune response. The minimally modified LDL particle (LDLmm) is then furthermore oxidized (LDLox), damaging all biomolecules within reach. The degradation of lipoprotein lipids forms a series of catabolic waste compounds, as phosphatidylcholine (LPC), which plays numerous and tangled roles in inflammation and atherogenesis. Its activities involve several cells like macrophages, vascular myocytes, white blood cells, and inclusive endothelial cells, regulating cell cycle, inflammation, immunity response, cell proliferation, and oncogenesis. Seems that LPC has a specific membrane receptor named G2a, member of the superfamily of G protein coupled receptors (GPCR). The interaction of LPC in its receptor initiates an intracellular signal cascade responsible of an inflammatory reaction and activation of target cells. In addition, LPC, other oxidized phospholipids, and LDLox, bind to Toll-like receptors, part de the pattern recognition receptors, which also awake an inflammatory response. In addition, since early atherogenesis, an autoimmune response, involving innate and adaptative components is unshackle. Moreover, cholesterol entrapped in the subendothelium crystallizes, and some of these sharpen microcrystals can cross the endothelial layer, causing small tears and holes through which LDLox can escape to bloodstream. LDLox acts as one the multiple ligands for the LOX-1 receptor, which is mainly placed in the caveola rafts of the endothelial cell membrane. The activated LOX-1 receptors start several signal pathways, eliciting endothelial dysfunction, oxidation, inflammation, apoptosis, autophagia, and expression of diverse cytokines, and molecules of monocyte attraction.

Fourth step. Activation of endothelial cells. Atherosis is completed when in additions to lipid accumulation, the activated endothelial cells, secrete several substances that attract monocytes to the vascular wall, immobilize them on the surface and impulse their translocation to the subendothelium. The monocytes, converted now in resident macrophages, gobble up the oxidized fat through pinocytic vesicles, phagocytosis, and scavenger receptors, until they are transformed in the so-called foam cells, pilled of lipids.

Fifth step. The response to the first injury. The body reacts to this primary injury, first sending macrophages to retire the extracellular fat. Macrophages are part of the mononuclear phagocyte system, in charge of eliminate foreign proteins and other type of debris from the blood and tissues. Angiotensin II (called the «honorary cytokine») plays a crucial role in this inflammatory reaction, as it is involved, among other actions, in the activation of oxidases and production of ROS, and in the awakening of the nuclear factor kappa B (NF-kappa B), a multiple transcription protein, capable of elicit a powerful inflammatory and immune response. At the beginning of atherogenesis, there is a dialectic confrontation between macrophage retention and its migration out of the vessel wall. As the process go on, the resident macrophages (mainly type 1, proinflammatory) loss mobility and remain confined in the atherosic lesion (the so-called «lobster trap»). Some of them initiate an apoptotic or necrotic dissolution, scattering their intracellular content in the nearby area: remains of the lysate proteins, oxidized lipids, and oxidized cholesterol, that together with the cellular debris form the necrotic core of what will be the atheroma. Myointimal cells (those migrant myocytes that changed their phenotype from contractile to secretory type) also have the capacity to scavenge lipids and convert themselves in foam cells. The latter produce all kind of tissue-harming substances: ROS, proinflammatory, proapoptotic and proautophagic cytokines, and ECM destroying enzymes like matrix metalloproteinases (MMP, as elastases, collagenases, gelatinases, fibronectinases, among others), which erode and debilitate the extracellular matrix. Teleologically, it seems that

this reaction tries to clear the way out to foam cells. But even if macrophages remain in the lesion, all these histotoxic substances damage the endothelium, first only functionally, but later also its anatomical structure. Endothelial denudation attracts and activates platelets, that not only initiate the first phase of coagulation paving the destroyed endothelium layer, but also through the secretion of growth factors (also coming from endothelial and myointimal cells). The substances launch a reparative, scaring process, stimulating the growth, proliferation, and mobilization of vascular myocytes and the fibrous dystrophy of the ECM. In this manner, the atherosclerotic plaque or atheroma is formed: an oxidized lipid and a necrotic debris core, with numerous inflammatory cells, cytokines, cholesterol crystals, tissue destroying enzymes, covered by a fibromuscular covering.

Sixth step. Evolution and destiny of the atheroma. Once the mature atherosclerotic plaque is formed (atheroma), its evolution can take several pathways. The young, soft, lipid-laden, inflamed plaque regularly has a very thin and fragile fibromuscular cap, likely to break up. It is called vulnerable plaque and its fracture induces a clot formation, which on many occasions shut down the lumen and unlashes an acute coronary syndrome. But there are many occasions in which the thrombus is limited or dissolved, and the fracture is spontaneously repaired. Other times, the plaque evolves slowly, decreasing its lipid content and inflammation, and thickening, hardening, and calcifying the fibrous cap. These phenomena make less possible the plaque rupture but compromise functional arterial lumen. The young plaques experiment an eccentric grow that do not reduce importantly the inner caliber of the vessel, while the hard, older atheroma grows concentrically, even up to the complete fibrotic closure of the artery.

Seventh step. Forces involved in atherogenesis and plaque fracture. There are two kinds of forces involved in plaque fracture. Some, internal, have already been mentioned: inflammation, and the lysis of ECM by tissue damaging enzymes. Others, are hemodynamic forces, playing in two different scenarios. Oscillatory perpendicular stress is a mechanical force applied to the thickness of the vessel wall, which depends on differential blood pressure and is governed by the Laplace's law ($S = [P \bullet r]/2h$, where S is the stressful force, P, systolic blood pressure, r, the cavity radium, and h the wall thickness). As the atherosclerotic plaque bulge into the lumen, the internal radius of the artery is smaller at the top of the atheroma and larger just at the site adjacent to the healthy vascular wall (the shoulder of the plaque). In this site, the sum of the accumulation of inflammatory cells and MMPs debilitating further the ECM and the perpendicular stress, conjugate to break up the cap. For these reasons, the plaque shoulder is the favorite place in which a perpendicular tear occurs. Other important mechanical factor is shear (misnamed «shear stress», because is not a force applied to the vessel thickness, but instead it is a tangential force on the surface of arterial inner layer). Normally, in most vessels flow is laminar, which means that hydric molecules are arranged in horizontal layers, rolling one over another. The flow stream has a parabolic front, since the liquid layers closest to the walls of the vascular container are slowed down by friction on the surface, and at the same time, the inner layers, free of shear, run faster. This frictional, «ironing» force is recognized by mechanoreceptors, arising signals that induce the normal development of the endothelium: its cells are arranged in an orderly direction in the same sense of flow current, have similar morphology and sizes, and very tight intercellular junctions. As well, the endothelium operates normally, secreting anti-inflammatory, antithrombotic, and antiproliferative substances. When laminar flow is lost and it is transformed in a disturbed, non-laminar one, shear is low and occurs the opposite; there is a derangement in the orientation of the endothelial cells, their size varies, and the intercellular junctions become looser and more distant. Furthermore, endothelium dysfunctions, and secretes «rogue» substances proinflammatory, prooxidants and proliferative. For that reason, in sites of low shear (for example, on external walls borders of bifurcations and branches) the development of atherosclerotic lesions is more commonly observed. But when shear is abnormally augmented there are also consequences:

platelets are activated, and the cutting effect of friction can cause longitudinal tears in the endothelial aspect of the atheroma.

Eighth step. Regression of some atherosclerotic lesions. Anichkov was the first who linked atherosclerotic lesions with cholesterol in rabbits fed with this lipid. He also documented that when experimental rabbits were returned to their normal vegetarian diet, lesions regressed dramatically. Recent studies utilizing intravascular ultrasound, a technique that allows to measure plaque volume, have shown that statins and PCSK9 antibodies can induce a small anatomical regression of the plaque, and a concomitant intraluminal gain. Notwithstanding, more important is a «biochemical regression», in which vigorous lipid treatment lessens the cholesterol content in the plaque, which in turn reduces inflammation, oxidation, and apoptosis, leading to less vulnerability to rupture and therefore a lower incidence of acute vascular syndromes.

BIBLIOGRAPHY

1. Ross R. Atherosclerosis- An inflammatory disease. N Engl J Med. 1999; 340: 115-126.
2. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001; 104: 365-372.
3. Gimbrone MA Jr, García-Cardeña G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. Cardiovasc Pathol. 2013; 22: 9-15.
4. Wold D, Ley K. Immunity and inflammation in atherosclerosis. Circulation Res. 2019; 124: 315-327.
5. Moore K, Sheedy F, Fisher E. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol. 2013; 13: 709-721.
6. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. Circ Res. 2016; 118: 692-702.
7. Patti G, Melfi R, Di Sciascio G. The role of endothelial dysfunction in the pathogenesis and in clinical practice of atherosclerosis. Current evidences. Recenti Prog Med. 2005; 96: 499-507.
8. Watanabe N, Ikeda U. Matrix metalloproteinases and atherosclerosis. Curr Atheroscler Rep. 2004; 6: 112-120.
9. Heo K-S, Fujiwara K, Abe J-I. Shear stress and atherosclerosis. Mol Cells. 2014; 37: 435-440.
10. Nissen SE, Nicholls AJ, Sipahi I, Libby P, Raiclen JS, Ballantyne CM et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. The ASTEROID Trial. JAMA. 2006; 295: 1556-1565.
11. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014; 114: 1852-1866.

Correspondence:
Eduardo Meaney, MD, PhD
E-mail: lalitomini1@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi:10.35366/100790

Free radicals, oxidative stress and the Pandora box

Radicales libres, estrés oxidativo y la caja de Pandora

Guillermo Ceballos, MD, PhD* Eduardo Meaney, MD, PhD*
Miguel Ortiz-Flores, PhD* Nayelli Nájera, PhD*

Free radicals are atoms or groups of atoms that have a missing electron, so they are very reactive, trying to capture an electron from other atoms in order to achieve their electrochemical stability. The term «free radical» emphasizes a higher reactivity compared to molecules whose atoms are linked to each other by covalence (bond by electron sharing). Once the free radical has managed to subtract the electron (reduction) that it needs to stabilize, the stable molecule that loses it (oxidation) becomes in turn a free radical (it is left with an unpaired electron), thus initiating a chain reaction.

Because reactive species do not have specific acceptors/receptors, they have an indiscriminate aggressive capacity to interact with and damage cells and tissues.

Free radicals were first described in 1900, with the decomposition of hexa-phenylethane into two triphenylmethyl radicals. In 1956 Denham Harman hypothesized that oxygen radicals could be formed as products of enzymatic reactions *in vivo* and described free radicals as «Pandora's box of evils». He postulated the theory of free radicals causing aging, based on the premise that a single and common process (toxicity of free radicals) that is modifiable (increased) by genetic and environmental factors was responsible for the aging and death of all living beings.

There are three mechanisms of free radical formation:

1. Electronic transfer, in which the transfer of an electron to a molecule occurs.
2. Loss of a proton from a molecule.
3. Homolytic breaking of a covalent bond, so that each fragment conserves one of the paired electrons of the bond.

In cells, free radicals are produced through electron transfer reactions, with or without enzymatic participation.

As a product of metabolism, different types of free radicals are generated, such as:

1. Reactive Oxygen Species (ROS) examples of which are: superoxide anion, peroxide anion, perhydroxyl radical, hydroxyl radical.
2. Reactive Nitrogen Species (RNS): nitric oxide, peroxynitrite, among others.

The main sources of reactive species in the human body are the mitochondria, lysosomes, peroxisomes, as well as nuclear, cytoplasmic, and endoplasmic reticulum membranes.

Free radicals are also generated by several external factors, examples of which are: environmental pollution, exposure to ionizing radiation, tobacco consumption, chemical additives in processed foods and some xenobiotics such as pesticides, herbicides, and fungicides.

Superoxide anion ($O_{2^-}^{\bullet}$) is the first free radical generated. This ROS induced the formation of other reactive species in the vascular endothelium, such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH*), and peroxynitrite (ONOO−). Superoxide is generated through the partial reduction of molecular oxygen by the mitochondrial electron transport chain (ETC), as well as by NADPH oxidases, uncoupled endothelial nitric oxide synthase (eNOS) and xanthine oxidase.

* Laboratorio de Investigación Integral Cardiometabólica. Escuela Superior de Medicina. Instituto Politécnico Nacional. Ciudad de México, México.

Received:
28/06/2021
Accepted:
09/07/2021

How to cite: Ceballos G, Meaney E, Ortiz-Flores M, Nájera N. Free radicals, oxidative stress and the Pandora box. Cardiovasc Metab Sci. 2021; 32 (s3): s164-s167. https://dx.doi.org/10.35366/100790

More than 95% of the O_2 consumed by the cells is reduced by the aqueous route to H_2O during mitochondrial respiration, while a small percentage (< 5%) is converted to superoxide. Once the free radical has been formed in the initial reaction, it has the ability to give up the electron to any other compound, originating new radicals, which constitutes the chain propagation reaction that can be amplified resulting in damage to body tissues. Superoxide anion is essentially produced in the mitochondria at the level of complex I and III, and its production is related to the leakage of electrons from the ETC that causes the partial reduction of molecular oxygen to O_{2}-* instead of water. ROS produced in the mitochondria can directly affect the functionality of the ETC complexes by oxidizing their iron-sulfur centers, thus exacerbating ROS production.

The NADPH oxidases (NOX), a family of membrane-bound enzyme complexes, catalyze the reduction of molecular oxygen to O_{2}-* by using NADPH as electron donor, this reflects their specific role in inducing a burst of ROS and bacterial killing in macrophages and other phagocyte cell types. NOX4 isoform is the most abundant in endothelial cells. Under physiological conditions, the NOX enzymes produce moderate levels of ROS that are required for normal redox signaling. In particular, the NOX2 and NOX4 isoforms induce proliferation and survival of endothelial cells activating MAPK and Akt. However, under pathological conditions, NOX4 may promote the formation of a pro-thrombogenic endothelial phenotype.

Nitric oxide synthases (NOS) are a family of enzymes that catalyze the production of NO and citrulline from oxygen and L-arginine. Electrons are transferred from NADPH to the heme iron and the cofactor tetrahydrobiopterin (BH4) to reduce and incorporate O_2 into L-arginine generating nitric oxide (NO) and citrulline. Three isoforms of NOS exist; neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial (eNOS). eNOS is the most abundant isoform expressed in endothelium. NO is a key determinant for vascular homeostasis since is the main vasodilatory substance release by the endothelium. However, under limited availability of substrates and/or cofactors, eNOS can generate superoxide instead of NO, a condition known as «uncoupling». Additionally, NO can react with superoxide generating peroxynitrite, another potent oxidant. Excessive peroxynitrite generation induces protein nitration contributing to mitochondrial dysfunction and endothelial cell dysfunction. Reduced BH4 bioavailability seems to be the main cause of eNOS uncoupling. In ROS-mediated endothelial dysfunction, BH4 is oxidized to dihydrobiopterin (BH2) that cannot function as a cofactor of eNOS leading to eNOS uncoupling. NOS uncoupling could also be induced by the endogenous competitive inhibitor asymmetric dimethylarginine (ADMA).

On the other hand, xanthine oxidoreductase (XOR) a key enzyme involved in purine degradation that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid, is expressed as a dehydrogenase form (XDH) but, under inflammatory conditions, a switch from the reductase form to the oxidase form (XO). ROS produced by the XO enzyme are the major source of oxidative stress under ischemia/reperfusion injury. XO is involved in the increased ROS levels and vascular injury observed in diabetes.

Interestingly, under normal physiological conditions, the body neutralizes ROS through various antioxidant mechanisms. When the capacity of antioxidant substances is exceeded, a situation known as oxidative stress (OS) is established. In other words, OS is a condition that manifests when the production of highly reactive substances exceeds antioxidant mechanisms. OS is related to numerous diseases such as obesity, cancer, type 2 diabetes mellitus and cardiovascular disorders.

Essentially, antioxidant defenses are divided into two large groups: enzymatic and non-enzymatic; the first group refers to enzymes that constitute the first line of cellular defense against oxidative damage and these provide a protective function against biological oxidants, decreasing the intracellular concentration of free radicals. Among them are, superoxide dismutases (SOD), catalase, glutathione peroxidase (GPx), peroxiredoxins (Prx) and thioredoxin (Trx), among others. The non-enzymatic group, as a second line of defense, is made up of residual free radical scavengers, examples of them are:

reduced glutathione, uric acid, transferrin, lactoferrin, taurine, ceruloplasmin, ubiquinol, bilirubin, carotenoids such as vitamin A, vitamin E, vitamin C, butylhydroxytoluene (BHT), melatonin, among others.

Superoxide dismutase is the first in line among the enzymatic antioxidant defenses. Superoxide dismutases are a family of enzymes that catalyze the conversion of the superoxide anion to H_2O_2. There are three isoforms localized in different cellular compartments: 1) a cytosolic copper-zinc superoxide dismutase (SOD1 or CuZnSOD), 2) a predominantly mitochondrial manganese superoxide dismutase (SOD2 or MnSOD) and 3) an extracellular CuZnSOD (SOD3) with affinity for cell surface heparin sulfate proteoglycans. In endothelial cells the scavenging of superoxide by SOD1 and the H_2O_2 production has been related with the hyperpolarization factor showing the relevance of the enzymatic activity in the normal endothelial functionality.

H_2O_2 is reduced to molecular oxygen and water by antioxidant enzymes, including catalase and peroxidases. Catalase participates in the adaptive response of cells to oxidative stress, and its expression may be increased in endothelial cells by oxidative factors, such as oxLDL.

Glutathione peroxidase (GPx) catalyzes the reduction of H_2O_2 to molecular oxygen and water by using monomeric glutathione as electron donor. Oxidized glutathione is subsequently converted into the reduced form by glutathione reductase enzyme. Four different glutathione peroxidases have been identified in mammals, the most abundant expressed is the isoform 1 or GPx-1 this enzyme is located both in the mitochondria and cytoplasm of endothelial cells.

The peroxiredoxins (Prx) are thiol specific-enzymes that inactivate H_2O_2 to water using cysteine residues. Six peroxiredoxin isoforms have been identified, Prx1 isoform is implicated in the anti-oxidative and anti-inflammatory effects of laminar shear stress *in vitro*.

Thioredoxins (Trx) are located in both the cytosol and mitochondria. In addition to its role in regulating the redox state Trx is involved in the regulation of endothelial cell survival. In endothelial cells, Trx protein levels are finely regulated by H_2O_2 at low concentrations H_2O_2 increased Trx levels and protected cells from apoptosis, while at higher concentrations (100-500 μM) it induced apoptosis of endothelial cells via the degradation of Trx. These facts suggest that the modulation of reactive species may have several important roles in the cellular homeostasis.

Various pathological conditions, including hyperglycemia, hyperlipidemia, and arterial hypertension, as well as, aging and exposure to specific drugs, may influence endothelial function by disrupting the molecular mechanisms regulating NO bioavailability.

Free radicals and their role in disease showed that living organisms are not only adapted to a harmful coexistence with free radicals, but also have mechanisms developed for beneficial use of these. So, the production of reactive species or free radicals by itself is not harmful since they are participants in several normal functions oxidative stress is the condition that must be avoided or controlled.

There are numerous physiological functions that are modulated or controlled by signaling pathways related to redox-type reactions. It is known that the action of free radicals or their derivatives as physiological mediators includes: regulation of vascular tone, perception of oxygen pressure, regulation of functions that are controlled by oxygen concentration, as well as enhancing intracellular signal transduction of various membrane receptors, including the lymphocyte antigen receptor and oxidative stress responses that ensure the maintenance of the redox system (oxidation-reduction reactions).

A remarkable example is nitric oxide, this radical is a unique molecule, with the characteristics of a neurotransmitter; It has vasodilator activity, stimulates vascular smooth muscle synthesis and modulate platelet function. In the immune system, free radicals act as physiological mediators against bacterial infections.

Another function of free radicals is to be mediators in the synthesis of prostaglandins, cholesterol and steroid hormones. The hydroxylation of the aminoacids lysine and proline, necessary for collagen biosynthesis requires the participation of the free radical

• OH. However, while it is true that free radicals are fundamental elements in metabolism, they also constitute a risk, especially for cells and biomolecules, such as nucleic acids, proteins, polysaccharides and lipids.

Oxygen radical are capable of react with the nitrogenous bases or the pentoses that constitute DNA, forming the peroxyl radical, which results in structural damage and possible mutations. The oxidative damage to molecules is usually irreversible and can lead to denaturation of the molecule. In enzymes, it can impede their catalytic activity and in structural polysaccharides it causes their depolymerization, which leads to degenerative processes.

Lipids, especially those containing polyunsaturated fatty acids, are especially susceptible to developing uncontrolled oxidation processes. Cell damage is mainly caused by peroxidation of membrane lipids, allowing the passage of free radicals and calcium, which causes mitochondrial damage, releasing more free radicals into the intracellular environment, which cause a chain reaction, oxidizing proteins in their path, carbohydrates, membrane lipids (mitochondrial, nuclear and reticulum) including DNA itself.

BIBLIOGRAPHY

1. Harman D. Ageing a theory based on free radical and radiation chemistry. J Gerontology. 1956; 11: 298-300.
2. Pignatelli P, Menichelli D, Pastori D, Violi F. Oxidative stress and cardiovascular disease: new insights. Kardiologia Polska. 2018; 76 (4): 713-722.
3. Forstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circ Res. 2017; 120: 713-735.
4. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular Pharmacol. 2018; 100: 1-19.

Correspondence:
Guillermo Ceballos, MD, PhD
E-mail: gceballosr@ipn.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100791

Diabetic dyslipidemia

Dislipidemia diabética

Juan José Parcero-Valdés, MD, FACC, FSCAI*

In 2015, it was estimated that there were 415 million (uncertainty interval: 340-536 million) people aged 20-79 with type 2 diabetes mellitus (DM2), 5 million deaths attributable to DM2, and the total global health expenditure due to diabetes were 673 billion U.S. dollars. Three-quarters (75%) of those with DM2 were living in low and middle-income countries. The number of patients with diabetes (20-79 years old) will rise to 642 million by 2040.[1] Because of this, diabetes prevalence, deaths attributable to diabetes, and health expenditure due to diabetes have continued to grow across the world with important social, financial, and health system implications.

ROLE OF DIABETES MELLITUS DYSLIPIDEMIA

Many patients with DM2 have dyslipidemia, which is essential in the rising of cardiovascular (CV) risk. Lipids and glucose play a crucial role in energy metabolism. It is well known that patients with diabetes often have dyslipidemia, characterized by increased triglycerides, low high-density lipoprotein cholesterol (HDL-c), a predominance of small-dense low-density lipoprotein (LDL) particles, and higher concentrations of apoB-containing particles.[2-4]

However, recent research indicates that lipid changes may not be the only consequence of diabetes since they may also cause disturbances in glucose metabolism. Lipid changes are observed in insulin-resistant persons with normal glucose tolerance and in those with metabolic syndrome years before the clinical diagnosis of DM2 occurs.[5] This suggests either co-associations of independent disorders or a pathophysiologic role for insulin resistance, rather than hyperglycemia itself, in the development of diabetic dyslipidemia.

Although not all patients with diabetes show all manifestations, 60 to 70% of them, present some lipid abnormalities.[6] Dyslipidemia is a major and probably the most critical link between diabetes and CV disease. However, hyperglycemia accelerates atheroma formation in the setting of diabetic dyslipidemia.

The metabolism of very-low-density lipoprotein (VLDL), the primary transporter of fasting triglycerides, is insulin-regulated at multiple levels. Insulin suppresses lipolysis and regulates circulating free fatty acids, which are substrates for VLDL cholesterol assembly and secretion. In the liver, insulin mediates the transfer of triglycerides to apoB and regulates lipoprotein lipase (LPL) activity to delipidate VLDL. LPL activity can be disrupted by increased circulating free fatty acids and inhibited by apoC III. In contrast, apoC III hinders hepatic uptake of triglyceride-rich lipoproteins and is itself inhibited by insulin. Thus, in the insulin-resistant state, hypertriglyceridemia may result from elevated free fatty acid levels and decreased degradation of apoB, leading to over-production of VLDL, impaired lipoprotein lipase activity, and decreased hepatic uptake of VLDL with reduced VLDL clearance.

Increased free fatty acids (FFA) impair insulin signaling and cause subclinical inflammation with subsequent pancreatic β-cell dysfunction. FFA increase may be involved in the induction of a pro-thrombotic state. Interestingly, increased concentration of triglyceride-rich lipoproteins leads to increased catabolism of HDL, lowering its plasma concentration.

* Centro de Estudios del Corazón Médica Norte, Tijuana, Hospital Ángeles Tijuana, México.

Received:
18/06/2021
Accepted:
30/06/2021

How to cite: Parcero-Valdés JJ. Diabetic dyslipidemia. Cardiovasc Metab Sci. 2021; 32 (s3): s168-s172. https://dx.doi.org/10.35366/100791

In contrast, triglyceride-enriched LDL particles undergo hydrolysis, decreasing particle size and shifting the LDL phenotype towards small and dense LDL, which are more atherogenic than «normal» LDL. As such, lipid changes may not only be a consequence of impaired glucose metabolism, but they may also cause it. Seems that elevated concentrations of FFA disrupt or modulate the cascade linking insulin receptors with glucose transporters and impair the normal function of the β-cell. Hypertriglyceridemia (HTG) may induce subclinical inflammation, which then leads to insulin resistance and β-cell dysfunction. These lipid changes are seen in patients with overt diabetes and patients with metabolic syndrome and obesity, and they reflect insulin resistance rather than hyperglycemia. HTG can worsen glucose metabolism. This fact explains why it is more challenging to control hyperglycemia in patients with HTG than those with normal triglyceride values. It also explains why patients usually require less intensive antidiabetic treatment once their hypertriglyceridemia has been resolved. Mechanisms underlying diabetic dyslipidemia remain incompletely understood.

LIPID-LOWERING THERAPY: STATINS IN DIABETES MELLITUS

Strong evidence showing that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Co-A) reductase inhibitors (statins) reduces ASCVD event rates in diabetes mellitus is available from clinical trials.

Some statin's benefits are potentially attributable to nonlipid-lowering related anti-inflammatory effects. The 2016 guidelines from the American College of Cardiology/American Heart Association recognize the patients with diabetes mellitus (ages 40 to 75 years) as one of the four principal groups to benefit from statins and recommend treatment with a moderate-intensity statin or a high-intensity statin for individuals with a ≥ 7.5% 10-year risk of cardiovascular disease.[7] In subjects under 40 or over 75 years of age, guidelines recommend individualizing statin therapy based on benefits of ASCVD risk reduction versus the potential for adverse effects, the interactions with other drugs, and patient preference. Statin-induced lowering of LDL cholesterol levels by 39 mg/dL (1 mmol/L) in high-risk individuals reduces coronary mortality risk by 19%, as demonstrated in a meta-analysis by the Cholesterol Treatment Trialists' Collaboration. The magnitude of mortality benefits was similar for those with or without diabetes mellitus.[7] A 21% reduction in major vascular events occurred per 1-mmol/L reduction in LDL cholesterol, irrespective of prior history of vascular disease, gender, age, body mass index (BMI), baseline systolic or diastolic blood pressure, smoking status, estimated glomerular filtration rate, cholesterol, or predicted annual risk of major vascular events. The collaborative atorvastatin diabetes study (CARDS) trial specifically assessed 2,838 patients DM2, including patients with a mean baseline LDL-c level of 117 mg/dL (3.0 mmol/L) randomized to atorvastatin 10 mg daily or placebo. Results of this trial show a 37% reduction in the primary cardiovascular composite outcome (time to first occurrence of acute coronary heart disease event, coronary revascularization, or stroke). The treating to new targets (TNT) study examined whether lowering LDL cholesterol below the threshold recommended at the time (100 mg/dL, 2.59 mmol/L) would result in more significant cardiovascular risk reduction. For that reason, 1,501 patients with diabetes mellitus and coronary artery disease (CAD) were randomized to atorvastatin 10 mg versus 80 mg daily. Treatment decreased LDL-c levels to a mean of 98.6 mg/dL (2.55 mmol/L) versus 77 mg/dL (1.99 mmol/L), respectively. There was also a 25% reduction in major cardiovascular events after 4.9 years of treatment. This study provides further evidence that more aggressive LDL-lowering reduces ASCVD in diabetes mellitus.

NON-STATIN LIPID-LOWERING

Despite the reduced risk of ASCVD with statin therapy, a residual risk remains for diabetic and non-diabetic patients, and further lowering of lipids may be of value. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) supports the use of a combination of simvastatin and ezetimibe, a nonstatin LDL-lowering

molecule (which reduces intestinal cholesterol absorption) to further lower cardiovascular risk. The primary composite cardiovascular endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke was 6% lower comparing ezetimibe with placebo administered with simvastatin, with a greater 14% cardiovascular benefit among those with diabetes mellitus.

PHARMACOLOGIC INTERVENTIONS TO MODIFY HYPERTRIGLYCERIDEMIA AND LOWER DL LEVELS HAVE NOT SHOWN A CLEAR REDUCTION IN CLINICAL HARDPOINTS

Targeting the diabetic lipid abnormalities; increased triglycerides, low HDL cholesterol, and small LDL cholesterol particle size will further benefit remains as a relevant question. Recent trials, as the lipid arms of action to control cardiovascular risk in diabetes (ACCORD) and the fenofibrate intervention and event lowering in diabetes (FIELD), examined fenofibrate effects. In the ACCORD trial, all patients were randomized to intensive glycemic control, and a subset of patients was enrolled in the ACCORD Lipid trial to receive simvastatin plus fenofibrate or placebo. Although there was no difference in the annual rate of primary composite outcomes of major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) for the fenofibrate in comparison with placebo group, subgroup analysis revealed 29% fewer events in those with baseline triglyceride ≥ 204 mg/dL (2.31 mmol/L) and HDL cholesterol ≤ 34 mg/dL (0.88 mmol/L). These results are consistent with the FIELD study in 9,975 individuals with DM2 not under statin therapy. No effect of fenofibrate was observed on the primary outcome of coronary events (coronary heart disease death or nonfatal myocardial infarction) in the entire cohort. However, a 14% cardiovascular event reduction in the subgroup with low cholesterol linked to high density lipoproteins (HDL-c) at baseline ($p = 0.02$) and a similar trend in those with HTG at baseline ($p = 0.07$) was observed.

In the atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides and impact on global health outcomes (AIM-HIGH), a study that evaluated the addition of niacin to intensive statin therapy (simvastatin plus ezetimibe if needed to maintain LDL concentrations of 40-80 mg/dL [1.04-2.07 mmol/L]) in patients with established cardiovascular disease and low HDL-c (median baseline of 35 mg/dL [0.91 mmol/L]), where approximately one-third of participants had diabetes mellitus, no difference in the primary composite endpoint was observed despite increasing HDL-c concentration from 35 to 42 mg/dL (0.91-1.09 mmol/L), lowering triglycerides from 164 to 122 mg/dL (1.85 to 1.38 mmol/L), and lowering LDL-c from 74 to 62 mg/dL (1.92 to 1.61 mmol/L).

Consideration can also be given to adding fibrate therapy for an individual with DM2 and residual HTG with low c-HDL levels, once the patient is on goals with statin therapy. In this context, ezetimibe may represent a reasonable choice for additional cardiovascular risk reduction, especially in those patients with DM2 and acute coronary syndrome. This is consistent with the most recent Standards of Medical Care for Diabetes by the American Diabetes Association (ADA),[8] which cite a level A evidence showing that the addition of ezetimibe to moderate-intensity statin therapy may be considered for patients with a recent acute coronary syndrome with LDL cholesterol ≥ 50 mg/dL (1.3 mmol/L) or for those patients who cannot tolerate high intensity statin therapy.

The 2019 European Society of Cardiology (ESC) Guidelines for the management of dyslipidemias,[9] suggest that if treatment goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended. The combination therapy with a statin and fibrate has not been shown to improve ASCVD outcomes in the broad diabetes mellitus population and is generally not recommended. Of note, the Scientific Statement on Prevention of Cardiovascular Disease in type 2 diabetes mellitus by the American Heart Association and American Diabetes Association (AHA/ADA) does not recommend the addition of a fibrate to statin therapy.

There is limited data on the impact of adding omega-3 fatty acids to statin therapy in patients with high plasma triglyceride

levels treated with statins. The REDUCE-IT trial examined the effects of icosapent ethyl 2 g b.i.d. on CV events in 8,179 high-risk patients with HTG under a statin therapy. Over a median of 4.9 years, a significant ($p < 0.001$) 25% reduction in the composite primary outcome of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina.

LDL-LOWERING WITH PCSK9 INHIBITION

The newest class of c-LDL-lowering formulations are monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 inhibitors prevent the degradation of LDL-c receptors, allowing for increased removal of LDL-c from the circulation. Alirocumab and evolocumab are 2 PCSK9 inhibitors recently approved by the Food and Drug Administration (FDA). Alirocumab was approved for use alongside diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or patients with clinical ASCVD who require additional lowering of LDL-c. A *post hoc* analysis of the effect of alirocumab on cardiovascular outcomes was performed in the long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy (ODYSSEY LONG TERM) trial showed a 48% reduction in major adverse cardiovascular events ($p = 0.02$). The cardiovascular outcome trial FOURIER[10] (the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk), was a placebo-controlled trial involving 27,564 patients with ASCVD and LDL-c concentrations of 70 mg/dL (1.8 mmol/L) or higher who received statin therapy, with a primary efficacy endpoint composed by CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. At 48 weeks, the percentual reduction in LD-cL concentrations with evolocumab, was 59%, from 92 mg /dL (2.4 mmol/L) to 30 mg/dL (0.78 mmol per liter) ($p < 0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary endpoint (1,344 patients [9.8%] vs 1,563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $p < 0.001$) and the key secondary endpoint (816 [5.9%] vs 1,013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $p < 0.001$). These findings show inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL-c to a median of 30 mg /dL (0.78 mmol/L) and reduced the risk of CV events.

This evidence shows that the strategy and primary objective of treating dyslipidemia in both non-diabetic and diabetic patients are to achieve the LDL-c goals determined by each patient's risk. This goal is < 55 mg/dL in very high-risk diabetic or non-diabetic patients with additional cardiovascular risk factors or ASCVD. The goal is < 70 mg/dL in high risk diabetic or non-diabetic patients and < 100 mg/dL in diabetic or non-diabetic patients with moderate risk.

CONCLUSIONS

Diabetes mellitus and dyslipidemia commonly occur together, with lipid abnormalities affecting 60% to 70% of patients with DM2 and hyperglycemia accelerates atheroma formation in the setting of diabetic dyslipidemia. Dyslipidemia is crucial in mediating the CV risk in diabetes. HTG and low c-HDL may also induce glucose metabolism disturbances and may thus be the consequence and the source of hyperglycemia. Diabetes mellitus exacerbates the mechanisms of atherosclerosis. Aggressive management of CV risk factors, particularly lowering of LDL-c concentration, provides substantial prevention of CV outcomes. The role of new potent lipid-lowering therapies (PCSK9 inhibitors) and lipid-lowering drugs that target triglycerides and HDL-c needs further studies. Although the overall management of diabetes mellitus has improved substantially over the past two decades, there is a significant unmet need for cardiovascular prevention.

ACKNOWLEDGMENTS

I am grateful to Ms. Margie Palmer and Dr Marissa Ortiz Lagardere for their collaboration and assistance with the preparation of this manuscript.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128: 40-50.
2. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008; 371 (9607): 117-125.
3. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011; 32 (14): 1769-818.
4. Lorenzo C, Hartnett S, Hanley AJ, Rewers MJ, Wagenknecht LE, Karter AJ et al. Impaired fasting glucose and impaired glucose tolerance have distinct lipoprotein and apolipoprotein changes: the insulin resistance atherosclerosis study. J Clin Endocrinol Metab. 2013; 98 (4): 1622-1630.
5. Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin-resistant states. Clin Chim Acta. 2006; 368: 1-19.
6. Low C, Hess C, Hiatt W, Goldfine A. Clinical Update: cardiovascular disease in diabetes mellitus atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus-mechanisms, management, and clinical considerations. Circulation. 2016; 133: 2459-2502.
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129 (25 Suppl 2): S1-S45.
8. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376: 1670-1681.
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-188.
10. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017; 4: 376 (18): 1713-1722.

Correspondence:
Juan José Parcero-Valdés, MD, FACC, FSCAI
E-mail: jjparcerovaldes@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100792

The art of interpretation (About dyslipidemias)

El arte de la interpretación (Sobre las dislipidemias)

José Manuel Enciso-Muñoz, MD*

Science can be described as art of systematic oversimplification.
Karl Popper

Dyslipidemias have a very close relationship with the broad nosological spectrum of atherosclerosis. The correct diagnosis of lipid disorders, immersed in the genetic, epigenetic, organic, and behavioral contexts of each patient, is essential to establish the most appropriate therapeutic approach. The above concept is easily expressed in just a few words, but the exercise is much more complex than it seems, because it requires the employment of hermeneutical tools and a rather complicated integrative process of knowledge and experience. After all, despite multiple attempts to use computational techniques, till the date, machine computers have not been able to outperform the ability of human brain in carrying out these tasks.

It is a common place to say that medicine is a science as well as an art. Indeed, is an applied science (the application of scientific knowledge to solve specific practical problems), but at the same time, it is an art, because its practice demands skills that practitioners have to get through learning experience, observation, or clinical research.[1] In that way the practicing physician, based on the scientific platform of lipidology, puts into practice the art of diagnosing and treating lipid disorders.

It is undoubtedly correct to refer to the lipid profile (the measure of the serum concentration of main lipids and lipoproteins) as something individual and unique for each considered patient. The science and art of medicine must unveil the lipid abnormalities through the interpretation of this profile into a more extensive clinical setting. The word *interpret*, derived from the Latin *interpretari*, has multiple and practical connotations, from which the term is defined as the meaning or explanation of something, to the elucidation of events or acts that can be understood in different ways. Interpretation reveals the meaning of some reality. For example, the art and technique of interpret texts (hermeneutics) leads to the discovery of their true meaning. In other words, interpretation gives meaning to expressions, texts, signs, numbers, or ideas. However, for Edgar Morin reality perceptions «are both translations and brain reconstructions». This fact implies that representation and interpretation of observational facts are subject to the risk of error and illusion.[2]

Scientists often generate working models that conceptually represent systems, ideas, hypothesis, or real physical, natural or biological phenomena. These scientific models must be confronted with our current knowledge, and they also must be verified by observations or research. Lipid metabolism is so complex that challenges the ordinary modelling processes used by scientists.[3] However, one of the most important duties of scientific medicine is to clarify to the practitioner those metabolic and physiological complexities, to provide pragmatic and useful tools that allow them to carry out their daily clinical tasks.

Some applicable concepts that we use in the interpretation of phenomena or data, are the following. *«Normal»*, means a usual, current, or accepted characteristic or value,

* Cardiology Department, Hospital San Agustin. Zacatecas, Mexico.

Received:
21/06/2021
Accepted:
29/06/2021

How to cite: Enciso-Muñoz JM. The art of interpretation (About dyslipidemias). Cardiovasc Metab Sci. 2021; 32 (s3): s173-s178. https://dx.doi.org/10.35366/100792

without exceeding or being below the average. «*Optimal*», in the other hand, signifies what is the best or insuperable, while «*desirable*», denotes a convenient acceptance to what is fair and correct for a given circumstance. On its part, «*high*», designates something above the considered usual or averaged values or concepts. «*Index*», means sometimes a quotient relating two variables (body mass index, waist-hip circumferences, etc.). In times, the term is applied to a variable normalized to compare values in different individuals: cardiac index, indexed ventricular volumes, etc. Very often, an index is a non-dimensional or pure number, without defining physical units (as Woods peripheral resistance units). In mathematics, an index is a number which is raised to a power. This one is also an index, signifying how many times it is necessary to multiply the number by itself. Finally, ratio is a proportion, the relation between two amounts. Such concepts are used very frequently to qualify clinically many variables as blood pressure, body temperature or serum lipids and lipoproteins concentrations, among many others.

Table 1 shows the interpretation of serum lipids and lipoproteins values, according with the experts of the Third Adult Panel of Treatment (ATP III), part of the National Cholesterol Education Program (NCEP), published in 2001.[4] The accepted «normal» values of lipids and lipoproteins have evolved drastically, from the time when the impact of lipids on cardiovascular events was practically unknown or underestimated, to the present day where scientific evidence has solidly established the role of lipids in atherogenesis. In recent times, the concept of «desirable values» is linked to the cardiovascular risk of each patient, according to the number and severity of the accumulated risk factors, the age, gender and already presence of cardiovascular disease. At higher risk, the decrease in atherogenic lipids should be greater. Contrary to what happens with the concentration of blood glucose or the level of blood systemic pressure, with serum lipids concentrations seem that there is not the so-called J-curve, that is, a rise in pathogenicity when very low levels of these variables are reached. *Table 2* shows the new target goals proposed by the European Society of Cardiology and the European Atherosclerosis Society (EAS).[5] Those values of LDL are not in fact «very low» concentration of atherogenic lipids and lipoproteins, bur instead represent their true physiological levels found in anthropomorphous apes, contemporary hunters-gatherers tribesmen, vegetarians, and human babies.

Table 3 shows the different composition of lipoproteins, that explains its physiologic and pathogenic behaviors. A differential characteristic of lipoproteins is the type of apolipoprotein that are structural part of their phospholipid/cholesterol cover. Apo B and Apo E, for example, function as ligands of high-affinity receptors in the liver and other tissues, which remove atherogenic lipoproteins from the circulation, while C-II apolipoprotein acts as a coenzyme of the capillary lipoprotein lipase which hydrolyze the triglyceride load of CHY and VLDL, and A-I apolipoprotein performs many activities, as reverse cholesterol trafficking, as well as numerous immunologic, anti-inflammatory, and anticoagulation actions.[6-8]

Table 1: Lipids and lipoprotein values, according with the ATP III.[4]

Lipid or lipoprotein, mg/dL	Interpretation
Total cholesterol	
< 200	Desirable
200-239	Borderline high
≥ 240	High
LDL cholesterol	
< 100	Optimal
100-129	Near optimal
130-159	Borderline high
150-189	High
≥ 190	Very high
HDL cholesterol	
< 40	Low
≥ 60	High
Triglycerides	
< 150	Normal
150-199	Borderline high
200-499	High
≥ 500	Very high

Table 2: New goals for LDL-c according with the risk category.

Risk category	LDL-c therapeutic goal, mg/dL
Low risk	< 115
Moderate risk	< 100
High risk	< 70
Very high risk	< 55

Although the paradigm of LDL-c «the cholesterol hypothesis» remains one of the strongest pillars of primary and secondary prevention of atherosclerosis, technological innovations, and current clinical and basic research, however, have expanded the relation between lipid pathology and atherosclerotic cardiovascular diseases (ASCVD). The role of hypertriglyceridemia in this regard has been somewhat underestimated, especially by the United States lipid guidelines. Notwithstanding, there is growing and compelling evidence about the importance of triglycerides (TG) and triglyceride-rich lipoproteins (TRLs) in the development of atherosclerosis and its cardiovascular outcomes, including death, mainly in overweighed/obese, insulin-resistant, aged patients. So, the cholesterol contained in very-low-density and intermediate density lipoproteins, are more atherogenic than LDL-c in this type of patients. This recognition is even more pertinent in our country, where hypertriglyceridemia and atherogenic dyslipidemia, linked to abdominal obesity and insulin resistance, affect a considerable proportion of our population.[9]

The importance of Lp(a), a small variant of LDL, with single copies of Apo B100 and apolipoprotein a has been extensively studied. It seems that is involved in several activities, as angiogenesis, tumor growth, inflammation, thrombosis, and atherogenesis, among others. Probably the cut-off value of Lp(a) is about 500 mg/L, from which the cardiovascular risk rises, although it has not been established in all ethnic groups.[10,11]

Interpretation of the lipid profile in clinical grounds is aimed to two main purposes: the estimation of the risk of suffer an episode of ASCVD or acute pancreatitis. *Table 3* concentrate different variables and markers of lipid atherogenicity. Instead, only TRLs, TG themselves, and the ratio TG/HDL-c, are markers or predictors of pancreatitis risk. Probably, in a not-too-distant future, we are going to change drastically the manner of interpret lipid and lipoprotein profile. The quantification of the number and size of atherogenic lipid particles, mainly the small and dense LDL will be the correct form of express lipid pathology.[12] But by the time being, as the most accurate method of measure LDL-c is by means of a costly and time-consuming ultracentrifugation technique, in practice generally is estimated employing the Friedewald's[13] formula:

$$LDL\text{-}c = TC - HDL\text{-}c - (TG/5)$$

The quotient TG/5 comes from the fact that in VLDL particles, cholesterol represents 20% of the lipid mass. The accuracy of the formula starts to decrease with a TG value of 250 mg/dL.[14] If TG exceed the value of 400 mg/dL, the formula is not applicable at all.[14] Despite how cheap and easy it is to estimate LDL-C in such manner, the method is very coarse and subject to many sources of error. To make the question more troublesome, if the European recommendation of measure non-fasting TG is followed, in many more patients, Friedewald formula will be less useful. US Guidelines[15] recommends the Martin adjustable reformulation of Friedewald equation for the estimation of LDL-c:

$$LDL\text{-}c = TC - HDL\text{-}c - (TG/\text{adjustable factor})$$

The adjustable factor can be selected from a table formed by the relation between TG and non-HDL-c values *(Table 4)* obtained from data of almost a million cases in which LDL-c was measured by ultracentrifugation. But again, the adjusted formula cannot be used in severe hypertriglyceridemia. The Sampson[16] formula, a rather complicated mathematical approach, seems to be more accurate and useful in the presence of severe hypertriglyceridemia, but still

needs more clinical verification. Other techniques for the estimation of LDL-c are the direct homogenous assays (not requiring ultracentrifugation), whose technical description is beyond the limits of this article. Suffice to say that these techniques have not attained universal acceptance for accuracy, complexity, and cost considerations.[14] Finally, as previously stated, a very promising method is the quantification of LDL particles, and the estimation of their size, by nuclear magnetic resonance (NMR) spectrometry. With this advanced and innovative technology, the atherogenic profile of patients can be easily disclosed.[12] The method not only measure directly and rapidly lipids and lipoproteins, but also the number of LDL particles and its subclasses, providing similar information about VLDL and HDL. *Table 4* exhibits the optimal or desirable values of all the lipid and lipoprotein variables commonly used to profile the ASCVD risk.

It is difficult to understand that to date in the first-contact clinics of our national health system, the complete profile of basic lipids is not measured, but only TC and TG. It is impossible, as was already discussed above, with these meager data, to correctly estimate the risk profile of the patient and establish accordingly the appropriate treatment or the decision to send the patient to a higher level of care. If this is done for financial and savings reasons, in the long run the cost of ASCVD care colossally exceeds the relatively cheap price of a good preventive medicine.

A special consideration about the laboratories reports is necessary. In general, with a few exceptions, the way in which public and private laboratories report lipid and lipoproteins results is outdated, causing confusion, anxiety, and discontent in both patients and practitioners. The inadequate use of «normal or reference values» may cause uncertainty in physicians and patients, and lead to erroneous, sometimes catastrophic, decisions. We must propose strongly that all laboratory reports do not include those misleading and confusing terms «*reference or normal values*». Instead, it would be helpful the following legend: *The interpretation of the reported values is the responsibility to the treating physician. This interpretation will be carried out in accordance with the individual cardiovascular risk level*.

In conclusion, the art and science of interpreting lipid data must be a generalized instrument in the hands of every physician. The correct diagnosis and treatment of dyslipidemias are one of the strongest pillars where cardiovascular prevention is supported.

Table 3: Composition of lipoproteins.

Lipoprotein	Cholesterol (%)	Triglycerides (%)	Apolipoprotein(s)	Density, g/L	Size, nm
Chylomicrons	5	90	A-I, A-II, A-IV, B48, C II, E	< 0.95	50-500
Remnants of chylomicrons	Triglyceride content > cholesterol		B48, E	< 1.006	< 30
	Variable relationship				
Very low-density lipoprotein	20	65	B100, C II, E	< 1.006	30-80
Intermediate density lipoprotein	35	30	B100, E	1.006-1.019	25-35
Low-density lipoprotein	50	10	B100	1.019-1.063	18-28
High-density lipoprotein					
(HDL2)	15	5	A-I, A-II	1.063-1.125	9-12
(HDL3)				1.125-1.210	5-9

There is an inverse relationship between density and the size of the lipoproteins. Lipoproteins can be separated on those with atherogenic capacities (with apolipoproteins B100 or E), and those protectives (HDLs). Also, they are distinguished in triglyceride-rich lipoproteins (TRLs) and those that serve to transport cholesterol to the tissues and from these back to the liver (LDL and HDLs). Each lipoprotein is characterized for a type of apolipoproteins, situated in the particle cover, with several functions (see text).
Modified from: Anonymous[6], Gotto A et al.[7]

Table 4: Atherogenic lipids, lipoproteins, apolipoproteins, and markers.[5,9]

Variable/units	Desirable or optimal values
LDL-c, mg/dL	Borderline < 130; desirable < 100; optimal ~50-70
TG, mg/dL	< 150
Non-HDL cholesterol, mg/dL (= TC - HDL-c)	Optimal ~< 100; borderline 100-129
Remnant cholesterol, mg/dL (= TC - LDL-c - HDL-c	Optimal < 19; desirable ~< 30
Apolipoprotein B, mg/dL	Optimal < 60; desirable < 100
VLDL-c, mg/dL	20-25
IDL-c, mg/dL	9-10
Number of particles of LDL, nmol/L	< 1,000
Number of particles of small and dense LDL (LDLsd), nmol/L	< 500
Size of LDLsd, nm	24.2-25.2
ApoB/ApoA quotient	Optimal < 0.6 men; < 0.5 women: desirable < 1 men; < 0.8 women
TC/HDL-c quotient	< 4.5 in men and < 4 in women in primary prevention, and < 4 in men and < 3 in women in secondary prevention
LDL-c/HDL-c quotient	< 3 in men and < 2.5 in women in primary prevention, and < 2.5 in men and < 2 in women in secondary prevention
TG/HDL-c quotient	Optimal < 2; desirable 2-3.9

Abbreviatures as in the text. Non-HDL cholesterol represents the whole set of atherogenic lipoproteins with Apo B. Its measure is particularly indicated in cases of severe hypertriglyceridemia, which prevents the use of Friedewald's formula. Remnant cholesterol is a measure of TRLs: CHY, its remnants, VLDL, and IDL. LDLsd is the number of small and dense highly atherogenic particles, whose proportion increase in hypertriglyceridemic states. The first three quotients of the table simply describe the direct relation between atherogenic cholesterol or apolipoprotein B and ASCVD risk, and the inverse relation between that risk and HDL-c or its main apolipoprotein, A-I. The last ratio, TG/HDL-c is more complex, because signals the state of insulin resistance and its relationship with atherogenic dyslipidemia.

REFERENCES

1. Panda SC. Medicine: science or art? Mens Sana Monogr. 2006; 4: 127-138.
2. Morin E. Los siete saberes necesarios para la educación del futuro. Bogotá: UNESCO, 1999, 18-19.
3. Schutzhold V, Hahn J, Tummler K, Klipp E. Computational modeling of lipid metabolism in yeast. Front Mol Biosci. 2016; 3: Article 57.
4. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486-2497.
5. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.
6. Anonymous. Lipids, lipoproteins and cardiovascular disease. [visited June 12th, 2021] Available in: https://basicmedicalkey.com/lipids-lipoproteins-and-cardiovascular-disease/
7. Gotto A, Pownall H. Manual of lipid disorders. Filadelfia. Lippincott Williams & Wilkins. 2003.
8. Frank PG, Marcel YL. Apolipoprotein A-I: structure-function relationships. J Lipid Res. 2000; 41: 853-872.
9. Castañer O, Pintó X, Subirana I, Amor AJ, Ros E, Hernáez A et al. Not LDL Cholesterol, is associated with incident cardiovascular disease. J Am Coll Cardiol. 2020; 76: 2712-2724.
10. Jawi, MM, Frohlich J, Chan SY. Lipoprotein(a) the insurgent: a new insight into the structure, function, metabolism, pathogenicity, and medications affecting lipoprotein(a) molecule. J Lipids. 2020; Article ID 3491764.
11. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease. New insights from a large national Biobank. Arterioscler Thromb Vasc Biol. 2021; 41: 465-474.
12. Aru V, Lam C, Khakimov B, Hosefsloot HCJ, Zwanenburg G, Lind MV et al. Quantification of lipoprotein profiles by nuclear magnetic resonance spectroscopy and multivariate data analysis. Trends Analyt Chem. 2017; 94: 210-219.
13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry. 1972; 18 (6): 499-502.
14. Wolska A, Remaley AT. Measuring LDL-cholesterol: what is the best way to do it? Curr Op Cardiol. 2020; 35: 405-411.

15. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 73: 3168-3209.
16. Sampson M, Ling C, Sun Q, Harb R, Ashmaig M, Warnick R et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol. 2020; 5: 540-548.

Correspondence:
José Manuel Enciso-Muñoz, MD
E-mail: jmenciso2@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100793

Serum lipids evaluation, is it all done?

Evaluación de lípidos en suero, ¿está hecho todo?

Guillermo Ceballos, MD, PhD* Nayelli Nájera, PhD*
Eduardo Meaney, MD, PhD* Miguel Ortiz-Flores, PhD*

The structural characteristics of lipids, being organic compounds essentially made up of carbon and hydrogen, give them the ability to be an energy reservoir since, when metabolized, they release nine kcal/g (compared to the four kcal/g released during carbohydrate metabolic degradation to CO_2 and H_2O). Nevertheless, the structure they have makes them insoluble in water. From a metabolic point of view, not interacting with this liquid is an advantage of fats stored as energy repositories, contrasted to carbohydrates. Given the significant interaction of carbohydrates with water, one would require approximately 30 kilograms of carbohydrates to obtain the power generated from only five kilograms of fat; however, their hydrophobicity makes the transport of lipids in biological fluids very difficult.

The chemical structure of these biomolecules is diverse; some examples of such entities are steroids, fatty acids, phospholipids, and glycolipids, among several.

To form part of biological structures or be transported in aqueous liquids such as blood, lipids must be modified or related to molecules that can interrelate with water. An example of those are phospholipids made up of two chains of fatty acids, a phosphate group and a glycerol or sphingosine group. Therefore, this association contains both fragments that attract (hydrophilic) and that repel (hydrophobic) water; that is, they are amphipathic molecules, which allows them to play a critical role in the constitution of cell membranes.

On the other hand, the two main types of fatty molecules in the blood are cholesterol (CHOL) and triglycerides (TGs). With fatty acids, CHOL can esterify; TGs, which should be named triacylglycerides, are constructed by three molecules of fatty acids (saturated and unsaturated) esterified to one of glycerol.

TGs are crucial in the body for energy storage/obtention. To be transported in the blood, these molecules need to mix with proteins, forming complexes known as lipoproteins that help the mobility of lipids in the bloodstream.

During digestion, the intestine releases into circulation the chylomicrons synthesized in the enterocyte. The hepatic delivery of TG-rich, very-low-density lipoproteins (VLDL) into the bloodstream is mainly dependent on TG *de novo* synthesis. This procedure aims to provide TG to peripheral tissues. The elimination of such molecules from VLDL and chylomicrons is mediated by different enzymes and gives rise to smaller sizes fragments and lower consolidation of TGs. They possess distinct thickness since it increases as their magnitude and content of fatty acids decrease. Low-density lipoproteins (LDLs) form in the process, with a high relative aggregation of cholesterol and low in TG.

Most of the LDLs are eliminated; nonetheless, up to 20% of them can infiltrate the vascular wall and can be oxidized and retained in the subendothelial space, initiating local reactions connected to the development of atherosclerosis. All lipoproteins with a diameter of fewer than 70 nanometers can permeate the arterial intima.

Under physiological conditions, the transporter named cholesteryl ester transfer protein (CETP) exchanges lipid molecules between the various lipoproteins. Mature

* Laboratorio de Investigación Integral Cardiometabólica, Escuela Superior de Medicina, Instituto Politécnico Nacional. Ciudad de México, México.

Received:
12/07/2021
Accepted:
20/07/2021

How to cite: Ceballos G, Nájera N, Meaney E, Ortiz-Flores M. Serum lipids evaluation, is it all done? Cardiovasc Metab Sci. 2021; 32 (s3): s179-s181. https://dx.doi.org/10.35366/100793

HDL-c, whose purpose is to bring cholesterol to the liver for its elimination or reprocessing, exchanges cholesterol with TG-rich lipoproteins (TRGs) as VLDL and remnants, receiving TG in turn. This action, added to the hydrolysis performed by capillary and hepatic lipases, results in smaller and depleted cholesterol LDL particles. Consequently, to obtain similar amounts of cholesterol, smaller LDL besides highly atherogenic elements will be needed.

The clinical evaluation of complex abnormalities in lipid metabolism is generally limited only to assessing the serum concentration of CHOL, TG, and high-density lipoprotein (HDL) with which LDL denseness is calculated. Nevertheless, direct methods can determine LDL aggregation. However, with conventional methods, it is not possible to measure the size and number of LDL units and, therefore, their atherogenic capacity, making the appraisal of the standard lipid profile a very limited procedure.

Multiple efforts have been implemented to solve that limitation. In this regard, to improve the clinical certainty of the risk linked to the concentration of serum lipids, the valuation of non-HDL CHOL, the remainders of cholesterol, or the apolipoprotein B aggregation have been used.

Non-HDL CHOL, in the fasting state, represents all atherogenic lipoproteins, and for that reason, its value has a very good correlation with cardiovascular danger. LDL appears with normal TG concentrated at 70-80% of non-HDL CHOL, permitting an estimate of the cardiovascular risk reasonably. This parameter is useful even in hypertriglyceridemia, except when very high accumulations of TG are present. When TG serum denseness is around or above 500-700 mg/dL, chylomicrons are present alone (type I dyslipidemia) or accompanied with VLDL (type V). But in both conditions, primary, genetic hypertriglyceridemia or secondary to diabetes or insulin resistance syndromes, the higher the TG concentration, the more notable incorporation of particles with lesser or absent atherogenic power (big, floating, parent VLDL, CHYLO, or its vestiges) to the estimation of non-HDL-c, lessening its risk prediction usefulness.

Moreover, the remnants of cholesterol are obtained by subtracting the build-up of HDL and LDL from total cholesterol accumulation; this value loses its relevance in high concentrations of TG (it presents the same disadvantages as the calculation with the Friedwald formula). On the other hand, the determination of Apo B is a very good approximation for the appraisal of the total of lipoprotein elements; it has a highly accurate correlation with cardiovascular events. Conversely, it does not define the relative distribution of lipoproteins; as an example, high aggregations of Apo B can be found in subjects with hypertriglyceridemia or hypercholesterolemia, making the differentiation a complex process.

Considering the complexity of lipid metabolism, the relationships between the diverse lipoprotein particles and the degree of atherogenicity they possess depend on both their amount and magnitude, not only on global lipid concentrations. Consequently, it becomes necessary to have more accurate methods to facilitate the lipoproteins measurements (number of elements and types), better define such variations, and allow a more precise individual cardiovascular peril assessment.

There are alternative possibilities for quantifying lipoproteins that use spectra obtained from them through nuclear magnetic resonance (NMR) techniques. Those methods are based on the physical properties of the methyl groups (-CH3) of cholesterol and TG in the lipoproteins as they «resonate» (vibrate or excite and de-energize) at different frequencies depending on the size of the particle and its content (small molecules do so at lower rates).

The first developed or one-dimensional NMR approach quantifies the various lipoproteins by decomposing the global signal into individual pointers or by statistical means through computational procedures. This method has advantages since it allows to determine the concentration of the lipoproteins more accurately; however, the sizes and numbers of those fragments are still arrived at indirectly.

The second NMR alternative, of more recent development, employs the benefits of resonance together with the diffusion characteristics of the lipoproteins. This type of NMR in two dimensions (NMR-2D) uses the molecules' hydrodynamic properties

(diffusion coefficient). From that, using the Stokes-Einstein equation, the particular extent of each lipoprotein is calculated. Because it depends on its magnitude and complexity, a lipoprotein carried by water on a matrix displaces differently.

This methodology quantifies total cholesterol, LDL (directly), HDL, non-HDL cholesterol, remaining CHOL, and triglycerides, as well as the composition of cholesterol and TG in VLDL, LDL, and HDL. It also determines the dimension and accumulation of particles (large, medium, and small) of the major classes of lipoproteins.

These determinations should admit a better characterization of the patients' risk in the initial evaluations. They also allow for an improved follow-up of persons with insulin resistance, obesity, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, lupus, and all those pathologies in which dyslipidemias can increase the cardiovascular danger.

The search for increasingly accurate diagnostic alternatives should grow the possibility of preventing cardiovascular events in patients. The quantification of the type, size, and quantity of lipoproteins by NMR techniques is an alternative that will make it possible to craft a higher-quality diagnosis and implement enhanced prevention and treatment measures for dyslipidemias.

BIBLIOGRAPHY

1. Di Angelantonio E, Sarwar N, Perry P et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009; 302: 1993-2000.
2. Nordestgaard BG, Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2013; 118: 547-563.
3. Contois JH, McConnel JP, Sethi AA et al. Apolipoprotein B and cardiovascular disease risk: position statement from the aacc lipoproteins and vascular diseases division working group on best practices. Clin Chem. 2009; 55: 407-419.
4. Cole TG, Contois JH, Csako G et al. Association of apolipoprotein B and Nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: Assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices. Clin Chem. 2013; 2013: 752-770.
5. Johnson C. Diffusion ordered nuclear magnetic resonance spectroscopy: principles and applications. Prog Nucl Magn Reson Spectrosc. 1999; 34: 203-256.

Correspondence:
Guillermo Ceballos, MD, PhD
E-mail: gceballosr@ipn.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100794

Scientific rationale for the evolution of LDL-c goals

Racionalidad científica para la evolución de las metas de LDL-c

Francisco Javier Guerrero-Martínez, MD*

INTRODUCTION

Dyslipidemia is a public health problem in Mexico. Its prevalence is very high, and most cases are not detected or treated. This favors the development of atherosclerosis and its organic complications such as myocardial infarction (IM) and ischemic stroke, two of the main causes of loss of years of productive life, disability, premature death, and high economic and social costs. The data from the 2012 National Health and Nutrition Survey are worrying; 87% of the patients were unaware of their cholesterol level and only 3% were diagnosed, treated and in control. This explains why the burden of cardiovascular disease in our population is very large and constantly increasing. Ischemic heart disease and cerebrovascular disease, closely linked to atherosclerosis, are among the leading causes of death in our country. An additional, continuous, and coordinated effort is required to adequately detect and treat patients, reduce the burden of atherosclerosis, and strengthen the health of our population.[1]

DYSLIPIDEMIA CAUSES ATHEROSCLEROSIS

Dyslipidemia is a heterogeneous group of diseases with a genetic background, which develop because of inadequate diet, sedentary lifestyle, and smoking, and which are frequently associated with abdominal obesity, arterial hypertension (HT) and diabetes mellitus (DM). They begin early in life, their evolution is subclinical, and they are characterized by elevated or inadequate levels of lipids and lipoproteins in plasma that cause atherosclerosis and organic complications. Their prevalence is very high *(Table 1)*, and they are considered the most common modifiable cardiovascular risk factors in Mexico. Given its «silent» nature, screening with a complete lipid profile in every health evaluation visit is a cost-effective strategy in cardiovascular prevention.[2]

ATHEROSCLEROSIS CAUSES CHRONIC ORGANIC DISEASE

Atherosclerosis is a disease of the arterial wall secondary to a chronic and progressive inflammatory process that begins in childhood and has a long subclinical course. Its main causal factor is the high or inadequate level of cholesterol, especially that transported in low-density lipoproteins (LDL-c), although smoking, abdominal obesity, HT, and DM accelerate it through various mechanisms. The damage begins with the entry, retention, accumulation, and oxidation of LDL in the intima of the arteries. This causes inflammation, endothelial dysfunction, changes in vascular reactivity, increased platelet aggregation, and activation of processes such as apoptosis, fibrosis, and angiogenesis. With the development of atheroma plaque, there is vascular remodeling, arterial lumen is gradually reduced, and blood flow is disturbed. The consequences are ischemia and organ damage and dysfunction *(Table 2)*. The clinical course of atherosclerosis is unpredictable and various types of intervention have shown that its natural history can be modified.[3,4]

* Hospital Médica Campestre León, Gto. México.

Received:
14/07/2021
Accepted:
20/07/2021

How to cite: Guerrero-Martínez FJ. Scientific rationale for the evolution of LDL-c goals. Cardiovasc Metab Sci. 2021; 32 (s3): s182-s191. https://dx.doi.org/10.35366/100794

ATHEROSCLEROSIS CAUSES ACUTE COMPLICATIONS

Atherosclerosis is a process that develops gradually over decades, although its acute complications generally occur suddenly and without previous clinical manifestations. This transition from an apparently stable to an unstable process is due to the progressive incorporation of lipids, inflammatory activity, the weakness of the fibrous layer, its increased stress, and damage to the endothelium with erosion or rupture. When this occurs, substances that activate coagulation are exposed and form the thrombus that partially or totally occludes the vascular lumen. This situation is optimally treated with reperfusion procedures, anti-ischemic, anti-thrombotic, and lipid-lowering drugs (statins), which together improve organ perfusion, accelerate tissue repair, and prevent new atherothrombotic outcomes. The rapid, significant, and sustained reduction of LDL-c, qualitatively modifies the atheroma, decreases its lipid content and inflammation, modifies macrophage activity, increases collagen content, strengthens the fibrous layer, decreases the production of thrombogenic substances, stabilizes the plate and reduces the risk of rupture. Despite this, the patient with complicated atherosclerosis continues at a very high-risk level (residual risk), for which more intensive treatment strategies have been developed with increasingly lower LDL-c goals.[5-7]

ATHEROGENIC LIPOPROTEINS

LDL is the main causal factor of atherosclerosis and LDL-c is the main goal of treatment.[8,9] However, LDL-c does not include other lipoproteins such as VLDL and its remnants that are triglyceride-rich particles (TG) with apolipoprotein B (ApoB), capable of diffusing to the sub endothelium and participating in the atherogenic process. Non-HDL cholesterol (mon-HDL-c), which includes LDL, VLDL and their remnants, and lipoprotein (a) or Lp(a), and ApoB levels, are the best markers of total atherogenic lipoproteins and are they can be used as a secondary goal of treatment in patients with elevated TG, DM, or abdominal obesity. Non-HDL-c is obtained by subtracting HDL-c from total cholesterol, correlates well with total lipoproteins with ApoB, is not affected by triglyceride level, it does not matter if the sample was not taken in fasting conditions, and its measurement does not add any cost. This parameter is important in our country where the combination of high TG levels and low HDL-c levels is present in 34.5% of adults.[1,3,9,10] Another atherogenic lipoprotein is Lp(a), which is a LDL particle with an apolipoprotein called apo (a) on its surface. In most patients (~90%) is genetically determined, can spread to the sub endothelium, and has pro-thrombotic and pro-inflammatory effects. Its elevated level is associated with a greater atherothrombotic risk, although this depends mainly on the increase it causes in the plasma level of LDL-c. Its measurement is recommended to identify

Table 1: Prevalence of dyslipidemia in Mexico.[1]

Phenotype	Diagnostic criteria (mg/dL)	Prevalence (%)
Hypercholesterolemia	≥ 200	30.6
Hypertriglyceridemia	≥ 150	47.4
Hypercholesterolemia + hypertriglyceridemia	≥ 200 + ≥ 150	22.1
Low HDL levels	< 40	55.2
Elevated LDL levels	≥ 100	56.1
Elevated Non-HDL levels	≥ 130	56.8

HDL-C = Cholesterol in high-density lipoproteins, LDL-C = Low-density lipoprotein cholesterol, Non-HDL-C = Total cholesterol minus HDL-C.

Table 2: Dyslipidemia causes atherosclerosis and organic complications.

Dyslipidemia	Vascular damage	Organic damage
Inadequate levels of: • LDL • VLDL • Remnants of VLDL • Lp(a) • Apo B • HDL • Non-HDL C	Atherosclerosis • Coronary • Carotid • Aortic • Peripheral	Complications • Ischemic heart disease; MI, UA, SD, arrhythmias, HF • Cerebrovascular disease; TIA, cerebral infarction, cognitive impairment • Aortic disease; Aneurysm, renovascular hypertension, CKD, mesenteric ischemia • Peripheral arterial disease

LDL = low-density lipoproteins, VLDL = very low-density lipoproteins, Lp(a) = Lipoprotein a. Apo B = Apolipoprotein B, HDL = high density lipoproteins, Non-HDL C = total cholesterol minus HDL. MI = myocardial infarction, UA = unstable angina, SD = sudden death, HF = heart failure.

patients with a high level of genetic origin (> 180 mg/dL), in those with a family history of premature atherosclerotic disease, and for reclassification in those with an intermediate risk level *(Figure 1)*.[1,9,10-14]

THE FIRST STEP IS TO ESTIMATE THE OVERALL CARDIOVASCULAR

The level of LDL-c is only one of the indicators used to estimate global cardiovascular risk. This is determined by the synergistic effect of all the risk factors present in the patient and exists from the beginning of the atherogenic process. Knowing the level of risk of suffering an atherosclerotic outcome is the critical step in the primary prevention strategy. To estimate it, algorithms designed based on the results of prospective cohort studies with medium and long-term follow-up are used that considering the rate of cardiovascular disease and death in each country. These algorithms are not exact, but they are a good approximation and an excellent educational resource to make the physician and the patient perceive the risk. In addition, they provide the opportunity to use additional risk indicators for reclassification or to complement the estimate with subclinical atherosclerosis detection studies. In secondary prevention, that is, in high or very high-risk patients, it is not necessary to make this estimate. Their main utility is that they help to identify the patient in whom the pharmacological intervention is more likely to be beneficial individually and socially. This strategy seeks the maximum net benefit of the intervention with the greatest safety and at the lowest cost for the patient.[9,15]

LDL-C, THE LOWER THE BETTER

In 27 clinical studies, that compared statin versus placebo and intensive versus less intensive statin regimen, it was shown that lowering the LDL-c level intensively, reduces major adverse cardiovascular events (MACE), coronary death, myocardial infarction, need for revascularization and ischemic stroke, in all risk groups. This benefit was directly proportional to the degree of LDL-Cc decrease and more evident at the highest risk level. In general, statins were able to reduce the atherothrombotic risk by 22% for every 38.6 mg/dL decrease in LDL-c during 5 years of treatment. The effect maintained throughout the studies was independent of baseline LDL-C and remarkably constant in all subgroups of patients. In the studies that compared the most intensive with the least intensive strategies, an additional decrease of 20 mg/dL of LDL-c was associated to an added reduction of 15% in higher outcomes, 13% in coronary outcomes, 19% in coronary revascularization, and 16% in Ischemic stroke. Total mortality was reduced by 10%, mainly because due to reduction

of coronary death and s from other cardiac causes. This benefit far outweighed any risk from the use of these drugs and allowed to conclude that greater decreases in LDL-c are safe and achieve a further reduction in the incidence of major vascular outcomes. These results permit to assume that the benefit is directly proportional to the absolute decrease in LDL-c, that is, the greater the 13% in coronary outcomes, 19% in coronary revascularization, and 16% in Ischemic stroke. Total mortality was reduced by 10%, mainly because on coronary death and on death from other cardiac causes. This benefit far outweighed any risk from the use of these drugs and allowed to conclude that greater decreases in LDL-c are safe and achieve a further reduction in the incidence of major vascular outcomes. These results permit the assumption that the benefit is directly proportional to the absolute decrease in LDL-c, that is, the greater the greater the decrease in LDL-c attained with statins, the greater the prevention of atherothrombotic outcomes *(Figure 2)*.[16-18]

REDUCING LDL-C INDUCES REGRESSION OF ATHEROSCLEROSIS

The atherosclerosis evaluation studies by intracoronary ultrasound demonstrated an inverse relationship between the degree of LDL-C decrease and the rate of progression of the atherosclerotic process. An early study compared a strategy of lower intensity, pravastatin 40 mg/day, with another of greater intensity, atorvastatin 80 mg/day, and showed that the higher intensity approach reduced LDL-c by almost 50% (20% more than the lower intensity treatment), greater decrease in other lipoproteins and inflammation markers, and lower rate of progression of coronary atheroma. These results confirmed that it is possible to change the natural history of the disease, slow its progression and achieve regression in some cases. A paradigm shift was generated towards more intensive lipid-lowering strategies to stop and reverse the atherogenic process.[19] This and other studies consistently demonstrated that the progression of coronary atherosclerosis could be halted if LDL-C levels were reached less than 70 mg/dL. However, intensive strategies with lower LDL-c goals finally achieved results compatible with regression of the atherogenic process. A study with rosuvastatin 40 mg/day, which attained an average LDL-c of 60.8 mg/dL, showed a reduction of both, the area and the volume of coronary atheroma plaques, and established that at this level of LDL-c, atheroma regression is reached in patients with coronary artery disease.[20] Another study compared rosuvastatin 40 mg/day versus atorvastatin 80 mg/day, and showed similar results in regression of coronary atheroma despite the fact that rosuvastatin achieved a lower LDL-C level than atorvastatin (62.6 vs 70.2 mg/dL).[21] Although it is inferred that there is clinical benefit from the regression of atherosclerosis, in these studies no correlation was made with clinical outcomes since this requires a greater number of patients, a higher rate of main outcomes, and longer time of follow-up. The above mentioned is a solid foundation for the concept that the regression of atheroma plaques is accomplished by reaching LDL-C levels below 70 mg/dL or by reducing it by at least 50% from the baseline level.

COMBINED LIPID-LOWERING THERAPY ACHIEVES BETTER RESULTS

Ezetimibe, a selective inhibitor of the Niemann-Pick C1-Like 1 (NPC1L1) protein that transports cholesterol from the intestinal lumen to the interior of the enterocyte, reduces cholesterol absorption, decreases LDL-c by 15-20%, and up-regulates of the LDL receptor in several tissues. In a comparative study between simvastatin and ezetimibe 40/10 mg/day versus simvastatin 40 mg/day, the combination achieved a lower LDL-c level (54 mg/dL) than monotherapy (70 mg/dL), a difference of 16 mg/dL (17%) which meant an additional 2% reduction in the absolute risk of the primary endpoint of analysis that included cardiovascular (CV) death, MI, unstable angina (UA), revascularization procedures and ischemic stroke. MI was reduced 13% and ischemic stroke 21%. There was no difference between groups in CVD or death from any cause. This result allowed ezetimibe to be included in the intensive treatment strategy, especially after an acute coronary outcome if

the LDL-c goal has not been achieved with a high-intensity statin at the maximum tolerated dose.[22] In a study of atherosclerosis regression the combination of atorvastatin (20-80 mg/day) and ezetimibe (10 mg/day) decreased LDL-c an additional 10% to monotherapy and achieved higher indicators of regression of coronary atheroma. Ezetimibe also suppressed the compensatory increase in intestinal cholesterol absorption that occurs with statins, which could explain part of the benefit.[23] Current guidelines recommend adding ezetimibe to patients who have not achieved the goal despite maximum tolerated doses of statins, in patients with primary hypercholesterolemia and in those who do not tolerate high doses of statins.

PCSK9 (Proprotein Convertase Subtilisin Kexin 9) is a soluble protein enzyme that participates in the regulation of cholesterol content in the liver. Its function is to bind together with LDL to the specific receptor, intern with the complex formed through endocytosis and promote the degradation of the receptor to reduce its expression on the surface of the hepatocyte. Evolocumab and alirocumab are PCSK9 inhibitor monoclonal antibodies that prevent the degradation of the LDL receptor, favoring its re-expression on the

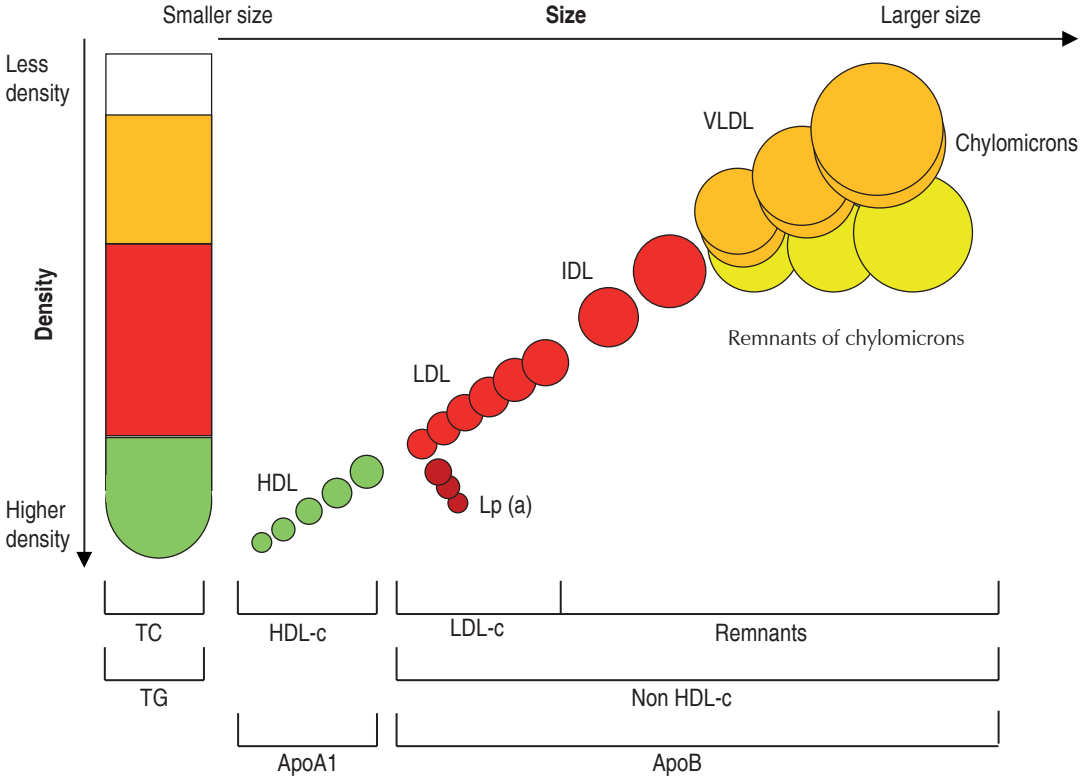
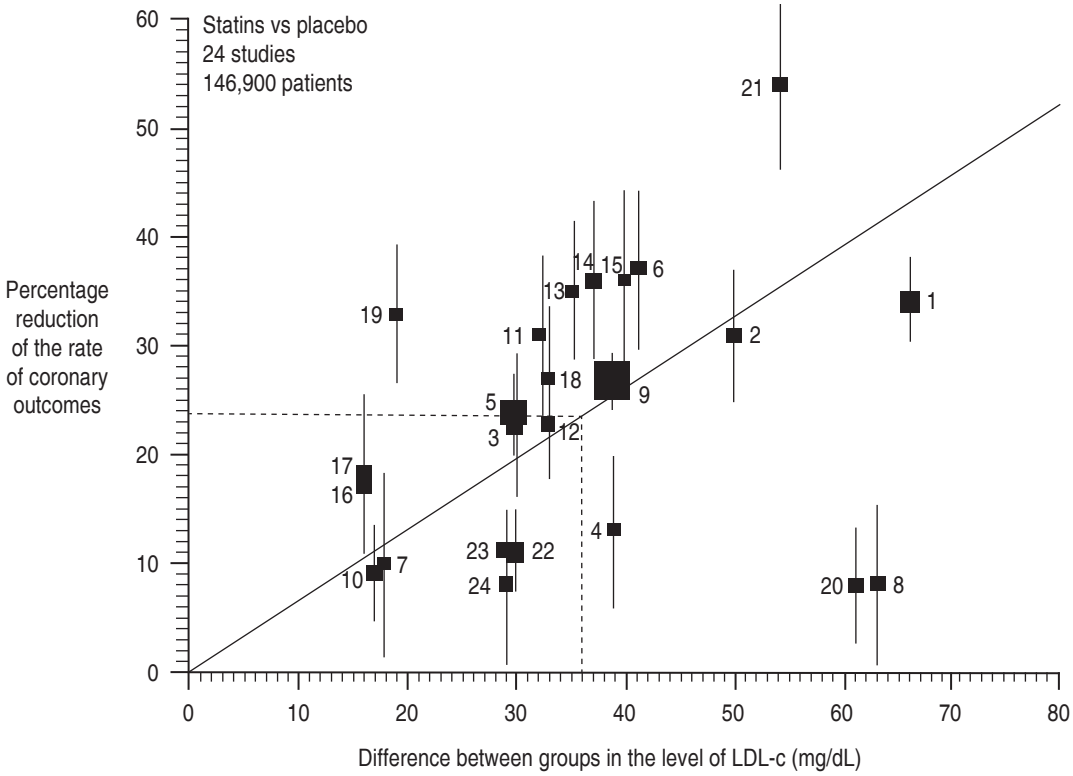


Figure 1: Plasma lipoproteins according to their density, size, and representativeness in the fractions measured in the laboratory.

Lipoproteins according with their density, size, and representativeness in the fractions measured in the laboratory. The typical lipid profile consists in the measurement of total cholesterol (TC), triglycerides (TG), cholesterol linked to high-density lipoproteins (HDL-c), cholesterol linked to very low-density Plasmatic lipoproteins (VLDL-c), and cholesterol linked to low-density lipoproteins (LDL-c). However, sometimes also are estimated the remnants of VLDL (Remnant-c), and the cholesterol no liked to HDL (Non-HDL-c). Remnant-c is calculated as follows: TC - HDL-c-LDL-c, i.e., the amount of cholesterol do not linked to LDL and HDL, representing only the TG-rich lipoproteins (VLDL, their remnants, and in the postprandial state, also the chylomicron remnant. Non-HDL is estimated as follows: TC-HDL-c, representing a total measurement of atherogenic lipoproteins. The measurement of Apo-I and Apo B100 is an alternative of estimating HDL and LDL lipoproteins. Cholesterol content o Lp(a), representing one third of the mass of this lipoprotein, is included in the estimation of TC, LDL and non-HDL-c. The measurement of Apo B, includes the content of this apolipoprotein in the Lp(a.)
Langlois MR et al.[10]



	Study	Reduction: C-LDL	Reduction: Outcomes
1	4S	66	34
2	WOSCOPS	50	31
3	CARE	30	23
4	Post-CABG	39	13
5	LIPID	30	24
6	AFCAPS/TexCAPS	41	37
7	GISSI-P	18	10
8	MIRACLE	63	8
9	HPS	39	27
10	ALLHAT-LLT	17	9
11	LIPS	32	31
12	PROSPER	33	23
13	ALERT	35	35
14	ASCOT-LLA	37	36
15	CARDS	40	36
16	ALLIANCE	16	17
17	4D	16	18
18	ASPEN	33	27
19	MEGA	19	33
20	CORONA	61	8
21	JUPITER	54	54
22	GISSI-HF	30	11
23	AURORA	29	11
24	SHARP	29	8
	Mean	36	24

The results of 24 clinical studies comparing the effects of statins versus placebo, that included 146,900 patients with diverse clinical conditions, showed that lessening LDL-c concentration, mainly in intensive form, is associated to a reduction of major outcomes (coronary death, myocardial infarction, need of revascularization, and ischemic stroke), in all risk categories.

Figure 2: Linear association between the decrease in the plasma level of LDL-C with statins and the reduction in the rate of coronary outcomes.

hepatocyte surface and lowering the LDL-c level an additional 40 to 60%. In a study that included 27,564 patients with atherosclerotic cardiovascular disease on statin treatment and a LDL-c level out of the recommended goal (70 mg/dL or non-HDL-c <100 mg/dL), evolocumab was able to decrease the LDL-c from 92 to 30 mg/dL while in the placebo group there was no significant change from baseline. This decrease bring-off an additional 1.5% reduction in the absolute risk of the primary endpoint of analysis that included CVD, MI, stroke, UA and coronary revascularization, during a median of 2.2 years of follow-up. The benefit was sustained during treatment, it was consistent in all the studied subgroups but greater in those that attained lower levels in LDL-c, as well than in those with the highest baseline absolute risk. There were no differences in CV death and death from any cause. Evolocumab also decreased the Lp (a) level by 27%, possibly contributing to the benefit.[24] Another study included 18,924 patients with history of a recent acute coronary outcome, on statin treatment at the maximum tolerated dose and with a level of LDL-c < 70 mg/dL, non-HDL-C < 100 mg/dL, or ApoB < 80 mg/dL. Alirocumab decreased LDL-c from 92 to 37 mg/dL what was associated to an additional 1.6% reduction of absolute risk of the primary endpoint of analysis, including MI, CVD, stroke, and hospitalization for UA, during a median of 2.8 years of follow-up. The risk reduction was greater in patients with baseline LDL-C ≥ 100 mg/dL than in those with a level below it. Although there was a 0.4-0.6% reduction in the absolute risk of CV death and death from all causes, the difference was not significant.[25] Both studies demonstrated that these drugs are safe and well tolerated, strengthening the concept that patients with atherosclerosis benefit from lowering LDL-C to a level less than 50 mg/dL and that at least in the medium term, there is no secondary harm from this. PCKS9 inhibitors are indicated in high and very high-risk patients (secondary prevention or severe primary hypercholesterolemia) who have not achieved the LDL-C goal despite ezetimibe and high-intensity statins at the maximum tolerated dose, or well in those who have had statin toxicity.

Another drug studied in combination with statins with the aim of reducing ischemic cardiovascular outcomes is ethyl-eicosapentaenoic acid (EPA), a highly purified and stable ethyl ester of EPA that decreases TG levels by reducing liver production of VLDL and increasing its depuration. The study included 8,179 patients with very high cardiovascular risk treated with statins, and with fasting TG between 135 and 499 mg/dL and LDL-c between 41 and 100 mg/dL, and compared a group treated with statins and ethyl-eicosapentaenoic acid 4 g/day versus another with statins and placebo. The primary endpoint of analysis was a composite of CV death, MI, stroke, UA, and coronary revascularization, with a median follow-up

Table 3: Evolution of the LDL-C goals* in cardiovascular prevention.

Risk level	ATP I 1988	ATP II-III 1994-2001	ATP III 2004	ESC/EAS 2011-2016	ACC/AHA 2013-2018	ESC/EAS 2019
Very high	< 130	< 100	< 70	< 70	< 70	< 55
High	< 160	< 130	< 100	< 100	< 100	< 70
Moderate	–	< 130	< 130	< 115	–	< 100
Low	–	< 160	–	< 115	–	< 116
* Values in mg/dL				≥ 50% reduction from basal level		

ATP = adult treatment panel, NCEP = National Cholesterol Education Program, ESC = European Society of Cardiology, EAS = European Atherosclerosis Society, ACC = American College of Cardiology, AHA = American Heart Association.

of 4.9 years. The combination decreased the TG level by 18.3% (39 mg/dL) while in the placebo group it increased 2.2% (44.5 mg/dL). LDL-c increased 3.1% (2 mg/dL) with the combination and 10.2% (7 mg/dL) in the placebo group, that is, about 6.6% (5 mg/dL) increased less with the combination than with placebo ($p < 0.001$). The primary endpoint of analysis was 25% lower with the combination, which meant a reduction of 4.8% in the absolute risk and a necessary number to treat (NNT) of 21 patients to treat for 5 years to avoid a primary outcome. In general, the incidence of ischemic outcomes was lower with the combination, and this included a 20% lower risk of CVD. It is important to note that these results were obtained in patients treated with statins and a baseline median LDL-c of 75 mg/dL. A safety aspect to consider is the higher rate of hospitalizations for atrial fibrillation or flutter (3.1 vs 2.1%, $p=0.004$) and the higher incidence of bleeding (2.7 vs 2.1%, $p = 0.06$) in the group that received ethyl acid-eicosapentaenoic. The magnitude of the result obtained is not sufficiently explained by the decrease in the TG level. Other effects, antithrombotic, anti-inflammatory, at the level of the atheroma plaque or on the stability of the membrane could be involved, Up to date, the mechanism or mechanisms responsible for the benefit are unknown. The divergence of the outcome incidence curves suggests a late onset of benefit from reducing the TG level or the start of other mechanisms.[26]

The combination of high-intensity statins with other lipid-lowering drugs with different mechanisms of action is a recommended therapeutic option in specific cases to achieve an additional decrease in LDL-c and a greater reduction in cardiovascular outcomes.[27]

EVOLUTION OF LDL-C TREATMENT GOALS

Clinical studies indicate that the greater the absolute decrease in LDL-C, the greater the reduction in atherosclerotic outcomes, and that the strategies of greater intensity are the ones that obtain the best results. It has also been shown that the higher the level of risk, the greater the benefit for achieving the recommended goals and that there is no threshold level of LDL-c below which the benefit is lost or there is some type of harm. The timely initiation of treatment and the achievement and maintenance of the goal are very important in the prevention of atherothrombotic outcomes. Clinical practice guidelines emphasize this, and the recommendations evolution is the product of advances in knowledge and better understanding of the biology of atherosclerosis. The goals have increasingly gone beyond what was previously established *(Table 3)*, especially, because, while the goals are more stringent, the preventive results are better.[9,28-35]

CONCLUSIONS

Reducing LDL-C and other atherogenic lipoproteins is the primary goal of prevention of atherosclerotic cardiovascular outcomes. The intensity of the therapeutic intervention should be proportional to the level of cardiovascular risk estimated in all patients. Therapeutic modifications in lifestyle are essential to improve the lipid profile and that of the other present risk factors. In most high-risk patients, the goal should be to lower LDL-c to below 70 mg/dL or to achieve a reduction of at least 50% from baseline LDL-c. In very high-risk patients, it is appropriate to reduce LDL-c below 55 mg/dL. If the goal is not achieved with a high intensity statin at the maximum tolerated dose, the addition of ezetimibe and if required, a PCSK9 Inhibitor is indicated. It is the significant and permanent reduction in LDL-c that has achieved the best results in clinical studies. LDL-c reduction, the sooner, faster, lower, and longer the better, is a concept that has solid scientific support. However, the residual risk continues to be high in most patients in secondary prevention and this has motivated the search for different intervention strategies. New lipid-lowering drugs are in development that have shown efficacy and safety in initial clinical studies. Changes in cardiovascular prevention strategies are likely to occur in the coming years.

REFERENCES

1. Hernández-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, Pedroza-Tobías A, Villalpando S, Shamah-

Levy T et al. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. Salud Pública Mex. 2020; 622: 137-146.
2. Aguilar-Salinas CA, Gómez-Díaz RA, Gómez-Pérez FJ. Dislipidemias; de lo clínico a lo molecular. Capítulo I, definición de dislipidemia. México, Editorial Intersistemas. 2008, 1-51.
3. Goldstein JL, Brown MA. Century of cholesterol and coronaries: From Plaques to Genes to Statins. Cell. 2015; 161: 61-172.
4. Glass CK, Witztum JL. Atherosclerosis: the road ahead. Cell. 2001; 104: 503-516.
5. Libby O. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013; 368: 2004-2013.
6. Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the mechanisms of acute coronary syndromes. The "vulnerable plaque" and superficial erosion. Circ Res. 2019; 124: 150-160.
7. Vergallo R, Crea F. Atherosclerotic plaque healing. N Engl J Med. 2020; 383: 846-857.
8. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017; 38: 2459-2472.
9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019; 41: 111-188.
10. Langlois MR, Chapman MJ, Cobbaert CH, Mora S, Remaley AT, Ros E et al. Quantifying atherogenic lipoproteins: current and future challenges in the era of personalized medicine and very low concentrations of LDL cholesterol. a consensus statement from EAS and EFLM. Clin Chem. 2018; 64(7): 1006-1033.
11. Van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. Circulation. 2016; 134: 611-624.
12. Gencer B, Kronenberg F, Stroes ES, Mach F. Lipoprotein(a): the revenant. Eur Heart J. 2017; 38: 1553-1560.
13. Watts GF, Chan DC, Somaratne R, Wasserman SM, Scott R, Marcovina SM, Barrett PHR. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. Eur Heart J. 2018; 39: 2577-2585.
14. Pirillo A, Catapano AL. PCSK9 inhibition and Lp(a) reduction: another piece of the puzzle? Eur Heart J. 2018; 39: 2586-2588.
15. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 140: e596-646.
16. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Cholesterol Treatment Trialists Collaboration. Lancet. 2010; 376: 1670-1681.
17. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet. 2012; 380: 581-590.
18. Michos ED, McEvoy JW, Blumenthal RS. Lipid management for the prevention of atherosclerotic cardiovascular disease. N Engl J Med. 2019; 381: 1557-1567.
19. Nissen SE, Tuzcu EM, Schoenhagen P, Brown G, Ganz P, Vogel RA et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004; 291: 1071-1080.
20. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM et al. ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. JAMA. 2006; 295: 1556-1565.
21. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011; 365: 2078-2087.
22. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P et al. for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015; 372: 2387-2397.
23. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K et al, for the PRECISE-IVUS Investigators. Impact of Dual Lipid-Lowering Strategy with Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients with Percutaneous Coronary Intervention. The Multicenter Randomized Controlled PRECISE-IVUS Trial. J Am Coll Cardiol. 2015; 66: 495-507.
24. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017; 376: 1713-1722.
25. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018; 379: 2097-2107.
26. Bhatt DL, Steg PGP, Miller M, Brinton EA, Jacobson TA, Ketchum SB et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019; 380: 11-22.
27. McCormack T, Dent R, Blagden M. Very low LDL-C levels may safely provide additional clinical cardiovascular benefit: the evidence to date. Int J Clin Pract. 2016; 70: 886-897.
28. Goodman DS, Hulley SB, Clark LT, Davis CE, Fuster V, LaRosa JC et al. Report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Arch Intern Med. 1988; 148: 36-69.

29. National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). Circulation. 1994; 89: 1333-1445.
30. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA. 2001; 285: 2486-2497.
31. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. Circulation. 2004; 110: 227-239.
32. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O et al. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011; 32: 1769-1818.
33. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart. 2016; 37 (39): 2999-3058.
34. Stone NJ, Robinson JG, Lichtenstein AH, Merz NB, Blum CB, Eckel RH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 129 (Suppl 2): S1-S45.
35. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/ PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139 (25): e1046-e1081.

Correspondence:
Francisco Javier Guerrero-Martínez, MD
Apolo XI Num. 101 interior 115,
Col: Futurama-Monterrey, 37180,
León, Guanajuato. México.
E-mail: fjgm@prodigy.net.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100795

An appropriate scale of atherosclerotic risk for Mexicans -in search of the Golden Fleece of epidemiological legitimacy-

Una escala adecuada de riesgo aterosclerótico para los mexicanos -en busca del vellocino de oro de la legitimidad epidemiológica-

Eduardo Meaney, MD, PhD* Martha Yolanda Martínez-Marroquín, MD, BSc*
Nayelli Nájera, PhD* Guillermo Ceballos, MD, PhD*

BACKGROUND

In the last decades Mexico have experienced accelerated epidemiological, nutritional, and anthropometric transitions, that have changed substantially the pathological profile of its population, as well as the main causes of general morbidity and mortality. This rapid transformation took health authorities, social security institutions, medical community, and society itself by surprise. The year before the pandemic of COVID-19, myocardial infarction was the leading cause of overall mortality, with more than 100,000 victims. Mortality from myocardial infarction in Mexico is the highest among the countries encompassed in the Organization for Economic Co-operation and Development (OECD), which groups together some of the most important economies in the world.

Beneath the increase in fatal and non-fatal cases of atherosclerotic cardiovascular diseases (ASCVD) in Mexico, lies the epidemic of diabesity and dysmetabolic obesity and overweight (the misnamed «metabolic syndrome»). Diabetes and obesity share many physio-pathological mechanisms, as the binomial insulin resistance/hyperinsulinism, lipid triad, chronic inflammation, nitroxidative stress, and hypertension, among others, all of them possessing powerful pro-atherogenic effects.

In fact, Mexican population has a very peculiar cardiometabolic profile: obesity or overweight ravage 70% or more of the adult population; at least, 60% of the population have low values of high-density lipoproteins (HDL-c), about half of our people have hypertriglyceridemia, more than half exhibits the so-called lipid triad (atherogenic dyslipidemia), and 25-30% suffered high blood pressure, among other relevant vascular risk factors.

Among the numerous factors and problems that hinder the adequate control of the atherosclerosis epidemic in Mexico are a corroded and technologically backward national health system, a lack of enough financial resources for health, insufficient number of trained physicians and nurses, absence of public policies focused in primary and secondary atherosclerosis prevention, an imperfect system of timely risk factor detection, and a slow and red-taped referral and counter-referral flow between the different levels of the health pyramidal system. In addition, we do not have a proper system of vascular risk scale that considers the peculiarities of contemporary Mexicans.

* Laboratorio de Investigación Integral Cardiometabólica. Escuela Superior de Medicina. Instituto Politécnico Nacional. Ciudad de México, México.

Received:
01/07/2021
Accepted:
12/07/2021

How to cite: Meaney E, Martínez-Marroquín MY, Nájera N, Ceballos G. An appropriate scale of atherosclerotic risk for Mexicans -in search of the Golden Fleece of epidemiological legitimacy-. Cardiovasc Metab Sci. 2021; 32 (s3): s192-s195. https://dx.doi.org/10.35366/100795

The correct estimation of risk has paramount importance in primary prevention because allows a scientific based prognosis, predicts vascular outcomes, differentiates high-risk patients, and guides and tailors the application of several preventive measures. Currently there are a handful of risk scales (SCORE, GLOBORISK, ASCVD Risk Calculator plus from AHA/ACC, etc.), none of them free of criticisms, which reflect the characteristic of other populations, quite different from our own.

These scoring systems are estimated from algorithms derived from certain national or international cohorts. In general, as these studies are very costly and burdensome, all the

Table 1: Lindavista cardiovascular risk score.

Risk factor grading	Score	Risk factor grading	Score
Age (years) female		140-159	1
< 30	-3	160-179	2
30-39	-1	≥ 180	3
40-49	0	Systemic diastolic blood pressure (mmHg)	
50-59	1	< 90	0
> 60	2	90-99	1
Age (years) male		100-109	2
< 30	-1	≥ 110	3
30-39	0	Fasting glycemia (mg/dL)	
40-49	1	< 100	0
50-59	2	100-126	1
> 60	3	127-140	2
Smoking (daily consumption)		≥ 140	3
Never smoked or former smokers (at least in the last year)	0	Total cholesterol (mg/dL)	
Cigarette consumption			
1-5 per day	1	< 200	0
6-10 per day	2	200-239	1
> 10 per day	3	240-279	2
Body mass index (kg/m^2)		≥ 280	3
< 25	0	Triglycerides (mg/dL)	
25-29.9	1	< 150	0
30-34.9	2	150-199	1
≥ 35	3	200-499	2
Abdominal circumference in women (cm)		≥ 500	3
< 80	0	HDL-c (mg/dL)	
80-84.9	1	≥ 60	0
85-89.9	2	40-59	1
≥ 90	3	30-39	2
Abdominal circumference in men (cm)		< 30	3
< 90	0	LDL-c (mg/dL)	
90-94.9	1	< 100	0
95-99.9	2	100-129	1
≥ 100	3	130-159	2
Systemic systolic blood pressure (mmHg)		≥ 160	3
< 140	0		

Table 2: Atherogenic quotient (triglycerides/HDL-c).

Atherogenic index value	Interpretation
< 2.0	Ideal
2.0-3.9	Low risk
4.0-5.9	Intermediate risk
≥ 6.0	High risk

current risk scales have been done in developed and rich countries, as the United States or some European Union nations. In less developed countries, the lack of this type of studies, force the care providers to use those systems that are meaningful for the populations that provided the data from which the scales were estimated. The claiming that all human beings share the same traits, ignores unscientifically human biodiversity, and the particularities given by different genetic, ethnic, dietary, and environmental influences.

In this context, our group took the data from the Lindavista study, an essay of multiple primary prevention interventions, which reflects the profile of a cohort of urban middle-class inhabitants of northern Mexico City, as a first step to develop a risk scale according with our anthropometric and metabolic idiosyncrasies.

The «Lindavista risk scale». The Lindavista cohort is composed by a convenient sample of 2,602 individuals aged 35 or older, of either gender, and free of clinical ASCVD at recruitment, and whose characteristics have already been published. Eleven traits, including age and gender were considered *(Table 1)*. Arbitrary values between 0 to 3 (positive or negative) were assigned to each factor, according to their magnitude, considering the contemporary concepts of «normality» of each one. The sum of all scoring variables (maximally 33) was named «Lindavista risk scale», representing both, the number of risk factors and its magnitude, as both correlates closely with the incidence of clinical outcomes.

Calibrating the «Lindavista risk scale». The risk scale was calculated in all cohort's participants. To calibrate the meaning of these numbers, we use an atherogenic index, national and internationally proven as a reliable and simple risk.

Index: the ratio between triglycerides (TG) and high-density lipoprotein (HDL-c), which high values reflect insulin resistance and lipid triad, correlating well with coronary mortality, endothelial dysfunction, dysglycemia, and vascular lesions extension. Using the conventional interpretation of the values of this index and its interpretation in terms of risk, we could assign the lowest risk characterization to Lindavista scores < 4, intermediate risk to 4 to 12, and high-risk beyond that value *(Table 2)*. The next steps should be to compare both the TG/HDL-c index and the Lindavista Risk Score values with the ASVCD risk estimated with the traditional scales, and of course to test both in prospective, long-term studies *(Figure 1)*.

This is only the beginning of the search for the epidemiological Golden Fleece (a sign of authority and legitimacy in Greek mythology), that can give scientific validity to the measurement of atherosclerotic vascular risk in our country.

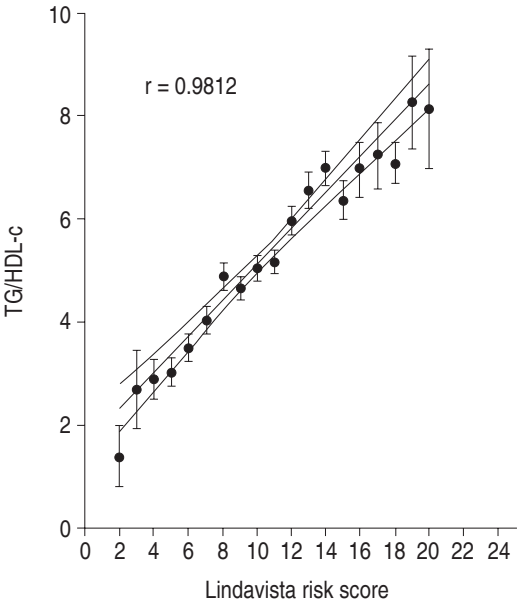


Figure 1: Lindavista cardiovascular risk score and TG/HDL-c index.

BIBLIOGRAPHY

1. Meaney E, Lara-Esqueda A, Ceballos-Reyes GM, Asbun J, Vela A, Martínez-Marroquín Y et al. Cardiovascular risk factors in the urban Mexican population: the FRIMEX study. Publ Health. 2007; 121: 378-384.
2. Fanghanel-Salmón G, Gutiérrez-Salmeán G, Samaniego V, Meaney A, Sánchez-Reyes L, Navarrete U, et al. Obesity phenotypes in urban middle-class cohorts; the PRIT-Lindavista merging evidence in Mexico: the OPUS PRIME study. Nutr Hosp. 2015; 32: 182-188.
3. Meaney A, Ceballos-Reyes G, Gutiérrez-Salmean G, Samaniego-Méndez V, Vela-Huerta A, Alcocer L et al. Cardiovascular risk factors in a Mexican middle-class urban population. The Lindavista Study. Baseline data. Arch Cardiol Méx. 2013; 83: 249-256.
4. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation. 1997; 96: 2520-2525.
5. He S, Wang S, Chen X, Jiang L, Peng Y, Li L, Wan L, Cui K. Higher ratio of triglyceride to high-density lipoprotein cholesterol may predispose to diabetes mellitus: 15-year prospective study in a general population. Metabolism. 2012; 61: 30-36.
6. Bittner V, Johnson D, Zineh I, Rogers WJ, Vido D, Marroquin OC et al. The TG/HDL cholesterol ratio predicts all cause mortality in women with suspected myocardial ischemia. A report from the Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2009; 157: 548-555.
7. Murguía-Romero M, Jiménez-Flores JR, Sigrist-Flores SC, Espinoza-Camacho MA, Jiménez-Morales M, Piña E et al. Plasma triglyceride/HDL-cholesterol ratio, insulin resistance, and cardiometabolic risk in young adults. J Lipid Res. 2013; 54: 2795-2799.
8. Lemos da Luz P, Favarato D, Faria-Neto Junior JR, Lemos P, Palandri Chagas AC. High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. Clinics. 2008; 63: 427-432.
9. Borrayo G, Basurto L, González-Escudero E, Díaz A, Vázquez A, Sánchez L et al. TG/HDL-c ratio as cardio-metabolic biomarker even in normal weight women. Acta Endocrinol (Buchar). 2018; 14: 261-267.

Correspondence:
Eduardo Meaney, MD, PhD
E-mail: emeaney@ipn.mx
lalitomini1@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100796

Dietary interventions to control dyslipidemias and cardiovascular risk

Intervenciones dietéticas para controlar las dislipidemias y el riesgo cardiovascular

Elisa Zárate-Chavarría, RD*

INTRODUCTION

Nutritional interventions for the prevention and control of dyslipidemia and in turn of cardiovascular risk have varied greatly over the last decade. Currently, it is suggested to follow an eating pattern of diets containing specific percentages of macronutrients. Guidance focused on specific dietary patterns is more likely to improve meals quality and promote cardiovascular health. Eating patterns can be defined as the combination of foods and beverages that a person consumes, adaptable to subject's characteristics, allowing the incorporation of foods usually consumed, and considering traditions, culture, and economic possibilities. They need to contain macronutrients, as carbohydrates, proteins, and lipids, as well as micronutrients like vitamins, minerals, and polyphenols. These regimes also must consider the water contained in food groups: fruits, vegetables, grains and seeds, meats, dairy products, fats, and oils. A healthy eating pattern must limit the ingestion of saturated fats (less than 10% of total energy), unsaturated fatty acids of the trans subtype, (that are proinflammatory and proatherogenic), as well as added sugars and sodium.[1]

Examples of eating patterns are the Mediterranean, vegetarian, Dash, and cornfield diet, among others.

WHAT TO EAT TO CONTROL HYPERCHOLESTEROLEMIA?

It is known that approximately 80% of circulating cholesterol in plasma is determined by the human genotype, age, gender, and physiological or pathological states. The remaining 20% is determined by the dietary ingestion of cholesterol and saturated fat.

Among the components of the diet that can help to control plasma lipids concentrations are phytosterols, sterols of plant origin whose chemical structure is very similar to that of cholesterol, and phytostanols (fully hydrogenated, saturated phytosterols). They are found in fruits, seeds, leaves and stems of practically all vegetables. Although more than 25 different compounds constitute this group, three of them are found in the highest proportion in foods: α-sistosterol, campesterol and stigmasterol, that together account for 95-98% of all identified phytosterols.

A consumption of 1.5 to 4 grams/day of phytosterols and phytostanols is recommended, which on average will reduce cholesterol by 10%.[2]

Based on their physicochemical characteristics, they are known to act as cholesterol-lowering agents because they lead to:

a) A decrease absorption of cholesterol by competition in two fronts. Firstly, as these

* Cardiology Service, Hospital Regional 1º de Octubre, ISSSTE.

Received:
22/06/2021
Accepted:
30/06/2021

How to cite: Zárate-Chavarría E. Dietary interventions to control dyslipidemias and cardiovascular risk. Cardiovasc Metab Sci. 2021; 32 (s3): s196-s199. https://dx.doi.org/10.35366/100796

compounds are more lipophilic, they limit the incorporation of cholesterol in the mixed micelle formed by the action of phospholipids and bile salts in the intestinal lumen. In this way, phytosterols take the place of cholesterol, and the non-emulsified cholesterol (displaced from the micelle) cannot be absorbed and is eliminated in the feces in the form of neutral sterols. Secondly, the only entrance way of all type of sterols through the brush border enterocyte membrane is a protein named Nieman-Pick C1L1. Both cholesterol and phytosterols and phytostanols compete for this single input, so the higher the amount of dietary plant sterols, the less cholesterol absorption.[3,4]

b) A reduction of cholesterol esterification in the enterocytes by inhibiting the activity of the enzyme acyl-Co-A-cholesterol-acyltransferase (ACAT). In this process the cholesterol is not re-esterified and as well, it is not incorporated into the chylomicrons, thus stimulating the flow towards the intestinal lumen of unesterified cholesterol.

c) Stimulating the efflux of cholesterol from the enterocytes into the intestinal lumen by increasing the activity and expression of the ABC-type transporters (ABCG5 and ABCG8, mainly), that are membrane proteins specialized in expelling metabolites from the cell.[4,5]

Dairy fats are generally rich in saturated fatty acids and are also high in monounsaturated fatty acids (MUFAs). The latter contrary to the former, decrease plasma cholesterol levels, stimulating the number of low-density lipoproteins (LDL) liver receptors.[6] Additionally, milk fats contain other biologically active lipids, including conjugated linoleic acid and low levels of long-chain n-3 polyunsaturated fatty acids (PUFAs) that have the potential to mitigate coronary heart disease risk factors. Also, dairy products are rich in calcium. Two meta-analyzes have reported an inverse relationship between higher calcium intake and reduced blood pressure.[7]

The consumption of eggs provides great nutritional value due to its richness in minerals (selenium, phosphorus, iodine, and zinc) and vitamins (A, D, B2, B12, pantothenic acid, and niacin). Eggs are rich in proteins of high biological value, its composition includes ovalbumin, the nutrient choline involved in the formation of cell membranes and highly bioactive carotenoids, such as lutein and its isomer zeaxanthin, important for the structure and function of the retina.[8]

In healthy people, the consumption of one egg per day can be salutary without increasing the risk of coronary heart disease or stroke. In patients with dyslipidemia, diabetes or high-risk of atherosclerotic cardiovascular diseases (ASCVD), it is advisable to be more cautious, limiting but not prohibiting the ingestion of cholesterol-rich foods, such as eggs and shellfish.[9]

On the other hand, there is a positive relationship between the consumption of red and processed meat with the risk of ASCVD, not only related to their content in cholesterol, saturated fat, trans-fatty acids, sodium, nitrites, and nitrates, but also to the possibility of conversion of meat choline or carnitine into trimethylamine (TMA) by intestinal bacteria of the genus Prevotella, which in the liver can be converted into trimethylamine N-oxide (TMAO). This compound blocks the synthesis of bile acids, reduces the reverse transport of cholesterol, facilitates the cellular influx of lipids, increasing its *in situ* synthesis, and suppressing their elimination, thus causing lipid accumulation and in consequence the increase of lipid-laden macrophages, what gives rise to the formation of foam cells; events that initiate the atherosclerosis process.[10]

The importance of eating vegetables is based in several facts, one of them is their richness in inorganic nitrates (spinach, lettuce, arugulas, beets, chard, etc.) that during chewing, thanks to oral bacteria, are converted in nitrites. Although nitrites in contact with acid content of the stomach form a variety of nitrogenous compounds, including nitric oxide (NO), that some authors have related to gastric cancerogenesis, the abundant amount of nitrates/nitrites swallowed with saliva is absorbed int the intestine and transported in the blood, being converted in some tissues in NO, which is, in general is a benefic molecule, with vasorelaxation, anti-inflammatory, antioxidant, antithrombogenic and, in some cells, antiapoptotic effects, among

many others.[11] So, although in the past, nitrate/nitrites were seen as inert by-products of the NO metabolism, now there are considered another source of the production of this gas.

The consumption of whole grains is recommended, while refined ones is not, particularly those subjects to ultra-processing. All type of fruits should be consumed, particularly those containing pectin such as peaches, apricots, hawthorn, apples, grapes, strawberries or oranges, lemons, grapefruits, and tangerines. However, the ingestion of juices is not recommended.

The consumption of legumes at least 3 times a week must be a priority due to their fiber content. A consumption of 20-30 grams of total fiber per day has shown to reduce cardiovascular risk 12 to 20%. On this regard, the consumption of fruit fiber (pectin) is associated with a 30% reduction in the risk of coronary heart disease.[12] The action of fibers in the digestive system determines their benefit for the control of dyslipidemias. In the stomach, soluble fiber (such as inulin, pectin, gums, and fructo-oligosaccharides) causes a reduction in gastric emptying, an increase in abdominal distention, helps to have a normal and balanced microbiota, and causes a greater feeling of satiety, useful in weight control. At the level of the small intestine, the absorption of cholesterol, saturated fats, and glucose decreases. There is also a reduction of bile acids reabsorption what leads in turn to the lessening of cholesterol levels, since the liver express more LDL receptors to keep the production of bile acids, whose basic structure comes from cholesterol. At the colon level, soluble fiber undergoes bacterial fermentation, which produces an increase of beneficial short-chain fatty acids (SCFA) with important effects on glucose and lipid metabolism. On the other hand, the insoluble fiber (cellulose, hemicellulose, lignin, and resistant to digestion starch) in the large intestine, causes a reduction in the contact time of carcinogens with the walls of the intestine. There is a significant increase in bacterial fermentation and production of SCFA, particularly of propionate, which once absorbed into the portal circulation reaches the liver and inhibits the enzyme HMG-Co-A reductase, key enzyme that control the endogenous synthesis of cholesterol.

For cardiovascular health, the consumption of cold-water fishes, such as salmon, mackerel, tuna, and anchovies is highly recommended for its content of omega 3 fatty acids (FFA): eicosapentaenoic acid (EPA) and docosahexaenoic (DHA). It was recommended to reduce cardiovascular risk, provide daily 250 to 500 milligrams of omega 3 FFA.[13] Although anti-inflammatory, antithrombotic, antiarrhythmic effects, and the triglyceride reduction of omega-3 FFA have been proved, clinically, their capacity to reduce cardiovascular risk had been controversial. However, a Japanese study on EPA showed a 19% reduction in cardiovascular death, myocardial infarction, that was associated to an increase in HDL-C levels and a concomitant reduction in TG.[14] Icosapent, a free FFA form of EPA, reduced 25% the relative risk of an endpoint composed by cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in high-risk hypertriglyceridemic patients.[15] Recently a huge metanalysis comprising 40 clinical studies and 135,267 patients, showed a dose related reduction of coronary heart disease events with EPA and DDH.[16]

The best oils and fat for cardiovascular health are those provided by nature such as avocado, oilseeds, and extra virgin olive oil.

Antioxidants. A dietary antioxidant is a substance that is part of certain foods that can prevent the adverse effects of oxygen and nitrogen reactive species on the normal physiological functions of our body. In recent years it has been shown that a diet rich in polyphenols improves health and reduces the incidence of cardiovascular diseases. Especially, those compounds named flavonoids, that are natural pigments present in vegetables. Many polyphenols, among several beneficial effects protect against the damage caused by oxidizing agents. As the human body cannot synthesize these protective chemicals, they must be obtained through food. In the regard, some of their actions are the synthesis/release of endothelial NO, the regulation of the production of reactive oxygen species substances, the prevention of LDL oxidation and cytotoxicity, and the inhibition

of platelet aggregation, among many others: Among the more than 8,000 polyphenols found in vegetables, the most remarkable are catechins, epicatechins, quercetin, and procyanidins, many of them found in products like green tea, blueberries, red onion, apple, and cacao.[17,18] It is necessary to add that aside from their antioxidant action, some of these polyphenols, such as epicatechin from cacao, have marked actions on glucose and lipid metabolism, endothelial function, blood pressure, myocardial infarction, neuroprotection, fatty liver, and striate muscle function, among many others.[19]

REFERENCES

1. US Department of Health and Human Services; US Department of Agriculture. 2015-2020 Dietary Guidelines for Americans. 8th ed. Washington, DC: US Dept of Health and Human Services; December 2015. Available in: http://www.health.gov/DietaryGuidelines
2. Valenzuela A, Ronco A. Fitoesteroles y fitoestanoles: aliados naturales para la protección de la salud cardiovascular. Rev Chil Nutr. 2004; 21 (S-1): 161-169.
3. Jia L, Betters JL. Yu L. Niemann-Pick C1-Like 1 (NPC1L1) Protein in Intestinal and hepatic cholesterol transport. Annu Rev Physiol. 2011; 73: 239-259.
4. Muñoz JAM, Alvarado OUC, Encina ZC. Fitoesteroles y fitoestanoles; propiedades saludables. Horizonte Médico. 2011; 11: 93-100.
5. Huff MW. Dietary cholesterol, cholesterol absorption, postprandial lipemia and atherosclerosis. Can J Clin Pharmacol. 2003; 10 (Supl. A): 26-32.
6. Fernandez ML, West KL. Mechanisms by which dietary fatty acids modulate plasma lipids. J Nutr. 2005; 135: 2075-2078.
7. Rong Y, Chen L, Zhu T, Song Y, Yu M, Shan Z et al. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ. 2013; 346: e8539.
8. Pascual V, Perez MP, Fernández JM, Solá R, Pallarés V, Romero SA et al. SEA/SEMERGEN consensus document 2019: Dietary recommendations in the prevention of cardiovascular. Disease Clin Investig Arterioscler. 2019; 31: 186-201.
9. Geiker NRW, Larsen ML, Dyerberg J, Stender S, Astrup A. Egg consumption, cardiovascular diseases and type 2 diabetes. Eur J Clin Nutr. 2018; 72: 44-56.
10. Backhed F. Meat-metabolizing bacteria in atherosclerosis. Nat Med. 2013; 19: 533-534.
11. Lundberg JO, Gladwin MT, Ahluwalia A, Benjamin N, Bryan NS, Butler A et al. Nitrate and nitrite in biology, nutrition and therapeutics. Nat Chem Biol. 2009; 5: 865-869.
12. Moreno FB, León LM, Andrés EEM, Ordovás JM, Casasnovas JA, Peñalvo JL. Ingesta de fibra soluble e insoluble y factores de riesgo de síndrome metabólico y enfermedad cardiovascular en adultos de mediana edad: la cohorte AWHS. Nutr Hosp. 2014; 30: 1279-1288.
13. Harris WS, Mosaffarian D, Lefevre M, Toner CD, Colombo J, Cunnane SC et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. J Nutr. 2009; 139: 804S-819S.
14. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y et al. JELIS Investigators, Japan. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008; 200: 135-140.
15. Bhatt DL, Steg G, Miler M, Brinton EA, Jacobson TA, Ketchum SB et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019; 380: 11-22.
16. Bernasconi AA, Wiest MM, Lavie CJ, Milani RV, Laukkanen JA. Effect of omega-3 dosage on cardiovascular outcomes: an updated meta-analysis and meta-regression of interventional trials. Mayo Clin Proc. 2021; 96 (2): 304-313.
17. Coronado HM, Vega y León S, Gutiérrez TR, Vázquez FM, Radilla VC. Antioxidantes: perspectiva actual para la salud humana. Rev Chil Nutr. 2015; 42: 206-212.
18. Pandey KB, Rizv SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2: 270-278.
19. Bernatova I. Biological activities of (−)-epicatechin and (−)-epicatechin-containing foods: Focus on cardiovascular and neuropsychological health. Biotech Adv. 2018; 36: 666-681.

Correspondence:
Elisa Zárate-Chavarría, RD
E-mail: nutricardio@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100797

Alcohol, tobacco, physical activity, duration and type of exercise recommended

Alcohol, tabaco, actividad física, duración y tipo de ejercicio recomendado

César Rodríguez-Gilabert, MD*

The non-pharmacological treatment to reduce cardiovascular risk consists of lifestyle modifications. These include, mainly a diet with the appropriate amount of calories, abundant in vegetables and seafood, decrease sugary drinks intake, total tobacco withdrawal, performed exercise at least 30 minutes of moderate to intense physical exercise, the maintenance of a body mass index (BMI) between 20 to 25 kg/m^2, and the limitation of alcoholic beverages consumption to one or two drinks per day in those subjects who are already habitual drinkers. The effectiveness of these behavior modifications increases if they are adopted early and are followed for the rest of life. It has been estimated that life span can be prolonged 14 years in women and 12 in men, when all recommendations are followed. Individually, the most significant benefit comes from physical exercise, which increases life expectancy by 8 years. On the other hand, the most harmful risk factor is tobacco smoke that shortens life by 9.5 years.[1] Patients between 45 and 64 years of age who comply for 20 years with lifestyle modifications like a healthy diet, exercise, not smoking, and body mass index between 20-25; have fewer cardiovascular events than those who did not comply (6% vs 45%).[2]

ALCOHOL RISKS AND BENEFITS

Ethanol is the key and universal compound of all alcoholic beverages. At least 5,000 years ago, humans discovered how to make these beverages from fermenting vegetables, founding its rewarding effects, and consumed them at the beginning in festivities, or for medicinal purposes, but later for simple pleasure. The abuse of consumption has been a significant social problem that led to its prohibition in the United States from 1920 to 1933, period in which, far from diminishing its consumption, it increased. Today it remains as a paramount health problem worldwide, causing 10% of all deaths in adults between 20 to 64 years of age, and being the cause of one third of all road accidents.

Several studies on long-term alcohol consumption have estimated than around 14 g of ethanol are found in a bottle of beer, a glass of wine or an ounce of distilled liquor. It is legally prohibited to drive a motor vehicle if the driver's blood has the alcohol content provided by the equivalent of two or two and a half drink. The level of alcohol in the body may vary according to BMI, food intake, gender, and individual metabolism. Alcohol metabolism mainly occurs in the liver, where alcohol dehydrogenase and aldehyde dehydrogenase, the most important enzymes involved, break down approximately 8 g of alcohol per hour. The oxidation affected other functions requiring the same enzymes, which produces an accumulation of lactate and acetyl coenzyme A, which directly increased free fatty acids and hepatic accumulation of triglycerides, decreasing at the same time the synthesis of methionine synthase, which in turn augments homocysteine concentrations.

* Centro Médico Veracruz, Ver. México.

Received:
29/06/2021
Accepted:
09/07/2021

How to cite: Rodríguez-Gilabert C. Alcohol, tobacco, physical activity, duration and type of exercise recommended. Cardiovasc Metab Sci. 2021; 32 (s3): s200-s203. https://dx.doi.org/10.35366/100797

Drinking a small amount of alcohol exerts an anxiolytic and disinhibitory effect. However, a greater quantity can produce euphoria, but also central nervous depression, which can sometimes lead to death.

It is established that moderate alcohol consumption reduces the risk of coronary heart disease; however, high consumption increases the occurrence of hypertension, arrhythmias, coronary heart disease, heart failure, and cerebral vascular events. Common sense establishes the personal limits of responsible alcohol ingestion. The recommendations are not to exceed two drinks a day for regular consumers and drinking alcohol is not recommended in no consumer persons, because benefit risk ratio has not been demonstrated, and for the peril of induce abuse consumption.

The meta-analysis of eight prospective studies that included 192,067 women and 74,919 men without apparent cardiovascular disease and diabetes, found an inverse relationship between alcohol consumption and the possibility of suffering from coronary heart disease,[3] once adjusted for different risk factors. This effect is mainly attributed to high-density lipoproteins (HDL) elevation, raising the subfractions of HDL 2 and 3, increasing apoprotein A1 synthesis and HDL's antioxidant capacity and its ability to reverse the cholesterol transport. Moderate alcohol consumption generally raises HDL without altering low-density lipoprotein (LDL) or triglycerides (TG); however, heavy consumption can elevate HDL and TG as well. A meta-analysis of studies that analyze lipid behavior in the face of alcohol consumption found that 30 g of alcohol per day raises C-HDL by a mean of 3.99 mg/dL, apoprotein A by 8.82 mg/dL, and TG's by 6.69 mg/dL without meaningful modification of C-LDL.[4]

A dangerous side-effect of alcohol consume is the elevation of blood pressure. More than seven drinks per week increase systolic and diastolic blood pressure between 1.5 and 3 mmHg and this increment become greater if consumption rises.[5] In this regard, alcohol consumption is related to a quarter of hypertension cases. Another adverse effect is heart toxicity, causing arrhythmias like atrial fibrillation (AF). High alcohol intake can damage myocardial tissue. After a long period of exposure, the toxic effects of alcohol can lead to alcoholic cardiomyopathy, and this, in its terminal stage, cause heart failure. On the other side, alcohol intake can aggravate heart function, and could worsen the clinical conditions of patients that already suffer other type of heart disease and heart failure. The type of alcohol is also a factor that needs to be thoughtful regarding alcohol percentage content. Theoretically, red wine, due to its high polyphenol content (mainly resveratrol) could offer some additional benefits, but this effect must be proved. Total alcohol withdrawal is needed when there is a family or personal history of alcoholism, hypertriglyceridemia, pancreatitis, liver disease, bleeding disorders, heart failure, or poorly controlled hypertension, pregnancy, and medications that interact with alcohol. The recommendations should individualize, considering the risks and potential benefits. If there is no contraindication and the patient already drink alcohol, one or two drinks a day can be considered safe. Young people should be clearly warned about the potentially dangerous effects of alcohol consumption in the long term and should never prescribe it to improve cardiovascular risk.

DANGERS OF TOBACCO USE

According to the World Health Organization, tobacco use still is the main preventable factor of death in the world. Its consumption is associated with 71% of lung cancers, 30% of all cancer, 42% of chronic obstructive pulmonary disease (CPOD), for at least 10% of coronary deaths, and it has been related to 60% of cerebral vascular events. Half of the smokers die from a tobacco-related disease. Increased sympathetic activity raises blood pressure and heart rate, facilitating a prothrombotic state, while tobacco toxicity leads to endothelial damage and cell dysfunction. Although nicotine is the most studied component, tobacco combustion generates more than 7,000 chemical elements of which at least 69 of them are carcinogenic, the main component is nicotine, considered the addictive element of tobacco, But tobacco fumes also contain acetic acid, ammonia, arsenic, cadmium, methanol,

toluene, carbon monoxide, carbonyls, benzene, phenol, cobalt, lead, carboxylic acid, N-nitrosamines, benzopyrene, nitrogen, carbon dioxide, acetaldehyde, methane, acetone, hydrocarbons, and others.[6] There are two phases during smoking, the tar-phase corresponds to the trapped material in the cigarette filter, that retains most of the tobacco particles with a size > 0.1 mm. The non-filtered particles containing a substantial number of free radicals can stay during long time in the mouth of smokers. The gas-phase is defined as the gaseous material that went through the cigarette filter, also containing a substantial number of free radicals, being more short-lived than tar material. The tobacco fume inhaled through the smoker mouth and then exhaled into ambient air is known as mainstream smoke, which contains more than 90% of gaseous material. The so-called sidestream smoke is the fume emitted from the burning end of a cigarette or cigar, which contains a greater proportion of toxic gas components. What is called environmental tobacco smoke results from the combination of majority sidestream smoke and a small proportion of exhaled mainstream smoke.[7] The regulation of banning smoking in enclosed spaces has been shown, in just one year, to reduce cardiovascular events by 39% and by 47% in three years.[8] Regarding serum lipid modifications, smoking has been linked to decreased HDL and its antioxidant capacity, increased triglycerides, LDL and lipid peroxidation. These effects are reversible when quitting smoking. In a study conducted over 21.8 years, with active or passive smokers and ex-smokers in comparison to non-smokers, the former raised their relative risk for coronary heart disease to 1.69 (95% CI: 1.32, 2.14), for a cerebral vascular event to 1.62 (95% CI: 1.08, 2.41), cardiovascular death to 1.49 (95% CI: 1.13, 1.96), non-cardiovascular death to 1.40 (95% CI: 1.08, 1.83) and death from any cause to 1.44 (95% CI: 1.19, 1.74).[9]

Recently, the fashion for e-cigarettes and vaporization equipment (vapers) has emerged. These devices work by boiling a liquid containing nicotine, flavorings and other additives, basically consisting of a nozzle, battery, coil, and reservoir for the liquid. According to the Center for Disease Control and Prevention of the United States, by 2018, one in five students used e-cigarettes or vapers. The idea that this method is less harmful than smoking is wrong. Vapers increases the risk of cerebral vascular events by 29% and myocardial infarction by 25%. The damage has been attributed to oxidation and inflammation that these chemicals produced in the body. There are hundreds of devices and different chemical components (more than 7,500) have been identified, most of them flavorings or conservatives, of which their possible pathogenic effects are unknown. A fundamental problem from using these devices is the increase of severe lung infections, partly due to pulmonary and systemic immune system damages, producing acute eosinophilic pneumonia and a typical injury called «popcorn lung», leading to obliterating bronchiolitis. Some of the toxic chemicals studied found in e-cigarettes and vaporizers are: 2.3-pentanedione, tin, lithium, silver, iron, aluminum, silicon, chromium, and formaldehyde.[10]

BENEFITS OF EXERCISE

Regular exercise prevents cardiovascular disease and prolongs better physical fitness, helping to get physical and mental well-being. Regular exercise has several beneficial effects like lowering systemic blood pressure, improving insulin resistance, and lessening serum concentrations of TG and LDL-c. Exercise also decreases fibrinogen and platelet adhesion, improves endothelial function, slows heart rate by decreasing sympathetic activity, diminishes oxygen consumption, and can promote the development of coronary microcirculation. All these effects benefit hypertensive, diabetic, coronary, and obese patients. Regular exercise is the most valuable lifestyle modification after tobacco withdrawal. Regarding cardiovascular exercise intensity: 30 minutes daily of moderate workout is enough to improve health in primary cardiovascular prevention. On the other hand, very intense exercise can lead to myocardial alterations, mainly fibrosis that can lead to arrhythmias like atrial fibrillation. In the Copenhagen city trial,[11] 17,589 healthy people were followed for 35 years, measuring the amount of exercise-

related to mortality compared to those who did not perform an exercise, the most significant reduction in mortality was 42% in those who work out between 1.2 and 4 hours per week, equaling between 5 to 6 Mets. More exercise did not significantly reduce mortality risk, and less exercise reduced mortality but to a lesser degree. Another problem with extreme exercise is that the possibility of coronary heart disease (CHD) is not regularly valued. For instance, CHD is the most common cause of death in marathon runners over 40 years old. During intense exercise in untrained people, the risk of death increases 56 times compared to other activities, in contrast to training people is whom increase only five times.[12] Sudden death in athletes under the age of 40 is mainly due to hypertrophic cardiomyopathy and cardiac channelopathies, while in older people the main cause is coronary atherosclerosis disease. All people over the age of 40 who perform competitive sports should be studied to rule out the possibility of coronary heart disease.

In patients with heart disease, any exercise produces benefits as it was showed by a systematic review and meta-analysis of 63 studies included 14,485 patients with coronary heart disease, with a median follow-up of 12 months. Exercise reduces the relative risk of cardiovascular mortality in 26% and hospital admissions in 18%.[13] The type of exercise is not essential in this regard, although thirty minutes of vigorous exercise produces the cardiac stimulation induced by 90 minutes of brisk walking. Exercise should be done according to individual preferences and physical conditions.[14] Moderate exercise should increase heart rate to 60% of the maximum rate expected for the age, while intense exercise should raise it to 80%. Even if it is suspended at a certain age, exercise produces benefits compared to people who have never exercised regularly before. However, it is most significantly beneficial, starting it at an early age and practicing throughout life.[15]

REFERENCES

1. Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH et al. Impact of healthy lifestyle factors on life expectancies in the US population. Circulation. 2018; 138 (4): 345-355.
2. Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD; ARIC Study Investigators. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011; 57 (16): 1690-1696.
3. Hvidtfeldt UA, Tolstrup JS, Jakobsen MU, Heitmann BL, Gronbaek M, O'Reilly E et al. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. Circulation. 2010; 121 (14): 1589-1597.
4. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ. 1999; 319 (7224): 1523-1528.
5. Okubo Y, Sairenchi T, Irie F, Yamagishi K, Iso H, Watanabe H et al. Association of alcohol consumption with incident hypertension among middle-aged and older Japanese population: the Ibarakai Prefectural Health Study (IPHS). Hypertension. 2014; 63 (1): 41-47.
6. Munzel T, Hahad O, Kuntic M, Keaney JF, Deanfield JE, Daiber A. Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function and clinical outcomes. Eur Heart J. 2020; 41 (41): 4057-4070.
7. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. J Am Coll Cardiol. 2004; 43: 1731-1737.
8. Khuder SA, Milz S, Jordan T, Price J, Silvestri K, Butler P. The impact of a smoking ban on hospital admissions for coronary heart disease. Prev Med. 2007; 45: 3-8.
9. Shaper AG, Wannamethee SG, Walker M. Pipe and cigar smoking and major cardiovascular events, cancer incidence and all-cause mortality in middle-aged British men. Int J Epidemiol. 2003; 32 (5): 802-808.
10. Boziera J, Zakaryaa R, Chapmanc DG, Olivera BGG. How harmless are E-cigarettes? Effects in the pulmonary system. Curr Opin Pulm Med. 2020; 26: 97-102.
11. Schnohr P, Marott JL, Lange P, Jensen GB. Longevity in male and female joggers: the Copenhagen City Heart Study. Am J Epidemiol. 2013; 177: 683-689.
12. Chugh SS, Weis JB. Sudden cardiac death in the older athlete. J Am Coll Cardiol. 2015; 65: 493-502.
13. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N et al. Exercise-based cardiac rehabilitation for coronary heart disease: cochrane systematic review and meta-analysis. J Am Coll Cardiol. 2016; 67 (1): 1-12.
14. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res. 2015; 117 (2): 207-219.
15. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol. 2014; 64 (5): 472-481.

Correspondence:
César Rodríguez-Gilabert, MD
E-mail: cesarr@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100798

Dyslipidemia in women, a current overview based on cardiovascular risk

Dislipidemia en la mujer, una revisión actual basada en el riesgo cardiovascular

Ana Elena Ancona-Vadillo, MD*

Right now, the main mortality cause in women is directly associated with cardiovascular (CV) disease. Women are currently exposed to traditional risk factors such as; hypertension, dyslipidemia, smoking, sedentarism, overweight, obesity and glucose metabolism disorders. On the other hand, women are also exposed to other unique gender risk factors such as, polycystic ovaries syndrome, high risk pregnancies, immunological diseases and hormonal disorders, all of them appearing mainly in the peri-menopause or menopause stages, resulting in a vulnerable population to suffers CV outcomes as microvascular angina, occlusive disease, coronary spasm, spontaneous coronary dissection, acute ischemic syndrome, Takotsubo disease, among others, placing women into an individualized and specialized consideration for diagnosis and treatment.

The main lipid metabolism disorders in our population, are accompanied by a lipidic profile known as the lipidic triad. This complex consists in; low concentration of cholesterol linked to high-density lipoproteins (HDL-c), hypertriglyceridemia (HTG), both directly related to the body mass index, and high cholesterol linked to low-density lipoproteins (LDL-c), whose particles undergo morphological modification (small and dense), which increases their atherogenic power.

In Mexico, CV disease represents the main mortality and morbidity cause in people > 70 years old. The data gathered by the ENSANUT survey (National Chronic Disease and National Health surveys), reveals that 32.7% of the population suffers cholesterol (CHOL) metabolism and triglycerides (TG) disorders (2018). Furthermore, when the survey was analyzed by gender, the percentage in women was 34.8% compared to 30.3% in men. Apart from dyslipidemia there are other highly relevant risk factors to take into account such as hypertension, type 2 diabetes mellitus (DM2), overweight, obesity, metabolic syndrome, among others. In presence of a more competitive female population with wider access to the labor market, social, economical, and psychosocial factors have been added to increase CV risk in women.

ETHYOLOGY AND PATHOGENESIS OF DYSLIPIDEMIA IN WOMEN

Lipidic profile during a woman's lifetime

During their lifetime, women experience hormonal changes, from puberty, reproductive age, and perimenopause to menopause stages. These changes induced variations in the amounts of blood lipids. After birth, LDL concentrations are about 65 mg/dL, in both men and women, progressively increasing in the first two years. Men and women have similar levels of cholesterol in this age, but in teenagers, ranging from 10 to 17 years old, the LDL concentrations are lower in men than in women. After 20 years of age, both men and women show an increase in their LDL concentrations, greater in men than in women. Interestingly, when men and women achieve

* Cardiology and Electrophysiology. Hospital General de México «Dr. Eduardo Liceaga». Mexico.

Received:
18/06/2021
Accepted:
09/07/2021

How to cite: Ancona-Vadillo AE. Dyslipidemia in women, a current overview based on cardiovascular risk. Cardiovasc Metab Sci. 2021; 32 (s3): s204-s208. https://dx.doi.org/10.35366/100798

mature adulthood, the HLD-c level is lower in men compared to women, resulting in a cardioprotective factor for women at this age.

It is relevant to consider the modifications that the lipid profile show during pregnancy, in which an increase of the hormones gonadotropin, β-estradiol, insulin, and progesterone occurs. These hormones are associated with an increment of total cholesterol (TC), TG, LDL-c, HDL-c, and apoprotein A1 concentrations, having their highest peak at the week 36 of pregnancy.

In studies made in women with high-risk pregnancies, dyslipidemia was related to a 3.6 times higher risk of preeclampsia development (PE). Also, PE has a strict relationship with pre-pregnancy dyslipidemia. HTG has also been related to a 1.6 probability increase of PE. Although to date there is no direct mechanism explaining the role of dyslipidemia and PE, probably endothelial dysfunction is the cause. In a study carried out in the IMSS (Mexican Institute of Social Security), were studied two groups (each of 100 patients) of pregnant women. Divided in those with normal pregnancy and the other with PE. The essay found that in PE, there were more patients with severe rise of TG and very low density lipoproteins (VLDL). In another study, the relevance of the lipidic profile during the third trimester of high-risk pregnancy in women between 18-50 years old and their children was determined. About 83.9% of women presented alterations in lipid metabolism. The study concluded that dyslipidemia in pregnancy is related with comorbidities such as DM2, hypertension, smoking, obesity, and preeclampsia. Among other pathologies that should draw our attention is the polycystic ovary syndrome (PCOS), an endocrinological disorder found at a reproductive age, associated with obesity, fertility problems, hyperandrogenism/ hyperandrogenemia, insulin resistance and dyslipidemia. The most relevant changes in the lipid metabolism in women with PCOS are increase of the LDL-c, the decrease of the HD-c, and the increase of the TG concentrations.

Other stages that nowadays have become a challenge for cardiology are pre-menopause and menopause, where the expression of risk factors joined the hormonal suppression, facts that forces cardiologists to have a multidisciplinary vision of the practice. The evaluation of the lipidic profile in menopause women is modified due to changes produced by aging and hypoestrogenism, resulting in a proatherogenic state, that expresses with the following traits: Increment of LDL-c and TG, with decrease of HDL-c. The intermediate density lipoproteins (ILD) concentrations are also related with the rise of CV disease in menopause women.

RELATIONSHIP BETWEEN THE LIPID METABOLISM AND ESTROGENS

The production of estrogens it is mainly performed by ovaries. In the bloodstream, estrogens have low affinity binding with albumin. They require for their mobility the action of sexual hormone transporting globulin (SHBG) and the corticosteroid transporting globulin (CBG). Estrogen actions define the main gender sexual characteristics, the psycho-emotional state, the bone metabolism, inhibiting the action of the osteoblasts, fat biosynthesis and proteins. Regarding lipid metabolism, they increase HDL-c, diminishing TG, and LDL-c. Also, the pancreatic β-cells sensitivity is augmented, with a decrease of insulin resistance. Among other actions, estrogens produce an increase of the blood flow at a cerebral level, inhibiting amyloid deposits formation.

Estrogenic action. The estrogens act through at least 2 independent steroid receptors placed in the cell nucleus or in the membrane. In turn there are two nuclear types, the estrogen receptors (ER) α and β, structurally different, and their location vary in the tissues. The steroid activation depends on the plasmatic concentrations of the free hormone, as well as, the receptor affinity. The ER-α plays a key role in the cardiovascular system, the liver, the hypothalamus, endometrium, cerebral cortex, adrenal gland, endothelium, and smooth vascular muscle. It is a prominent agent for CV protection. On the other hand, ER-β causes vasodilatation, neovascularization. and inhibition of cellular apoptosis in cardiac muscle.

ER-α has many polymorphic variables. There are two significant polymorphisms of the alpha receptor (XBA-1 and PVull). The

latter polymorphism is related to alterations in bone mineralization (osteoporosis), CV system, endometriosis, breast cancer, changes in the lipid profile, hypertension, and coronary atherosclerosis.

The Rotterdam study involving 4,000 women found that those with the genotype IVS1-397TT, faced a high risk for developing heart disease, while those with the genotype PVull TT were prone to weight increase, hypertension and DM2.

LIPID PROFILE INDICATORS IN WOMAN AND HEART DISEASE RISK

The study of women with dyslipidemia must be integral. Clinical evaluation let identify the traditional risk factors for both men and women like, age, hypertension, smoking, dyslipidemia, DM2, physical conditions, sedentary behavior, diet, and family history of disease, among others. Clinical study, ss well, unveil non-traditional factor gender-related, such as risky pregnancies, autoimmune disorders, chronic kidney disease, chest wall radiation, cardiotoxic chemotherapy, and the like. Hormonal factors as premature menopause, menopause, hormone therapy, polycystic ovarian syndrome, obesity, and cardio-metabolic risk also are revealed in the basic clinical examination. Added to these factors, the social determinants of health that intervene in an important way are, ethnicity, education, income, living conditions, etc., and on the other hand, psychological risk factors such as, depression, anxiety, loneliness, perceived stress, that through diverse mechanisms increase cardiovascular risk. Finally, it should be mentioned the main responsible factor of chronic inflammation, endothelial dysfunction, and the existence of subclinical atherosclerotic lesions. Both silent processes are behind are behind the threat of the clinical expression of atherosclerotic CV diseases (ASCVD). It is important to mention that early stage identification of CV risks starts in routine check-ups, complemented by laboratory studies, as identification of biochemical risk markers, such as glycemia, glycated hemoglobin, kidney damage, and lipid profile.

In patients with chronic kidney disease, the most frequent lipid alterations are the increase of TG and low of HDL-c, raising of LDL-c and TC are less significative.

Women with autoimmune diseases like; rheumatoid arthritis, erythematous lupus, anti-phospholipid syndrome, distinguish themselves for showing, at an earlier age, and with high frequency, ASCVD, and cardiovascular mortality in higher rates.

In women with DM2, the usual lipid profile found is HTG, low HDL-c and the arise of LDL-c with mor proportion of smaller, denser and more atherogenic particles. Hypothyroidism is commonly associated with the 56% cases of the hypercholesterolemia.

It is relevant to consider familiar hypercholesterolemia in groups of young women, since this is associated with premature coronary disease, caused by high concentrations of LDL-c. These conditions should be suspected when LDL-c concentrations are > 190 mg/dL, after excluding other secondary causes.

LIPID PROFILING IN WOMEN

The traditional lipid profile includes total TC, LDL-c), HDL-c), TG, non-HDL cholesterol (non-HDL-c); and the atherogenic indexes or quotients TC/HDL-c, non-HDL-c/HDL-C, LDL-c/HDL-c, and TG/HDL-c. It has been proposed a new ischemic indicator for women in the menopause stage, known as atherogenic index in plasma (AIP), estimated by a molar transformation of TG and HDL-c concentrations ratio. The index is an independent predictor for cardiovascular disease risk in women post-menopause, related to the size lipid particles.

In the recent past, imaging techniques become useful for the patient's CV risk re-stratification. Detection of coronary artery calcification by non-contrasted computed tomography (CT scan), femoral or carotid ultrasound, and many others imaging studies are excellent supporting clinical tools, whose description is beyond the limit of this text.

DISLIPIDEMY TREATMENT IN WOMEN

The treatment for patients with dyslipidemia should not only be integral and multidisciplinary, but must include lifestyle changes, mainly

eating habits. For all patients it is advisable the following recommendations:

1. Fatty acids ingest reduction to less than 10% of the total energetic intake, and preferably replacing them with polyunsaturated fats. Avoid highly processed foods. Fats must represent less than 30% of the total calorie intake. Reduction the consumption of simple and complex carbohydrates, specially the refined ones, and also avoid the excessive consumption of alcohol.
2. Reduce the amount of salt intake (average 5 grams of salt per day).
3. Consumption of fiber.
4. Increase physical activity, as it has multiple health benefits such an increase HDL-c concentrations, decrease of TG concentration, maintaining healthy weight contributes to enhances CV health.
5. Quit smoking as a priority. Mainly in women with low HDL-c.

Pharmacological treatment

The main criteria exposed in the Dyslipidemia Study Guidelines by the European Society of Cardiology (ESC) on 2019, as well as the US American guidelines ACC/AHA, do not specify the treatment considering the patient's gender. Women have less possibilities of receiving treatment with statins than man, as well as, more of them abandon the treatment or receive insufficient dosing.

Studies with statins in primary prevention in women have been controversial. The recommendations in primary prevention of CV disease in women are shown in *Figure 1*.

The STELLAR study confirms the statin treatment efficacy, diminishing the LDL-c in a range of 21 to 57%, in a six-week period, depending on the statin and dosage used. The study concluded that statin therapy is efficient to reduce CV events in women, like what happens in men. Both STELLAR and JUPITER Study support the usage of rosuvastatin in primary prevention. The latter study showed the beneficial effects of rosuvastatin in subjects with elevated concentrations of high sensitivity c-reactive protein individuals of both genders.

The therapy combined with ezetimibe (inhibitor of intestinal absorption of cholesterol and phytosterols) and high or medium effect statin have been prescribed mainly in patients

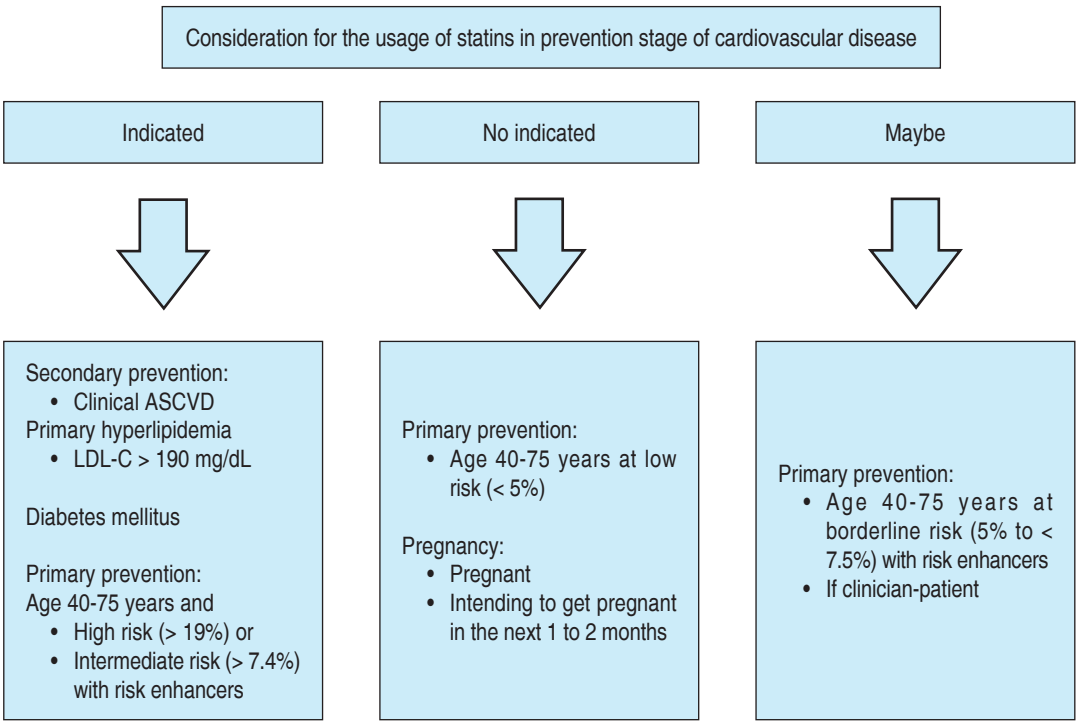


Figure 1:

Considerations about the use of statins for cardiovascular disease prevention.

Modified from: Cho L et al.

that require a quicker effect control, also to diminish the secondary effects.

PCSK9 inhibitors, in the treatment of dyslipidemia in women. Several studies (FOURIER, ODYSSEY OUTCOMES, SPIRE) have not shown any gender differentiated response to these innovating drugs. These inhibitors will be described in detail in other section of this text. The management of HTG in women, depends on the associated factors, as well as the type of lipid disorder. It is important to mention that in pregnancy, mainly in the last trimester they could rise, for which diet measure should be reinforced. The usage of fibrates (gemfibrozil) is limited to people with high triglyceride risk > 500 mg/dL. limited to people with high level triglyceride (>500 mg/dL) with high risk of pancreatitis. Nowadays, multiple multicentric studies are focused on the use of omega-3 fatty acids, like eicosanpentanoic (EPA) and docosahexaenoic (DHA).

CONCLUSIONS

Dyslipidemia is very common in feminine adult population, phenomenon magnified in the menopause stage. In this moment, dyslipidemia in consonance with other risk factors, skyrocket, in exponential fashion, the ASCVD risk. In most of the large studies on lipids and ASCVD, women are underrepresented. The dyslipidemia treatment in primary and secondary stages, is plagued of shortcomings: absence or delay of lipid-lowering drugs prescriptions, inadequate doses, and more frequent abandon of treatment. Finally, the combined therapies should be a reasonable option to attain therapeutic goals. Also, physicians should not ignore the advice on therapeutic modifications of lifestyle. This point should be always a priority in medical practice.

BIBLIOGRAPHY

1. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75 (20): 2602-2618.
2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-188.
3. Freedman DS, Bowman BA, Otvos JD, Srinivasan SR, Berenson GS. Levels and correlates of LDL and VLDL particle sizes among children: the Bogalusa heart study. Atherosclerosis. 2000; 152 (2): 441-449.
4. Phan BA, Toth PP. Dyslipidemia in women: etiology and management. Int J Womens Health. 2014; 6: 185-194.
5. Feitosa ACR, Barreto LT, Silva IMD, Silva FFD, Feitosa GSF. Impact of the use of different diagnostic criteria in the prevalence of dyslipidemia in pregnant women. Arq Bras Cardiol. 2017; 109 (1): 30-38.
6. Pinkas J, Gujski M, Wierzbinska-Stępniak A, Owoc A, Bojar I. The polymorphism of estrogen receptor α is important for metabolic consequences associated with menopause. Endokrynol Pol. 2016; 67 (6): 608-614.
7. Lewandowski KC, Płusajska J, Horzelski W, Lewiński A. Prevalence of dyslipidaemia and pre-diabetes among women with polycystic ovary syndrome (PCOS): do we overestimate cardiovascular risk? Horm Metab Res. 2019; 51 (8): 539-545.
8. Guo Q, Zhou S, Feng X, Yang J, Qiao J, Zhao Y et al. The sensibility of the new blood lipid indicator--atherogenic index of plasma (AIP) in menopausal women with coronary artery disease. Lipids Health Dis. 2020; 19 (1): 27.
9. Ajufo E, Rader DJ. Recent advances in the pharmacological management of hypercholesterolaemia. Lancet Diabetes Endocrinol. 2016; 4 (5): 436-46.
10. Welty FK, Lewis SJ, Friday KE, Cain VA, Anzalone DA. A comparison of statin therapies in hypercholesterolemia in women: a subgroup analysis of the STELLAR study. J Womens Health (Larchmt). 2016; 25 (1): 50-56.
11. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010; 121 (9): 1069-1077.

Correspondence:
Ana Elena Ancona-Vadillo, MD
E-mail: cardioancona@yahoo.com.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100799

Special populations in dyslipidemias: elderly people, children, and patients with chronic kidney disease

Poblaciones especiales en dislipidemias: ancianos, niños y pacientes con enfermedad renal crónica

César Rodríguez-Gilabert, MD, FACC, FAHA*

Lipid lowering therapy is the most efficient way to reduce atherosclerosis associated cardiovascular risk. The intensity and timing for starting treatment may vary according to the individual risk. Children, elderly people, and patients with chronic renal disease, are underrepresented in lipid lowering therapies clinical trials, for this reason there may be different opinions of when initiate treatment and with what level of intensity. These topics will be discussed in this article.

Elderly people (75 and over). Cardiovascular diseases increase with age due to accumulation of risk factors and vascular deterioration. Cholesterol level and blood pressure are the main modifiable risk factors in the elderly (although with less benefit when compare when therapy is implemented at younger ages)**.** The evidence of the effectiveness of lipid lowering therapies to reduce the cardiovascular risk in elderly people comes from meta-analysis in which patients from different trials are grouped. A recent study[1] which included 21,492 patients over the age of 75 years, most of them in secondary prevention, encompassed in 29 trials of cardiovascular outcomes, using a LDL cholesterol-lowering drug. The reported reduction in cardiovascular events was of 26% per each 38 mg/dL reduction of LDL-c (low density cholesterol lipoprotein) (RR 0.74 [95% CI 0.61-0.89]; p = 0.0019), similar to the one found in the underage population, fact that supports the recommendation of the different guidelines that in secondary prevention the initiation of treatment and targets should be the same as the proposed for the rest of the population, decreasing C-LDL levels by more than 50% and reaching targets < 70 mg/dL. Analyzing outcomes in the elderly without cardiovascular disease, a study in persons from 70 to 100 years of age followed in average 7.7 years, a LDL-c higher than 190 mg/dL increases the risk of heart attack by 2.9 times when compared to lower than 115 mg/dL levels and for every 38 mg/dL of LDL-c, the relative risk of myocardial infarction increased 34%,[2] demonstrating that cholesterol elevation at these ages relates to myocardial infarction as in younger people. However, it remains to be demonstrated whether the adequate treatment reduce the risk in the same manner. Another study in primary prevention[3] in 46,864 people of 75 years of age or older, without cardiovascular disease followed by 5.6 years, in whom the use of statins was evaluated, showed a reduction of risk for cardiovascular events by 24% (RR 0.76, 95% CI, 0.65-0.89), but this benefit was only found in people who were diabetic and under 85 years of age. The Jupiter primary prevention study,[4] which analyzed the effect of 20 mg daily of rosuvastatin versus placebo, in patients without cardiovascular events, and C-LDL concentration lower than 130 mg/dL, with different risk factors and high sensitivity C-reactive protein greater than 2 mg/L, showed that in people over the age of 70, the risk reduction of events in the rosuvastatin group was 39% (hazard ratio 0.61;

* Centro Médico Veracruz, Ver. México.

Received:
07/07/2021
Accepted:
13/07/2021

How to cite: Rodríguez-Gilabert C. Special populations in dyslipidemias: elderly people, children, and patients with chronic kidney disease. Cardiovasc Metab Sci. 2021; 32 (s3): s209-s211. https://dx.doi.org/10.35366/100799

[95% CI, 0.46 to 0.82]; p < 0.001). Therefore, the recommendation is to start treatment in primary prevention in patients who are at high risk. If the C-LDL level is > 160 mg/dL, even when there are no other risk factors besides age, it is necessary to consider lipid lowering therapy after discussing with the patient the risks and benefits. It is recommended that the statin treatment starts at a low dose because the metabolic differences and frequent polypharmacy, can increase more statin side effects at this age.

Children, adolescents and young adults: it is known that endothelial alterations that precede atherosclerosis begin in early ages. Studies in children and young people show that fatty streaks and fibrous plaques can occur from early age and these are related to risk factors, being the C-LDL and the non-high-density lipoprotein cholesterol (non-HDL-C) levels the most important. The Bogalusa study, a histopathological essay[5] in children who died accidentally, showed the presence of fatty streaks in 50% of kids between the age of 2 and 15 years, while lesions were present in 85% in subjects between 21 and 38 years old. Fibrous plaques in the coronary arteries were found in 8% of those aged 2 to 15 and 69% in young adults from 26 to 39 years old. The lesions extent was significantly related to LDL-c level, smoking, blood pressure and body mass index.

The Pathobiological Determinants of Atherosclerosis in Youth[6] study, analyzed the anatomical pieces of people killed in accidents and found that between the age of 15 and 24 years old there were already lesions (mostly fatty streaks) in 30 to 60% of the cases. The presence and extension of those lesions depended on the aggregation of risk factors. The most significant were a non-HDL-c > 130 mg/dL level, high blood pressure, obesity, hyperglycemia with glycated hemoglobin ≥ 8% and smoking. The management of risk factors in childhood should, initially, be lifestyle modifications. It is recommended to determine the level of lipids before 10 years of age, since at puberty LDL-c decreases between 10 and 20% and, if possible, have other determination before the age of 20 years. It is considered appropriate a total cholesterol level lower than 170 mg/dL, LDL-c under 100 mg/dL, non-HDL-c below than 120 mg/dL and triglycerides (TG) less than 75 mg/dL.[7] Guidelines advise to start medication treatment in children with familial hypercholesterolemia, where the use of statins has shown clear benefits in patients with LDL-c level ≥ of 190 or ≥ of 160 mg/dL Even if there is a family history of hypercholesterolemia and premature cardiovascular events, there are no studies to date in children or adolescents with *lipid lowering therapies* with LDL-c levels lower than 160 mg/dL. Cumulative hypercholesterolemia exposure in early adulthood is important for future development of atherosclerosis. For every 38 mg/dL of cholesterol elevation at the age of 22, the risk for cardiovascular events rises 1.7 times and 2 times for cardiovascular mortality, 27 to 42 years later.[8] When analyzing cases of myocardial infarction (MI) in young adults, it was seen that most of them were not treated before the MI because they did not meet the guidelines indications for lipid therapy, so the risk was minimized due to their age.[9] In a study of 2,324 patients with myocardial infarction under 55 years of age[9] with average LDL-c around 117 mg/dL (91-143 mg/dL), 46.4% of them qualified according to current recommendations for receiving lipid lower therapy in primary prevention, but only 2.7% of them received it. Guidelines for young population[10] recommend in cases of suspected or proved heterozygous familial hypercholesterolemia to start treatment between the age of 10 and 14 years, preferably with statins and if necessary, ezetimibe, ot proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and keep treatment for life. The initial target should be LDL-C < 130 mg/dL and ideal < 110 mg/dL. Children with LDL-c levels between 100 and 160 mg/dL should be monitored, being strict in adequate lifestyle and if there are family data of premature atherosclerosis disease, it should be analyzed, in conjunction with their families, the possibility of initiating statins before the age of 20. Children with homozygous familial hypercholesterolemia, in general, do not have substantial benefit with the abovementioned therapy (see the section about primary hypercholesterolemia).

Chronic renal failure: any decrease in renal function increases cardiovascular risk, independently of other risk factor. Stage 3 and higher of chronic kidney disease (CKD) should be considered a high-risk condition, even in primary prevention. Renal failure modifies lipids pattern, increasing TG, non-HDL-c, and lipoprotein (a) and reducing HDL-c. Although LDL-C increase only in about 40% of patients with advanced CKD, augments the proportion of small and dense, more atherogenic LDL. Several studies have shown that in patients who are not in dialysis, the use of lipid lowering therapies decrease cardiovascular risk and they are safe. Statins with or without ezetimibe reduced the risk in patients at stage 3 or more, however, data in dialysis patients have not been conclusive.[11] Based on these studies the use of statins with or without ezetimibe is recommended in all patients with renal impairment stage 3-5 (estimated glomerular filtration rate [eGFR] < 60 mL/min per 1.73 m^2). In advanced kidney failure it is not recommended to start treatment when the patient is already in dialysis, but if patients are already taking statins and/or ezetimibe they can continue with treatment. In case of statin intolerance, the PCSK9 inhibitors are safe and effective in these patients. Renal transplant patients are at increased risk of atherosclerotic cardiovascular disease, so it is also considered appropriate to treat them with statins to attain goals according to their risk. In children with renal impairment, treatment with statins and/or ezetimibe after age 18 is suggested, but there are not studies in younger patients.

REFERENCES

1. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet. 2020; 396 (10263): 1637-1643.
2. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70-100 years: a contemporary primary prevention cohort. Lancet. 2020; 396 (10263): 1644-1652.
3. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. BMJ. 2018; 362: k3359.
4. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010; 152 (8): 488-96, W174.
5. Newman WP 3rd, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. N Engl J Med. 1986; 314 (3): 138-144.
6. McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill HCJ. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. Pediatrics. 2006; 118 (4): 1447-1455.
7. Steinberger J, Daniels SR, Hagberg N, Isasi CR, Kelly AS, Lloyd-Jones D et al. Cardiovascular health promotion in children: challenges and opportunities for 2020 and beyond: a scientific statement from the American Heart Association. Circulation. 2016; 134 (12): e236-255.
8. Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY et al. Serum cholesterol in young men and subsequent cardiovascular disease. N Engl J Med. 1993; 328 (5): 313-318.
9. Zeitouni M, Nanna MG, Sun JL, Chiswell K, Peterson ED, Navar AM. Performance of guideline recommendations for prevention of myocardial infarction in young adults. J Am Coll Cardiol. 2020; 76 (6): 653-664.
10. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, hypertension, and obesity in youth committee, council of cardiovascular disease in the young, with the council on cardiovascular nursering. Circulation. 2007; 115 (14): 1948-1967.
11. Tonelli M, Wanner C. Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline. Ann Intern Med. 2014; 160 (3): 182.

Correspondence:
César Rodríguez-Gilabert, MD, FACC, FAHA
E-mail: cesarr@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100800

Statin treatment. The evidence and role in primary and secondary prevention

Tratamiento con estatinas. La evidencia y el papel en la prevención primaria y secundaria

Enrique C Morales-Villegas, MD* Kausik K Ray, MD, M Phil‡

ENDO, GOLDSTEIN, AND BROWN. THE PIONEERS

In 1976, the Japanese biochemist Akira Endo discovered the first statin (ML-236B or compactin), extracted from *Penicillium citrinum*.[1] Four and five years later, Yamamoto and Endo[2] and Mabuchi,[3,4] published the first two clinical trials demonstrating a significant reduction in total cholesterol (TC) and LDL-C with a statin in individuals with familial hypercholesterolemia (FH). During the 1970s, Michael Brown, Joseph Goldstein, and Richard Anderson described a low-density lipoprotein receptor (LDL-R) in cultured fibroblasts and established that mutations in the gene that encode it cause severe hypercholesterolemia and early atherosclerosis in individuals with homozygous and heterozygous HF.[5]

In their Nobel Lecture[6] and their account of the discovery of LDL-R, Goldstein, and Brown[7] summarized a series of investigations whose results marked the beginning of the statin's era, namely:

1. LDL transports 66% of circulating cholesterol.
2. Hepatic LDL-Rs, are designed to recognize apoB100 in the circulating LDL, and by endocytosis, introduce 66% of these lipoproteins into the hepatocyte for the intracellular metabolism of the 1,500 molecules of esterified cholesterol contained in each LDL. LDL-R is encoded by a gene located in the short arm of chromosome 19 (19p13.1-13.3).
3. The concentration of nonesterified cholesterol in the membranes of the hepatocyte's endoplasmic reticulum is the biological signal that initiates transcription and translation processes leading to the synthesis of LDL-R. When this concentration decreases, the expression of the transcription factor called sterol regulatory element-binding protein 2 (SREBP2) initiates the synthesis of LDL-R.
4. Statins recreate the cellular environment that determines LDL-R synthesis by competitively inhibiting HMG-CoA-reductase activity, blocking the cellular synthesis of cholesterol.
5. Thus, statins increase the synthesis of LDL-R, favor the hepatic clearance of LDL, and increase the hepatobiliary elimination of the esterified cholesterol without compromising the cellular concentration of cholesterol.

For his discovery, Akira Endo was «baptized» by Goldstein and Brown as «the father of the penicillin for cholesterol». Recognizing that, the millions of lives saved and prolonged using statins is due to the discovery of compactin.[8]

CTT 2005 AND 2010 META-ANALYSES. EVIDENCE IN 170,000 INDIVIDUALS

The evidence of therapeutic benefit of statins is summarized in the 2005[9] and 2010[10] CTT meta-analyses. These studies evaluated 170,000 individuals, «patient-by-patient», included in 26 statin-era RCTs. For this reason,

* Centro de Investigación Cardiometabólica de Aguascalientes, México.
‡ Imperial Centre for Cardiovascular Disease Prevention, School of Public Health, Imperial College London, London, UK.

Received:
01/07/2021
Accepted:
09/07/2021

How to cite: Morales-Villegas EC, Ray KK. Statin treatment. The evidence and role in primary and secondary prevention. Cardiovasc Metab Sci. 2021; 32 (s3): s212-s216. https://dx.doi.org/10.35366/100800

they are considered one of the strongest scientific evidence for the efficacy and safety of HMG-CoA inhibitors.

CTT 2005 meta-analysis[9]

This first meta-analysis included 90,000 individuals in 14 RCTs and analyzed the benefit of treatment with statins (moderate-intensity statins) versus control or placebo. The now-classic results showed that treatment with statins for five years, with a reduction of 1 mmol/L in LDL-C (≈ 40 mg/dL) is associated with a 20% relative risk reduction for an ASCVD (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and/or coronary revascularization). On average, 0.50% relative risk reduction for each mg/dL decrease in LDL-C *(Figure 1)*.

In recent years, the HOPE-3 trial[11] confirmed the result of the CTT 2005 meta-analysis in individuals with intermediate cardiovascular risk treated with a moderate-intensity statin.

Currently, any moderate-intensity statin (simvastatin 20 mg or 40 mg, atorvastatin 10 mg or 20 mg, or rosuvastatin 5 mg or 10 mg) can reduce the circulating level of LDL-C by 30%. That means an LDL-C reduction of approximately 40 mg/dL in an individual with LDL-C of 120 mg/dL; therefore, it decreases the relative risk of an ASCVD by 20%.

CTT 2010 meta-analysis[10]

Under the hypothesis «lower equals more benefit with equal safety», this second meta-analysis included 170,000 individuals in 26 RCTs analyzed 39,612 individuals in five trials that compared the benefit of treatment with statins (high-intensity statins, like atorvastatin 40 and 80 mg or rosuvastatin 20 and 40 mg) versus moderate-intensity statins. Likewise, the analysis of the benefit of treatment with moderate-intensity statins versus control or placebo was extended to 129,526 individuals included in 21 RCTs (2005 cohort expanded with 7 more RCTs).

In the first subgroup (high-intensity statin vs moderate-intensity statin), with an average LDL-C level of 98 mg/dL, the high-intensity statins showed an additive reduction of 0.50 mmol/L of LDL-C (20 mg/dL) and an additive decrease of 15% in the relative risk of an ASCVD. In the second subgroup (moderate-intensity statin vs. control or placebo), with an average LDL-C level of 143 mg/dL, the result confirmed previous reports on average, 0.50% relative risk reduction of ASCVD for every mg/dL decreased in LDL-C *(Figure 2)*.

In the joint analysis of both subgroups, the benefit of statin treatment for five years with a reduction of 1 mmol/L in LDL-C (40 mg/dL) in the different types of ASCVD was as follows:

1. 24% significant reduction in the relative risk for non-fatal and fatal myocardial infarction.
2. 25% significant reduction in the relative risk for surgical or percutaneous coronary revascularization.
3. 16% significant reduction in the relative risk for stroke, with a significant reduction of 31% in the relative risk for non-fatal ischemic stroke, non-significant reduction for fatal stroke and a non-significant increase of 12% in risk relative for hemorrhagic stroke.
4. 10% significant reduction in the relative risk for all-cause mortality, mainly influenced by the reduction in risk for coronary death. Reduction in risk for non-cardiovascular death was non-significant.

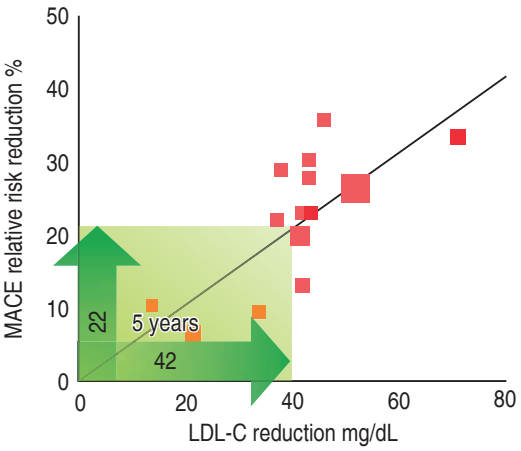


Figure 1: Moderate intensity statin vs placebo or control. Starting from a baseline LDL-C of 147 mg/dL without treatment, 42 mg/dL lower LDL-C with an intermediate-intensity statin equals 22% lower risk of a major adverse cardiovascular event (MACE) over five years of treatment. 40/20 rule.
Modified from: Cholesterol Treatments Trialist's (CTT) Collaboration.[10]

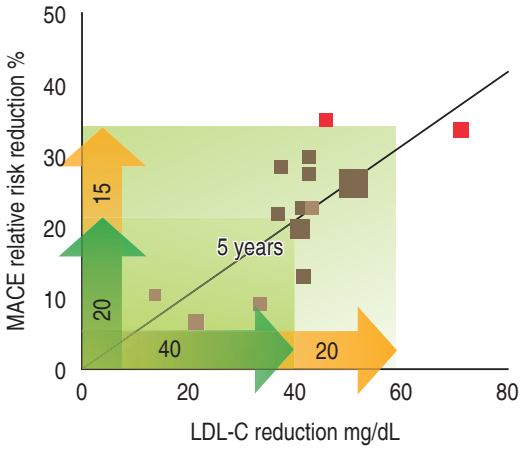


Figure 2: High intensity statin vs moderate intensity statin. Starting from a baseline LDL-C of 98 mg/dL on treatment with a medium-intensity statin, 20 mg/dL lower LDL-C with a high-intensity statin equals an extra 15% lower risk of a major adverse cardiovascular event (MACE) over five years of treatment.
Modified from: Yusuf S et al.[11]

The benefit was homogeneous for the different subgroups, regardless of baseline risk (high, moderate, low), gender (men or women), age (< 75 years or ≥ 75 years), baseline LDL-C (> 100, 70-100 or < 70 mg/dL) and high-density lipoprotein cholesterol (mg/dL percentiles). No subgroup showed an excess risk for any type of cancer. Rhabdomyolysis incidence was 4/10,000 individuals treated with high-intensity statins versus moderate-intensity statins, all of them treated with simvastatin 80 mg, and 1/10,000 individuals treated with moderate-intensity statins versus control or placebo.

The authors concluded that statin treatment for five years, that reduction of 1 mmol/L (40 mg/dL), 2 mmol/L (80 mg/dL) and 3 mmol/L (120 mg/dL) in LDL-C reduced the relative risk of an ASCVD by 20%, 40%, or 50% respectively without a significant increase in the risk of cancer, intracranial hemorrhage and/or rhabdomyolysis.

GUIDELINES FOR HYPERCHOLESTEROLEMIA AND ATHEROSCLEROTIC CARDIOVASCULAR RISK REDUCTION

The guidelines[12,13] for the treatment of hypercholesterolemia and the prevention of ASCVD are based on the following three fundamental concepts:

1. Hypercholesterolemia, understood as an inappropriate or pro-atherogenic level of LDL-C, and not as the average population level (131.5 mg/dL in Mexico), is the most important causal risk factor for an ASCVD.
2. Estimating the absolute risk over ten years is the best strategy with therapeutic benefit for reducing blood LDL-C level and the risk of an ASCVD.
3. To date, statins are the best strategy for reducing LDL-C levels and the risk of an ASCVD.

The way to achieve this goal differs conceptually among the different guidelines. The current American and European recommendations for prescribing statins in secondary and primary prevention are presented separately below.

AHA/ACC 2018 guidelines (recommendations for starting statins)

The recommendations in this guideline[12] are based exclusively on RCT results. It has a strong orientation towards cost-effectiveness, especially for high-cost strategies (ex. monoclonal antibodies vs. PCSK9). It presents the use of therapeutic thresholds (LDL-C value above which a high-cost strategy is justified by cost-effectiveness) and the efficacy of the treatment is based on the percentage of reduction in LDL-C expected with the different strategies (ex. reduction between 30 and 50% with a moderate-intensity statin and ≥ 50% with a high-intensity statin).

The main recommendations for statins are as follows:

1. In individuals ≤ 75 years with ASCVD, the recommendation is to start a high-intensity statin (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg). Recommendation class I, level A.
   In individuals > 75 years or ≤ 75 years intolerant to a high-intensity statin, the recommendation is to start a moderate-intensity statin (atorvastatin 10 or 20 mg,

rosuvastatin 5 or 10 mg, or simvastatin 20 or 40 mg). Recommendation class I, level A.

2. In individuals > 21 years with severe hypercholesterolemia with LDL-C ≥ 190 mg/dL without ASCVD, the recommendation is to start a high-intensity statin. Recommendation class I, level B-R.
   In individuals > 21 years who are intolerant to a high-intensity statin, the recommendation is to start a moderate-intensity statin. Recommendation class IIa, level B-R.
3. In individuals with diabetes mellitus (DM) between 40 and 75 years and LDL-C between 70 and 189 mg/dL, without ASCVD, the recommendation is to start a moderate-intensity statin regardless of the absolute risk level of ASCVD. Recommendation class I, level A.
   With the same age and LDL-C parameters, if the absolute risk of ASCVD at ten years estimated by pooled cohort equations (PCE) is ≥ 20%, the recommendation is to start a high-intensity statin. Recommendation IIa, level B-NR.
4. In individuals between 40 and 75 years and LDL-C between 70 and 189 mg/dL, without ASCVD or DM, with an absolute risk of ASCVD at ten years estimated by the PCE between 7.5 and 19% (intermediate risk), the recommendation is to start a moderate-intensity statin. Recommendation class I, level A.
   With the same age and LDL-C parameters, if the absolute risk of ASCVD at ten years estimated by the PCE is ≥ 20%, the recommendation is to start a high-intensity statin. Recommendation class I, level A.

ESC/EAS 2019 guidelines

Beyond RCT results, the recommendations in this guideline[13] are based on all the evidence that supports the «LDL-centric» principle. It does not consider cost-effectiveness analysis for any strategy. Treatment efficacy is based on target LDL-C values (ex. < 116, < 100, < 70, and < 55 mg/dL for low, moderate, high, and very high-risk individuals, respectively).

The main recommendations for statins are as follows:

1. In very-high-risk individuals with a history of myocardial infarction, unstable angina, stable angina, stroke, cerebral hemorrhage, transient ischemia, peripheral arterial disease, and/or arterial revascularization, start a high-intensity statin, or the maximum tolerated dose with a goal of < 55 mg/dl of LDL-C. Recommendation class I, level A.
2. In individuals at very-high-risk with subclinical atherosclerosis by CT angiography or arterial ultrasound with ≥ 50% stenosis, type 1 or type 2 DM with microangiopathy and/or ≥ 3 risk factors, type 1 DM with ≥ 20 years of evolution, chronic kidney disease (CKD) stages IV-V, FH with ASCVD or ≥ 1 risk factors, or risk estimated by SCORE ≥ 10%, start a high-intensity statin or the maximum tolerated dose with a goal of < 55 mg/dL of LDL-C. Recommendation class I, level C.
3. In individuals at high-risk with TC ≥ 310 mg/dL, LDL-C ≥ 190 mg/dL, blood pressure ≥ 180/≥ 110 mmHg, type 1 or type 2 DM with ≥ 10 years of evolution, without microangiopathy and < 3 risk factors, CKD stage III, FH without ASCVD, and without other risk factors or risk estimated by SCORE ≥ 5% and < 10%, start a high-intensity statin or the maximum tolerated dose with the goal of < 70 mg/dL of LDL-C. Recommendation class I, level A.
4. In individuals at moderate-risk with type 2 DM with < 50 years of age and < 10 years of evolution, without microangiopathy and without risk factors, type 1 DM with < 35 years of age or risk estimated by SCORE ≥ 1 and < 5%, start a high-intensity statin, or the maximum tolerated dose with a goal of < 100 mg/dL of LDL-C. Recommendation class IIa, level A.
5. In low-risk individuals with a risk estimated by SCORE < 1%, start a high-intensity statin, or the maximum tolerated dose with a goal of < 116 mg/dL of LDL-C. Recommendation class IIb, level A.

REFERENCES

1. Endo A, Kuroda M, Tsujita Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by *Penicillium citrinium*. J Antibiot (Tokyo). 1976; 29 (12): 1346-1348.

2. Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis. 1980; 305: 259-266.
3. Mabuchi H, Haba T, Tatami R, Miyamoto S, Sakai Y, Wakasugi T et al. Effect of an inhibitor of 3-hydroxy-3-methyglutaryl coenzyme A reductase on serum lipoproteins and ubiquinone-10-levels in patients with familial hypercholesterolemia. N Engl J Med. 1981; 305 (9): 478-482.
4. Brown MS, Goldstein JL. Lowering plasma cholesterol by raising LDL receptors. N Engl J Med. 1980; 305: 515-517.
5. Goldstein JL, Brown MS. Lipoprotein receptors: genetic defense against atherosclerosis. Clin Res. 1982; 30: 417-426.
6. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Nobel Lecture, 9 December 1985. Available in: https://www.nobelprize.org/prizes/medicine/1985/summary/
7. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009; 29 (4): 431-438.
8. Brown MS, Goldstein JL. A tribute to Akira Endo, discoverer of a "penicillin" for cholesterol. Atherosclerosis. 2004; 5: 13-16.
9. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005; 366 (9493): 1267-1278.
10. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376 (9753): 1670-1681.
11. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016; 374 (21): 2021-2031.
12. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 73 (24): 3168-3209.
13. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-188.

Correspondence:
Enrique C Morales-Villegas, MD
E-mail: drmorvi@prodigy.net.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100801

Current treatment beyond statins in hypercholesterolemia: the lower the better in prevention of atherosclerotic diseases

Tratamiento actual más allá de las estatinas en la hipercolesterolemia: cuanto más bajo mejor en la prevención de las enfermedades ateroscleróticas

Enrique Benito Gómez-Álvarez, MD* Alejandro Alcocer-Chauvet, MD‡
Kevin René Hernández-Flores, MD§

INTRODUCTION

Until 2020 and the appearance of COVID-19, atherosclerotic cardiovascular disease (ASCVD) still was one of the leading causes of death worldwide. One of its most important risk factors is dyslipidemia and the associated increase in low-density lipoprotein cholesterol (LDL-c) level. Statins via their mechanism of action inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase blocking the cholesterol synthesis in the liver, lowering the low-density lipoprotein cholesterol up to 50% depending on the statin therapy intensity (moderate or high). Over the last decades, the use of statins has lowered the risk of ASCVD by 37%,[1] consequently placing statins as the first-line drug of choice in the treatment of dyslipidemia. The use of statins has demonstrated both in large randomized controlled trials and epidemiologic studies reduction in major cardiovascular events.

The American College of Cardiology and the American Heart Association 2018 guidelines recognize that with higher reductions in density lipoprotein cholesterol with statin therapy, the benefit will have a major impact on patients clinical course.[1] However, there is a group of patients with special needs and residual risk, such as those with severe primary, genetic dyslipidemias like familial hypercholesterolemia or those with intolerance or adverse reactions to statins,[2] in whom the therapy goals with high-intensity statin therapy are not met and therefore are still at risk of recurrent ASCVD.

Breakthroughs in the development of new drugs have provided alternatives such as injectable biological products, and RNA-based therapies which offer the possibility of less frequent dosage prescriptions. Among the non-statin therapies, there are two alternatives which have shown additional LDL-c levels cardiovascular eve reduction and prevention of residual risk of nts, namely ezetimibe and in the case that the therapeutic goals are not met, the anti-PCSK9 monoclonal antibodies (mabs-PCSK9).[3] The following review addresses the mechanism of action, clinical indications, and current evidence supporting the use of these drugs.

EZETIMIBE

Mechanism of action

The first known mechanism of action was to inhibit the enzyme acyl-coenzyme cholesterol acyltransferase known as ACAT, however, during its development, it was demonstrated that ezetimibe inhibits the uptake of cholesterol in the small intestine where it binds to a transporter protein identified as Niemann-Pick C1-Like 1. This protein is the only intestinal entrance

* Chief of Cardiology, CMN 20 de Noviembre, ISSSTE. Mexico.
‡ Interventional Cardiology, Hospital Regional 1º de Octubre, ISSSTE. Mexico.
§ Cardiology Fellow, CMN 20 de Noviembre, ISSSTE. Mexico.

Received:
01/07/2021
Accepted:
16/07/2021

How to cite: Gómez-Álvarez EB, Alcocer-Chauvet A, Hernández-Flores KR. Current treatment beyond statins in hypercholesterolemia: the lower the better in prevention of atherosclerotic diseases. Cardiovasc Metab Sci. 2021; 32 (s3): s217-s224. https://dx.doi.org/10.35366/100801

gate for all type of sterols; so cholesterol, oxysterols and phytosterols compete to enter the enterocyte, reducing thereby cholesterol absorption. NPC1L1 proteins are not only found in the intestine but are also greatly expressed in the liver where ezetimibe, and its metabolite ezetimibe-glucuronide, reduce the reabsorption of cholesterol from bile.[4]

How does this process unfold, step-by-step? After ingestion, 80% of ezetimibe undergoes a biochemical process of glucuronidation, being the enzymes responsible for this step the intestinal glucuronosyltransferases in the liver, forming a complex ezetimibe-glucuronide which has more affinity for the NPC1L1 transporter than the original compound. Both, trough the entero-hepatic cycle. Secondarily, some phytosterols and phytostanols activate other type of membrane proteins, the ATP-binding cassettes transporters (ABCC2, ABCC3, and ABCG2) which expel the already absorbed cholesterol to the intestine lumen.

The estimated half-life of ezetimibe and its metabolite is around 22 hours.[4]

In conclusion: ezetimibe is a specific inhibitor of the cholesterol transporter found in the brush border of the enterocyte (NPC1L1). By inhibiting this transporter ezetimibe causes a decrease in the absorption of cholesterol and precipitates a decrease of decrease of serum LDL-c cholesterol. In addition, ezetimibe blocks also de liver NPC1L1, impeding the excess of biliary cholesterol *(Figure 1)*.[3,4]

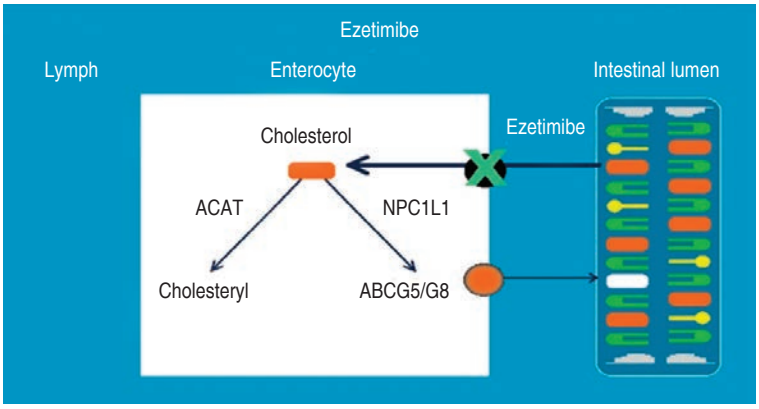


Figure 1: Mechanism of action of ezetimibe.
NCP1L1 = Niemann-Pick CIL1 protein; ABC G5 and G8, proteins of the ABC (ATP-bound cassettes) superfamily. Modified from: Lipids Online Slide Library.

Drug tolerability

Given that its main effect is exerted in the enterohepatic system, its systemic exposition is limited, which leads to a low potential for adverse drug interactions.[5] Ezetimibe presents some pharmacological interactions. Its bioavailability increases when it is co-administered with gemfibrozil, fenofibrate or cyclosporine.[4] Notably, ezetimibe is a well-tolerated drug with lower intolerance and hepatic impairment rate than statins.[5]

Impact of ezetimibe in atherosclerosis: is there a difference to statins?

Ezetimibe may or may not act in different atherosclerotic pathways than statins, therefore impacting the risk of atherosclerotic cardiovascular events; the pathways involved are briefly summarized below *(Figure 2)*.

Effects in blood lipids: ezetimibe has been shown to reduce low-density lipoprotein levels up to 22.3% compared to placebo. This effect is added to the lowering action of statins, so in some studies a reduction from 35 to 60% has been shown. In addition, produce beneficial effects on high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) and apolipoprotein B100.[5,6]

Effects on glucose metabolism: the beneficial effect of ezetimibe on glucose metabolism cannot be asserted, as there are no studies to prove it, emphasize that its benefit on the incidence of type 2 diabetes mellitus is not clear.[6]

Inflammation: inflammation is an important component of the process of atherogenesis. Several randomized controlled trials have investigated the effect of ezetimibe alone or in combination with statins in the reduction of high-sensitivity CRP (hs-CPR), but the available data from various meta-analyzes do not conclude a significant effect on hs-CRP levels when used as monotherapy.[5]

Platelet aggregation: even though statin therapy has been associated with reduced platelet aggregation due to their pleiotropic effects and a mechanism that is LDL independent, no such effect has been demonstrated with ezetimibe as monotherapy.[6]

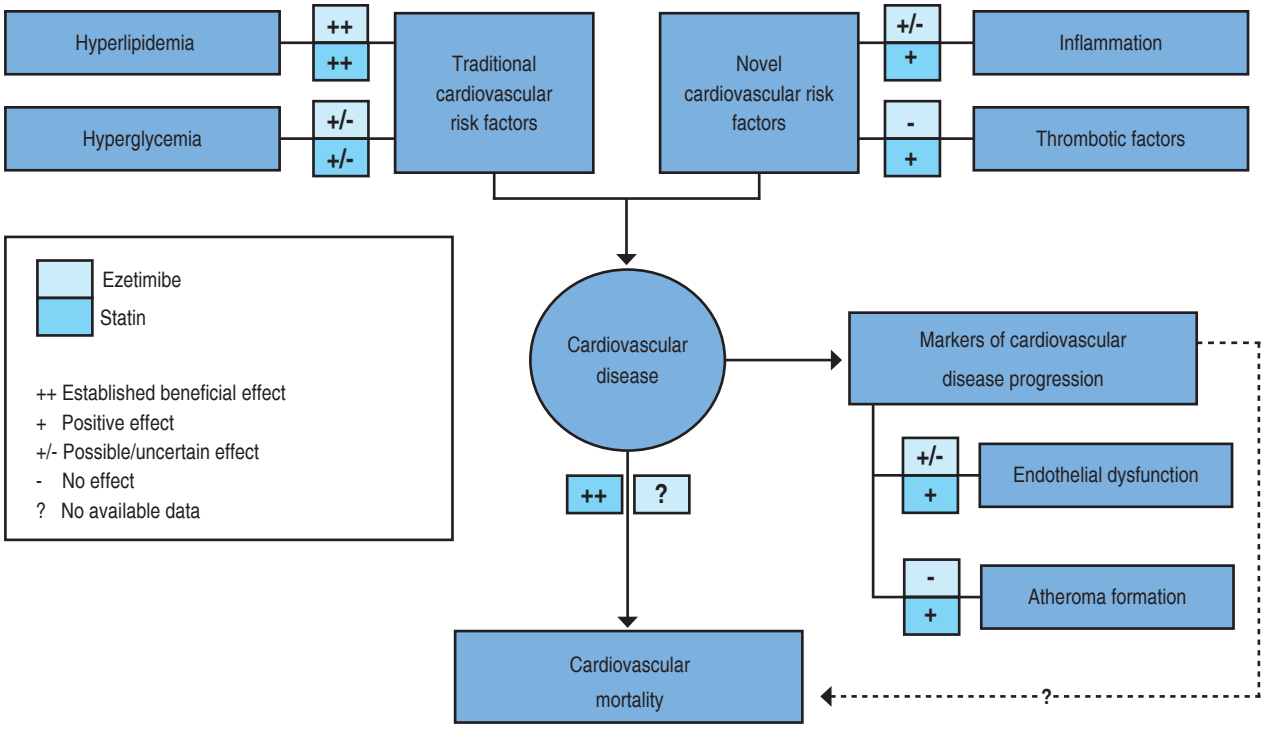


Figure 2: Established or possible cooperative actions of statins and ezetimibe to reduce CV risk. Modified from: Al Badarin FJ et al.[6]

Indications and clinical evidence

The American College of Cardiology and the American Heart Association 2018 guidelines recognize the importance of the adequate management according to individualized risk of major cardiovascular events (MACE) in patients with a history of ischemic heart disease, ischemic cerebrovascular disease or peripheral arterial disease. In these patients, low-density lipoproteins should be reduced vigorously to optimal levels. The more it is reduced the better. As an example, in a high-risk patient, the recommended therapeutic goal of proposed low-density lipoprotein levels is less than 70 mg/dL or a reduction of 50% compared to baseline.[7]

The importance of using ezetimibe or mabs-PCSK9 if therapeutic goals of LDL-C have not been reached was previously mentioned. Ezetimibe, has specific indications for the reduction of total cholesterol (TC), low-density lipoproteins, and apolipoprotein B, in the following scenarios: primary hyperlipidemia, either alone or in combination with statins, mixed hyperlipidemia when co-administered with fenofibrate, and homozygous familial hypercholesterolemia co-administered with statins, in order to reduce total cholesterol and low-density lipoproteins.[5] The suggested dose, which is 10 mg/day, should be prescribed, with the advantage that it can be administered at any time since it has no direct effect on statin potency or metabolism. The patient should be followed every three to six months *(Table 1)*.[8]

PROPROTEIN CONVERTASE SUBTILISIN/ KEXIN TYPE 9 INHIBITORS

Mechanism of action. The role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in the metabolism of LDL-C was discovered after identifying a gain of function in mutations in PCSK9 in some French families with familial hypercholesterolemia, while mutations in other genes had previously been ruled out.[9,10] Posteriorly, other investigators showed that subjects carrying PCSK9 loss-of-function (LOF)

mutations, after discarding the inhibition in the synthesis and/or the absorption of cholesterol as the determinant factors, reduced LDL-C levels, with a lower rate of cardiovascular events.[11] All of these evidences were the basis for investigations on a potential pathway for efficient therapies to further reduce the LDL-C levels, beyond the currently used therapies.[9]

Step-by-step mechanism of action. LDL-C receptors (LDL-R) are synthesized mainly in the liver. The synthesis is regulated by the transcription factor SREBP2 dependent on the intracellular levels of cholesterol (less intracellular cholesterol yields to more SREBP2 transcription, more LDL-R units, more, and less blood cholesterol levels. After its synthesis, the LDL-R is inserted in the hepatocyte cell surface where it captures LDL-C particles and internalizes them forming an endosome. Lastly, the endosome will fuse with lysosomes, whose enzymes degrade LDL-c particles. The LDL-R withstands the enzymatic action of degradation and is recycled to the cellular surface. This recycling process can occur up to 150 times in 24 hours.

What is the role of the PCSK9? The PCSK9 protein is released into the circulation after being synthetized in the liver and the intestine, it is also regulated by the SREBP2 factor transcription. PCSK9 account as a counter-regulatory protein

Table 1: Summary the main clinical studies that evaluated combined therapy with ezetimibe and statin vs statin alone.

Study	ENHANCE (2008) Phase III	SHARP (2011) Phase III	IMPROVE-IT (2015) Phase III
Intervention	Simvastatin 80 mg daily or a combination of simvastatin 80 mg + ezetimibe 10 mg daily	Simvastatin 20 mg vs ezetimibe/ simvastatin 10 mg/20 mg	Simvastatin 40 mg vs ezetimibe/ simvastatin 10 mg/40 mg
Patient population	720 patients with familial hypercholesterolemia and LDL-C ≥ 210 mg/dL	9,270 patients with chronic kidney disease with no known history of myocardial infarction or coronary revascularisation	18,144 patients hospitalized in the last 10 days for an ACS, who were 50 years or older, low-density lipoprotein levels between 50 and 100 mg/dL if they received lipid-lowering therapy or 50 to 125 mg/dL if they did not receive lipid-lowering therapy
Duration	24 months	4.9 years	6 years
Primary endpoint	Increase in carotid intima-media thickness (cIMT)	Major vascular events (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) and progression to ESRD (in nondialysis patients)	Composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (≥ 30 days after randomization), or nonfatal stroke
Results	Change in the cIMT was 0.0058 ± 0.0037 mm in the simvastatin-only group and 0.0111 ± 0.0038 mm in the combined-therapy group	Combined therapy produced a 17% proportional reduction in major atherosclerotic events (11.3% simvastatin plus ezetimibe vs 13·4% placebo; rate ratio [RR] 0·83, 95% CI 0·74-0·94; log-rank p = 0.0021)	Rate for the primary end point at 7 years was 32.7% in the simvastatin-ezetimibe group, as compared with 34.7% in the simvastatin-monotherapy group (absolute risk difference, 2.0 percentage points; hazard ratio, 0.936; 95% confidence interval, 0.89 to 0.99; p = 0.016)

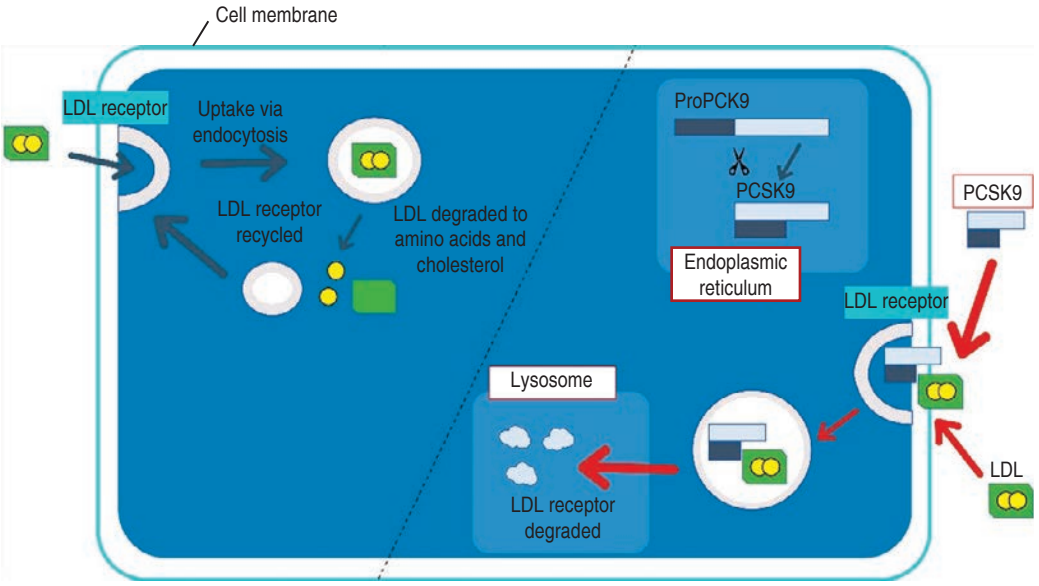


Figure 3:

Mechanisms of action of PCSK9 inhibitors. Modified from: Ogura M.[11]

(Ying-Yang), by preventing the excess of intracellular cholesterol and its potential cytotoxic effects, due to the increased LDL-R synthesis and expression, by means of maintaining the LDL-R levels controlled and constant. After being released, PCSK9 binds to LDL-R and prevents the receptor from adopting its spatial configuration necessary to avoid degradation *(Figure 3)*.

The result is that the number of LDL-R diminishes, and by doing so, the capacity of the liver of clearing circulating LDL particles. PCSK9 inhibitors are produced with the replacement of genomic sequences between mice and humans. First, the genomic sequences that encode the synthesis of immunoglobulins are eliminated in the mouse and these are replaced by human genomic sequences; in this way, MABs-PCSK9i (complete human monoclonal antibodies) are produced, «the mouse produce full human immunoglobulins» with the advantage that an immune response is not generated from the human host to neutralize its effects. The MABs-PCSK9i while in the plasma avoid the PCSK9 union to the LDL-R, blocking its effects on the receptor and its recycling. Therefore the receptor can extend its biological cycle resulting in increased concentration of LDL-R in the cell surface, producing a better internalization capacity of LDL particles, and more degradation of LDL particles, finally decreasing the LDL-c blood levels.[12]

Security and tolerability

Currently, there are two MABs-PCSK9i, alirocumab and evolocumab both of which are human monoclonal antibodies. Both drugs are safe and minimal adverse reactions have been reported, including some very common such as injection site pain and nasopharyngitis. Interestingly, the risk of myalgias or muscular toxicity is low, thus making them an excellent option when there is a history of statin-associated myopathy. Also, no statistical significance has been found regarding neurocognitive disorders (delirium, dementia, amnesic conditions, or cognitive alterations), even with very low LDL cholesterol levels.[13]

Clinical evidence

Several large randomized, controlled trials have studied the use of MABs-PCSK9, among which the most important is the FOURIER trial, in which more than 27,000 patients with atherosclerotic cardiovascular disease and low-density lipoprotein levels outside of adequate or optimal ranges despite high-intensity statin treatment, were randomly assigned to a PCSK9 inhibitor (evolocumab) or placebo. The other important trial is ODYSSEY study. Outcomes which confirmed

the benefit of alirocumab in reducing the risk of atherosclerotic cardiovascular disease *(Table 2)*.

Indications and therapeutic algorithm

The European Society of Cardiology 2019's update guidelines, suggest that patients with high cardiovascular risk should achieve blood LDL cholesterol levels in the blood of 70 mg/dl, but there is in a group of patients with a higher risk known as very high risk, even further reductions are recommended (55 mg/dL or less). Therefore, to achieve these very challenging goals, the great majority of patients will require the addition of potent pharmacological agents.

According to the European Society of Cardiology (ECS), patients can be classified according to their risk of major cardiovascular events, emphasizing two determining groups: high risk and very high risk. Each group different characteristics, thus, high-risk patients are those with a SCORE qualification between 5% and 10%, TC ≥ 310 mg/dL, LDL-c ≥ 190 mg/dL, blood pressure ≥ 180 mg/dL, chronic kidney disease with glomerular filtration rate between 30 and 59 mL/min and diabetic patients without damage to target organs, or more than 10 years after diagnosis. Finally, there are included patients with familial hypercholesterolemia without other major risk.

The other group of patients are those at very high risk, who present a risk SCORE greater ≥ 10%, familial hypercholesterolemia but with significant risk factors, chronic kidney disease with a glomerular filtration rate less than 30 mL/min, diabetics with damage to target organs or type 1 diabetics lasting more than 20 years. Obviously, all of these are characteristics that suggest a very high risk of cardiovascular events, so control must be optimal.[9]

In general, the indications by the ESC suggested that the use of PCSK9i can be divided into primary and secondary prevention: all patients with a very high risk, in the context of primary prevention, without a history of familial hypercholesterolemia, whom do not reach the goal of LDL cholesterol with statins at the maximum tolerated dose plus ezetimibe, adding a PCSK9 inhibitor may be considered.

Table 2: Main clinical studies that evaluated therapy with PCSK9i.

Study	FOURIER (2017)	ODYSSEY outcomes (2018)
Intervention and design	Evolocumab (either 140 mg every 2 weeks or 420 mg monthly) vs placebo 1:1 randomization with 69% px in high-intensity therapy, 31% moderate or low-intensity, and 5% ezetimibe	Alirocumab subcutaneously 75 mg every 2 weeks vs placebo 1:1 randomization with 89% px in high-intensity therapy, 8% moderate or low-intensity, and 3% ezetimibe
Patient population	27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg/dL or higher who were receiving statin therapy	18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, who were previously under optimal tolerated treatment with high-intensity statins, but with serum levels of non-HDL cholesterol of at least 100 mg/dL, apolipoprotein B of at least 80 mg/dL, or LDL cholesterol of at least 70 mg/dL
Duration	2.2 years	2.8 years
Median cholesterol baseline value	92 mg/dL	92 ± 31 mg per deciliter
Primary endpoint	Composite of cardiovascular death, myocardial infarction, stroke, unstable angina that requires hospitalization, or coronary revascularization	Composite of cardiovascular death, non-fatal myocardial infarction, fatal or nonfatal ischemic stroke, angina that requires hospitalization
Results	Evolocumab treatment significantly reduced the risk of the primary end point from 11.3% to 9.8% (hazard ratio 0.85; 95% CI; p < 0.001)	Alirocumab treatment reduced the risk of composite primary end-point event from 11.1% to 9.5% (HR 0.85; 95% CI, 0.78 to 0.93; p < 0.001)

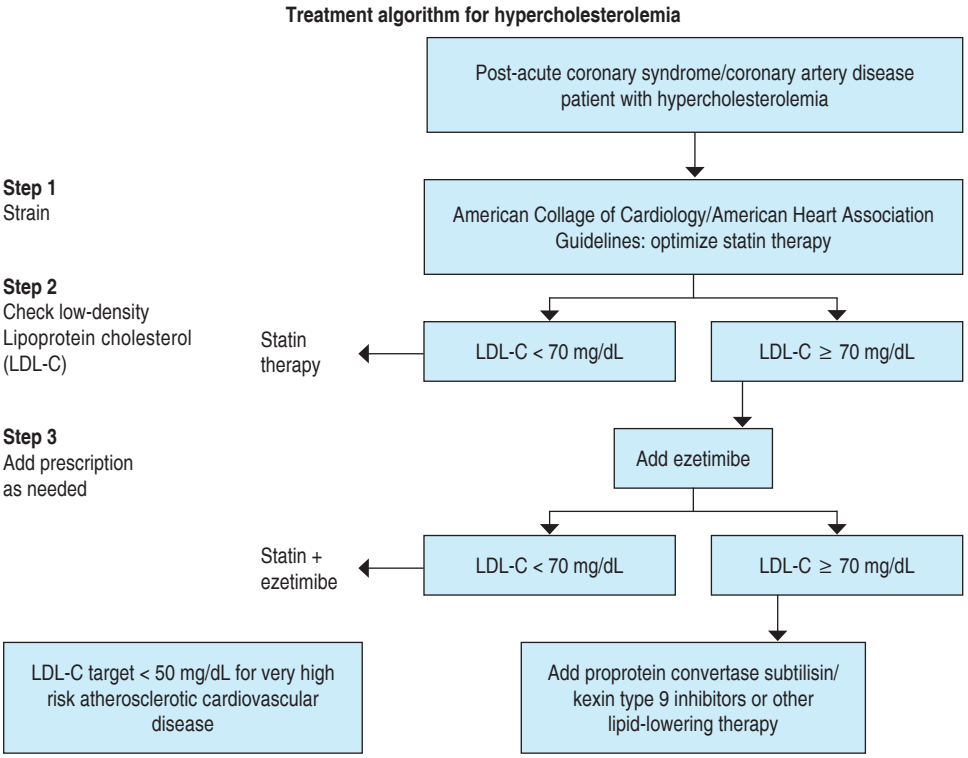


Figure 4:

An algorithm for the treatment of hypercholesterolemia. Modified from Rosenson et al.[9]

However, the indication is even stronger in the context of secondary prevention, since it is highly recommended to add a combination with PCSK9 inhibitor in high risk patients who do not achieve objectives despite the use of statins at the maximum tolerated dose plus ezetimibe. In the setting of patients with documented familial hypercholesterolemia, the combination of a PCSK9 inhibitor is also recommended in case the goals with statins plus ezetimibe at the maximum tolerated dose are not achieved. In case the patient does not tolerate a statin regimen at any dose, should be considered the use of a PCSK9 inhibitor.[9]

Finally, we have the following scenario: high-risk patients with acute coronary syndrome, the ESC recommends with a high level of evidence to add a PCSK9 inhibitor if the therapeutic goals of LDL cholesterol are not reached at four or six weeks with statins at the maximum tolerated dose plus ezetimibe. The level of evidence is lower in patients with acute coronary syndrome, who were already taking a maximum tolerated dose of statin plus ezetimibe, but who did not have optimal LDL cholesterol levels at the time of the event, in this scenario we should considered adding a PCSK9 inhibitor early during hospitalization.[9]

Figure 4 describes the level of evidence and therapeutic algorithm suggested by current 2018 guidelines by the American College of Cardiology and American Heart Association and the European Society of Cardiology 2019's update.[14,15]

CONCLUSIONS

In conclusion, despite the use of statins and their benefits, reducing the rate of ASCVD, the concept of residual atherosclerotic risk is very important in a specific group of patients who cannot achieve therapeutic goals of LDL-c, even with the maximum dosage of statins, or who are intolerant to them. In those patients, both; ezetimibe and MABs-PCSK9 have sufficient evidence that justifies their use and ultimately demonstrates their importance in reducing significantly atherosclerotic cardiac events, making these drug classes an excellent therapeutic option in addition to their tolerability and security.

REFERENCES

1. Choi JY, Na JO. Pharmacological strategies beyond statins: ezetimibe and PCSK9 inhibitors. J Lipid Atheroscler. 2019; 8 (2): 183-191.
2. Landmesser U, Chapman MJ, Stock JK, Amarenco P, Belch JJF, Borén J et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J. 2018; 39 (14): 1131-1143.
3. Ray KK, Corral P, Morales E, Nicholls SJ. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. Lancet. 2019; 394 (10199): 697-708.
4. Ma YB, Chan P, Zhang Y, Tomlinson B, Liu Z. Evaluating the efficacy and safety of atorvastatin + ezetimibe in a fixed-dose combination for the treatment of hypercholesterolemia. Expert Opin Pharmacother. 2019; 20 (8): 917-928.
5. Agarwala A, Kajani Z, Miedema MD, Virani SS. The role of ezetimibe in the treatment of cardiovascular disease. Curr Atheroscler Rep [Internet]. 2016; 18 (2). Available in: http://dx.doi.org/10.1007/s11883-016-0560-y
6. Al Badarin FJ, Kullo IJ, Kopecky SL, Thomas RJ. Impact of ezetimibe on atherosclerosis: Is the jury still out? Mayo Clin Proc. 2009; 84 (4): 353-361.
7. Correction to: Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2019; 73 (24): 3234-3237.
8. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-188.
9. Rosenson RS, Hegele RA, Fazio S, Cannon CP. The evolving future of PCSK9 inhibitors. J Am Coll Cardiol. 2018; 72 (3): 314-329.
10. Stoekenbroek RM, Kastelein JJP, Huijgen R. PCSK9 inhibition: the way forward in the treatment of dyslipidemia. BMC Med. 2015; 13 (1): 258.
11. Ogura M. PCSK9 inhibition in the management of familial hypercholesterolemia. J Cardiol. 2018; 71 (1): 1-7.
12. Steffens D, Bramlage P, Scheeff C, Kasner M, Hassanein A, Friebel J et al. PCSK9 inhibitors and cardiovascular outcomes. Expert Opin Biol Ther. 2020; 20 (1): 35-47.
13. Sabatine MS, Giugliano RP, Wiviott SD. for the open-label study of long-term evaluation against ldl cholesterol (OSLER) investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015; 372: 1500-1509.
14. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. J Am Coll Cardiol. 2019; 73 (24): e285-e350.
15. Dixon DL, Pamulapati LG, Bucheit JD, Sisson EM, Smith SR, Kim CJ et al. Recent updates on the use of PCSK9 inhibitors in patients with atherosclerotic cardiovascular disease. Curr Atheroscler Rep. 2019; 21 (5): 16.

Correspondence:
Enrique Benito Gómez-Álvarez, MD
E-mail: egomezal@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100802

Present and future of the hypolipidemic treatment, new molecules in sight

Presente y futuro del tratamiento hipolipemiante, nuevas moléculas a la vista

Úrsula Medina, MD, PhD* Rafael Almendra-Pegueros, RD, BSc‡
Antonio Gordillo-Moscoso, MD, PhD*

INTRODUCTION

In Mexico, despite dietary and pharmacological interventions, dyslipidemias represent a public health problem, the most prevalent are elevated LDL-C and hypoalphalipoproteinemia, highlighting the phenotype of elevated triglycerides/low HDL-C in men and women between 40 and 59 years old (43.3% and 43.7%, respectively). However, it is even more alarming, the low number of patients under treatment, of only 3.7%.[1]

Therefore, considering the substantial risk of associated cardiovascular events, it is necessary to perform an analysis of current and emerging therapies. In this way, it is intended to identify those with therapeutic potential, that have regulatory approval, quality control necessary in the development of any drug and that may in the future be accessible to the population.[2]

DEVELOPMENT OF NEW DRUGS

The development of new drugs starts with an exhaustive search of new molecules, that can interact with receptors, enzymes, proteins, and genes involved in the physiopathology of dyslipidemia. These molecules could be considered as molecules candidates for hypolipidemic treatment.

The process for considering a molecule as a New Molecule Candidate (NMC), from discovery to market can last more than 12 years *(Figure 1)*. It is crucial to consider the necessary economic investment that is required for the development that increases as the discovery and development processes become more complex. This is point to consider in the decision-making for the implementation of new pharmacological therapies since if the cost/benefit is high (not adequate), patient will not achieve an adequate attachment and therefore, success rate will be reduced.[3]

DISCOVERY PHASE

At this stage, study objective is defined and a new NMC is proposed. This can be based on 1) efficacy similar to other drugs authorized, 2) genetic evidence of interaction in the disease, 3) involvement in components of a specific physiopathology and, 4) selective analysis of synthesized compounds capable of interact with a therapeutic target.

DEVELOPMENT OR PRE-CINICAL PHASE

Once NMC have been postulated, they must demonstrate specific efficacy and safety characteristics according to the molecule type (chemical, biological, biotechnological). Pharmacokinetic properties should be reproducible and demonstratable in multiple laboratory trials, at different therapeutic doses, in different study models (in vitro, animal models), under conditions as physiologically similar to the specific pathology and should provide information on the occurrence of adverse effects, before starting human testing. NMC whose effects become reproducible

* Laboratorio de Investigación Traslacional en Farmacología, Facultad de Medicina, Universidad Autónoma de San Luis Potosí. Mexico.
‡ Escuela de Ciencias de la Salud, Universidad del Valle de México, Campus San Luis Potosí. Mexico.

Received:
03/07/2021
Accepted:
12/07/2021

How to cite: Medina Ú, Almendra-Pegueros R, Gordillo-Moscoso A. Present and future of the hypolipidemic treatment, new molecules in sight. Cardiovasc Metab Sci. 2021; 32 (s3): s225-s230. https://dx.doi.org/10.35366/100802

and meet the above conditions must submit a results report and starts the clinical phase to seek approval from major regulatory agencies (FDA, EMA, COFEPRIS).

However, the lack of trial reproducibility is the main limitation. Around 90% of NMC do not meet these requirements and have pharmacokinetic/pharmacodynamic deficiencies, in vitro/in vivo toxicity, or lack of efficacy and therefore they are not promoted to the next stage of development.

CLINICAL PHASE

This phase consists of four stages and involves human testing. Phase I is performed in a small group of healthy volunteers (< 100). The objective of phase I is to determine signs of acute toxicity. The average time is around six to 12 months. Main limitation of this phase is the recruitment of study subjects since they are usually young men with weight and average size (170 cm/70 kg).

In phase II, the drug is administered in groups of patients with an early stage of the study pathology (100-200). The objective is to verify the effectiveness of the candidate drug in the proposed pathology. It is usually performed by comparing the new formulation against placebo or the current therapeutical gold standard. The average development time is two to three years. The main limitations are the tests are performed realized in patients in the early stages of pathology evolution and without previous data of failure to standard treatment.

Phase III is carried out in multiple research centers, in different populations (100-1,000), with a diversity of characteristics. The objective is to verify safety and efficacy profiles and detect toxicity not previously manifested. The average development time of this phase is three to five years because it depends on specific selection criteria. The last phase (phase IV) is performed after authorization of the drug. The main objective is to perform pharmacovigilance and detect rare and long-term adverse effects.

Despite the high investment in the development of new pharmacological agents, many of them have failed. To improve the translational pharmacology scope, Horvath P et al, 2016 proposes that before seeking a new goal or proposing a new pharmacological target, the following points must be reviewed: 1) adequate cell lines or preclinical models, 2) population where they will be developed, 3) improve statistical and methodological robustness in both previous points and 4) safety and toxicity problems because cardio or hepatotoxic effects are mainly evidenced in post-authorization phase.

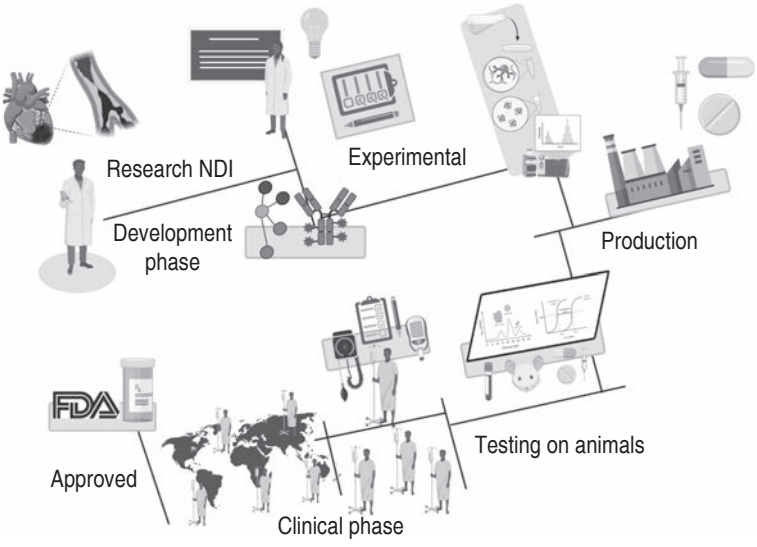


Figure 1: Drug development phases.

THERAPEUTIC TARGET MOLECULES: THEIR USEFULNESS AND SEARCH

The descriptive work on the cholesterol cycle and its relationship to atherosclerotic disease in subjects with homozygote familial hypercholesterolemia, carried out by Goldstein and Brown in 1970, in conjunction with reports from the Framingham Study, determined the importance of lowering serum cholesterol levels for the prevention and treatment of vascular atheromatic disease.[4] Dietary changes demonstrated little effect on cholesterol level in family hypercholesterolemic patients, leading to an increased interest in endogenous cholesterol synthesis at liver level as a cause of pathological serum lipids increase.

The first pharmacological approach to reduce serum lipids was the use of dietary fibers and fat-absorbing resins that decrease

cholesterol absorption at the intestinal level. It's non-specific and modest antilipidemic effect was associated with significant adverse effects at gastrointestinal level.

In 1980, a molecule to specifically alter serum cholesterol levels by interfering with its synthetic pathway was used. Akira Endo et al[5] described the effects of the compound **ML-236B** (lovastatin-competitive inhibitor of the 3-hydroxy-3-methyl glutaryl CoA reductase enzyme), in subjects with primary hypercholesterolemia. An average of 27% reduction in serum cholesterol levels was observed. Since then, the strategy to decrease cholesterol levels and particularly its most atheromatous subfraction: low-density cholesterol (LDL-C), has focused on identifying key proteins in exogenous, endogenous, and reverse phases of the cholesterol cycle. The basis for such therapeutic orientation is that a specific blockage or functional alteration, will result in a reduction in serum concentrations. This blockage will prevent the formation of obliterating atheroma and/or decrease its size in a long-term form.

Identification and validation of these proteins as modifiable targets allows performing designs and simulations *in silico*, biochemical or molecular synthesis, or genetic engineering techniques initially tested in cell or tissue cultures, natural and chimeric animal models and follow the processes previously described in this review.

To this point, several proteins with potential use as therapeutic targets have been found. Here the most important under investigation, as well as the lipid cycle phase in which they exert their function are described:

Apolipoprotein E (APO-E): internal ligand of the LDL receptor, participates in metabolic regulation of lipoproteins, through the transport of lipids to and from different tissues. Participates in exogenous and endogenous phases of the cholesterol cycle.

Apolipoprotein A1 (APO-A1): participates in the formation and molecular structure of HDL cholesterol, activates the enzyme lecithin cholesterol acyl transferase (LCAT), and stimulates reverse transport of cholesterol.[6]

ATP-citrate-lyase (ACLY): participates in cholesterol synthesis. This enzyme catalyzes conversion of citrate and coenzyme A to acetyl Co-A; condensation of three molecules of Acetyl Co-A generate the 3-methyl-glutaryl coenzyme A, which in successive steps will generate mevalonate and finally the cholesterol molecule.

Proprotein convert subtilisin/kexin type 9 (PCSK9): liver origin protein. In the hepatocyte membrane, it joins to the LDL receptor (LDLR), the LDLR-PCSK9 complex is internalized to the cytoplasm in endosomes/lysosomes, allowing the degradation of LDLR, preventing its recycling and decreasing LDL-cholesterol clearance.[7] It participates in the endogenous and exogenous phases of cholesterol.

INNOVATIVE MOLECULES IN DEVELOPMENT

Since its creation in 1997, the registration ClinicalTrials.gov has allowed to follow the process of new drugs development, recording phase I, II, and III studies of new molecules, as well as other processes or developments that do not relate to drugs.[8] Assignment of a registration number allows to track the evolution of a study and facilitates but does not ensure, publication in academic journals and subsequent authorization by the U.S. Drug Administration (FDA).

A systematic search was done using the words, «Hypercholesterolemia» and «Early phase I, II, III». Twenty-eight «innovative» molecules were identified at different stages of development.

Of the innovative molecules identified, nine are new recombinant anti-PCSK9 antibodies, with small modifications to those currently authorized. The first antisense oligonucleotide molecule with extensive improvements to previous anti-PCSK9 drugs was suspended by significant immunological adverse reactions. Showing the difficulties to design biotechnological drugs. One identified development includes a prosthetic drug without biological antibody activity created to bind to PCSK9 to prevent its digestion. Two developments in this group attract powerful attention, although they are in early stages of

Table 1. Characteristics of approved innovative molecules.

Molecule	Lomitapide	Mipomersen	Permafibrate	Inclisiran	Bempedoic Acid
Approval year	2012	2013	2017	2020	2020
Indication	Familial Hypercholesterolemia	Familial Hypercholesterolemia	Familial Hypercholesterolemia and hyperlipidemia	Familial Hypercholesterolemia	Familial Hypercholesterolemia
Route of administration	Oral	Subcutaneous	Oral	Subcutaneous	Oral
Dosage	5mg/day	200mg/week	0.1mg/12hours	300mg/6 months	180mg/day

development: an oral administration PCSK9 inhibitor and a vaccine created with RNA coding a PCSK9 blocker protein that would have subcutaneous application every three months.

In addition, one drug classified as anti-angiogenic is developing as a hypolipidemic agent by blocking the angiopoietin-3 receptor. Another molecular mechanism under development is the creation of mimetic peptides of apolipoproteins B and E, that block lipid receptors and decrease levels of LDL-C. A mimetic molecule of Apo-1 increases lipid uptake by HDL-C. Two other anti-senses oligopeptides (siRNA), which block the expression of angiopoietin-3 are in their first stage of development.

Synthetic molecules, although in a smaller proportion, are represented by a nicotinic acid receptor agonist, two beta-hydroxysteroid dehydrogenase inhibitors, and a cholesterol ester transferring protein (CEPT) inhibitor.

It is notable that, of these 28 prospects, most are reported on Clinicaltrials.gov as completed. Less than 15% of those have reported results and fewer have been published. This phenomenon diminishes the credibility of the control that motivated the register.

Finally, 19 molecule development projects located were suspended for different causes. Some causes of this suspension are ineffectiveness, important adverse events (liver damage, kidney damage, or increased cardiovascular events), up to a case of interruption without specifying details by the production company despite having authorization for its marketing. These projects are published even less frequently.

INNOVATIVE APPROVED MOLECULES

After a search in PubMed with the following keywords: *Hyperlipidemias*, *Drugs-Investigational*, *Drug Approval*, and *Drug Development* and using the last 10 years and human species as filters, one hundred and forty-eight articles were obtained, after revision of title and abstract, 50 articles about currently approved molecules were maintained. Finally, 24 articles were included in this review.

Lomitapide: is a selective microsomal triglyceride transfer protein inhibitor for lowering LDL-C levels in adults with familial hypercholesterolemia *(Table 1)*.[9] Lomitapide binds to and suppresses microsomal triglyceride transfer protein (MTP), producing lipoproteins that contain apo-B in the hepatocytes and the enterocytes leading to a decrease in the generation of very-low-density lipoprotein (VLDL) and chylomicrons and hence decreasing LDL-C levels in plasma. It is effective in reducing LDL-C, alone (35% reduction in LDL-C), or in combination with ezetimibe, fenofibrate, and atorvastatin (66% reduction in LDL-C). Similarly, it has been observed that under these schemes reductions of up to 50% of serum triglyceride levels and up to 3% of weight loss is achieved.[10] Several studies make such observations; however, report of adverse events is important.

In phase II and III clinical studies, about 90% of the population suffers from gastrointestinal discomfort, 30% report diarrhea, nausea, vomiting, and dyspepsia. About 20% report abdominal pain, discomfort, gases and flatulence.[10] It is important to add that in

some cases, side effects are those related to hepatic transaminases elevation (approximately 30% of patients, this is a reversible situation within two weeks of drug discontinuation) and accumulation of liver fatty tissue, situations to be considered in clinical use.

Mipomersen: second generation oligonucleotide antisense drug for Apo-B, approved for treatment of family hypercholesterolemia in patients over 12 years, by weekly subcutaneous injections of 200 mg. Mipomersen binds to the region-specific segment encoding RNAm for apo-B, reducing the translation of RNAm into protein by multiple mechanisms including, activation of RNase H-mediated degradation of the cognate mRNA, thus dissipating the synthesis of ApoB in the liver and its transport.

It use has achieved a 25% reduction in LDL-C levels. Similarly, changes in lipid metabolism indicators such as total cholesterol, and APO-B have been observed.[11] However, certain adverse effects were identified, including reaction in the area of application of the drug (84%), flu symptoms (30%), and the elevation of hepatic transaminases (up to 40%). For that reason, the FDA alert about the non-free use of mipomersen. Current use require that patients consuming it receive a follow-up from pharmaco-surveillance in an close manner.[10]

Permafibrate: is a highly selective peroxisome proliferator activated receptor (PPAR)-α, developed for the treatment of hyperlipidemias. Permafibrate is > 2,500 times more efficient than fenofibrate with reduced adverse effects. The mechanism of action is the reduction of triglyceride-rich protein (TLR), acting together in lipoprotein metabolism in the liver, small intestine, as well as macrophages.

Recently, permafibrate has been approved by the FDA for the treatment of hyperlipidemias, achieving a reduction of 44.3% in triglycerides and 49.1% in cholesterol remnants. After treatment with permafibrate, the proportion of patients with triglycerides less than 150 mg/dL was 81.5%.[12] The use of permafibrate as coadjutant therapy to statins has also been shown to reduce up to 53.4% in triglycerides at doses of 0.2 mg/dL. The main role of permafibrate is the reduction of triglycerides by more than 45% after 12 to 24 weeks of administration, this reduction is comparable to the reduction achieved by fenofibrate, but with a considerable decrease in adverse effects.

In addition to these effects, the ability to reduce non-HDL cholesterol, Apo-B, ApoB48, and ApoC3, with increased HDL-C has been reported with a reduction of cardiovascular risk. Permafibrate has adverse effects of less than 5%, including nasopharyngitis, increased creatinine and uric acid, and altered liver function. Among them, no death or rhabdomyolysis has been reported.

Inclisiran: first interference RNA (siRNA) biotechnology drug, recently approved by the FDA and under current review; to reduce LDL-C levels and prevent cardiovascular events.

The reported mechanism of action is reduction of intra and extracellular production of PCSK9, from conjugation with triantennary N-acetylgalactosamine (GalNAc) that provides high-affinity binding to hepatocyte receptors, which reduce the dose and volume of drug required and the highly specific liver uptake should result in less chance of off-target effects.[13,14] Efficacy on LDL-C reduction has been demonstrated in phase II and III ORION studies, with participation of more than twenty thousand patients worldwide,[14] who were under maximum dosing of statins and/or more ezetimibe and with significant risk factors for cardiovascular disease, achieving a reduction in LDL-C of approximately 50%, allowing up to six months between doses.

Inclisiran, not only achieves LDL-C reduction, Khan et al. in a meta-analysis of three clinical trials with 3,660 patients describe that compared to placebo, it also significantly decrease ($p < 0.001$) total cholesterol (37%), ApoB (41%), non-HDL cholesterol (45%) and major cardiovascular events (24%). Despite its effectiveness, adverse effects, considered moderate, have been reported, occurring in the same proportion that in placebo group. However, there are still certain limitations that should be explored such as the comparation of inclisiran vs PCSK9 inhibitor monoclonal antibodies and the cost they will represent for health and patient services.

Bempedoic acid: it is a pro-drug rapidly absorbed by the small intestine, which allows its passage to the liver where it is activated by very-long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA.9, this active metabolite inhibits

adenosine triphosphate- citrate lyase (ACLY), an enzyme upstream of HMG-CoA reductase. Inhibition of ACL decreases cholesterol biosynthesis and causes an upregulation in lipoprotein receptors to increase LDL-C clearance.[15]

Efficacy of bempedoic acid was evaluated in four phase III randomized double-blind clinical trials: CLEAR Tranquility, patients with a history of statin intolerance and use of ezetimibe; CLEAR Serenity, subjects with statin intolerance but hypolipidemic therapy for primary prevention; CLEAR harmony, patients in statin therapy with maximum tolerable and CLEAR Wisdom, in patients at high cardiovascular risk and in statin therapy at tolerable maximums. A daily dose of 180 mg achieved LDL-C reduction from 12.6 (at 52 weeks of follow-up) to 23.6% (within 12 weeks of surgery). Side effects were similar in both groups. Main reported adverse events were nasopharyngitis, urinary tract infections, arthralgia, hyperuricemia, gout, decreased glomerular filtration rate, and risk of tendon rupture.[15] Despite the observed results, it is considered an expensive therapy.

CONCLUSIONS

The introduction of silico design, molecular biology, and genetic engineering in the design of new hypolipidemic drugs forces us as clinicians to be updated in new drug molecules that are a potential alternative against the process of formation of obliterating vascular atheroma.

This work offers an update on this topic, with a streamlined explanation of the process of drug developing and reviewing the pharmacological developments authorized for clinical use, that will soon be available to the cardiological group.

REFERENCES

1. Hernández-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, Pedroza-Tobías A, Villalpando S, Shamah-Levy T et al. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. Salud Publica Mex. 2020; 62 (2): 137-146.
2. Graham I, Shear C, De Graeff P, Boulton C, Catapano AL, Stough WG et al. New strategies for the development of lipid-lowering therapies to reduce cardiovascular risk. Eur Heart J Cardiovasc Pharmacother. 2018; 4 (2): 119-127.
3. Mohs RC, Greig NH. Drug discovery and development: role of basic biological research. Alzheimers Dement Transl Res Clin Interv. 2017; 3 (4): 651-657.
4. Thompson GR. FH through the retrospectoscope. J Lipid Res. 2021; 62: 100036.
5. Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis. 1980; 35 (3): 259-266.
6. van der Vorst EPC. High-density lipoproteins and apolipoprotein A1. In: Hoeger U, Harris JR, editors. Vertebrate and invertebrate respiratory proteins, lipoproteins and other body fluid proteins [Internet]. Cham: Springer International Publishing; 2020 [cited Jan 13, 2021]. pp. 399-420. (Subcellular Biochemistry; vol. 94). Available in: http://link.springer.com/10.1007/978-3-030-41769-7_16
7. Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. Circ Res. 2014; 114 (6): 1022-1036.
8. Gómez-Restrepo C, Reveiz Narváez Y. The registration of clinical trials. Rev Colomb Psiquiatr. 2008; 37 (3): 452-456.
9. Feingold KR. Cholesterol lowering drugs. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K et al, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited Jan 13, 2021]. Available in: http://www.ncbi.nlm.nih.gov/books/NBK395573/
10. Sirtori CR, Pavanello C, Bertolini S. Microsomal transfer protein (MTP) inhibition-a novel approach to the treatment of homozygous hypercholesterolemia. Ann Med. 2014; 46 (7): 464-474.
11. McGowan MP, Moriarty PM, Backes JM. The effects of mipomersen, a second-generation antisense oligonucleotide, on atherogenic (apoB-containing) lipoproteins in the treatment of homozygous familial hypercholesterolemia. Clin Lipidol. 2014; 9 (5): 487-503.
12. Yamashita S, Masuda D, Matsuzawa Y. Pemafibrate, a new selective PPARα modulator: drug concept and its clinical applications for dyslipidemia and metabolic diseases. Curr Atheroscler Rep. 2020; 22 (1): 5.
13. Tomlinson B, Chan P, Zhang Y, Lam CWK. Efficacy and safety of add on therapies in patients with hypercholesterolemia undergoing statin therapy. Expert Opin Pharmacother. 2020; 21 (17): 2137-2151.
14. Kosmas CE, Muñoz Estrella A, Skavdis A, Peña Genao E, Martinez I, Guzman E. Inclisiran for the treatment of cardiovascular disease: a short review on the emerging data and therapeutic potential. Ther Clin Risk Manag. 2020; 16: 1031-1037.
15. Nguyen D, Du N, Sulaica EM, Wanat MA. Bempedoic acid: a new drug for an old problem. Ann Pharmacother. 2021; 55 (2): 246-251.

Correspondence:
Antonio Gordillo-Moscoso, MD, PhD
E-mail: gordillo@uaslp.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100803

Triglycerides: are they or are they not a cardiovascular risk factor?

Triglicéridos: ¿son o no son un factor de riesgo cardiovascular?

Edith Ruiz-Gastélum, MD, FACC* Alejo Díaz-Aragón, MD‡ Humberto Álvarez-López, MD§

INTRODUCTION

Hypertriglyceridemia (HTG) is a biochemical diagnosis based on the concentration of fasting plasma triglycerides. Current guidelines define it as such triglycerides (TG) being above 150 mg/dL. According to the American Heart Association standards, two categories are considered: mild to moderate with or without fasting, with amounts in the 150 to 499 mg/dL range, and severe if greater than 500 mg/dL.[1]

For years, attempts have been made to define the role of TG as a cardiovascular (CV) risk factor. However, its link with reducing high-density cholesterol (HDL-c), considered with alleged cardioprotective properties, has favored confusion. This symbiosis has led to therapeutic interventions to increase the latter without reducing CV outcomes, further diverting attention from the benefit of HTG treatment. HTG has recently become a new point of interest, recognizing that its presence is associated with the elevation of triglyceride-rich lipoproteins (TRL) and their remnants since these particles represent an increasingly important role in the genesis of atherosclerosis.[2] The evidence in favor of the relationship between low-density cholesterol (LDL-c) and CV danger, as well as the benefit of the various remedial alternatives, is unequivocal. However, once LDL-c has been reduced to the therapeutic target, a high CV peril persists, partly due to the residual lipid hazards favored by HTG, which is part of the so-called atherogenic dyslipidemia, related with a decrease in HDL-c and qualitative alterations of LDL-c fragments in size and density which favor the continuum of CV probability.[3] To determine the role of HTG and TRL as an independent predictor of atherosclerotic cardiovascular disease (ASCVD), various epidemiological, genetic, and pharmacological intervention investigations have been carried out.[4]

EPIDEMIOLOGICAL STUDIES

In the general population, studies consistently show a strong association of HTG with the risk of ASCVD. The Framingham Heart Study found a simple linear relationship between serum TG and the subsequent development of coronary artery disease (CAD), statistically significant, particularly in women. However, the most definitive evidence of danger was found when evaluating the relationship connecting an elevation of TG (> 150 mg/dL) and a low level of HDL-c (< 40 mg/dL), regardless of the main risk factors. It was observed that the threat of CAD doubled in the following 14 years of the investigation.[5] The PROCAM study (Prospective Cardiovascular Münster) evaluated the incidence of ASCVD in 4,860 men. It demonstrated that total cholesterol (TC), HDL-c, LDL-c, and TG had a significant age-adjusted bond with major coronary events. CV danger increased when the TG was higher than 200 mg/dL, related with the LDL-c/HDL-c index greater than five, which profiles a sixfold atherogenic menace of developing CAD in the following eight years.[6]

* Clínica de Hipertensión y Riesgo Cardiovascular. ISSSTESON. Hermosillo, Sonora, México.
‡ Facultad de Medicina de la Universidad Autónoma Benito Juárez de Oaxaca. Mexico.
§ Hospital de Especialidades Puerta de Hierro Andares. Guadalajara, Jalisco, Mexico.

Received:
29/06/2021
Accepted:
07/07/2021

How to cite: Ruiz-Gastélum E, Díaz-Aragón A, Álvarez-López H. Triglycerides: are they or are they not a cardiovascular risk factor? Cardiovasc Metab Sci. 2021; 32 (s3): s231-s235. https://dx.doi.org/10.35366/100803

A meta-analysis of 61 papers quantitatively evaluated the relation between TG concentrations with CV and total mortalities. Compared to the reference value (90 to 149 mg/dL), the relative risk of CV mortality and total mortality connected to TG amounts, it was noticed that borderline-high (150 to 199 mg/dL), and high TG (≥ 200 mg/dL), grew 15% and 9% in the group with borderline-high TG, and by 25% and 20% in the group with HTG, respectively. Overall, the threat of CV and total mortalities rose by 13% and 12% respectively, for every mmol/L of TG concentration increase.[7]

The BIP registry (Bezafibrate Infarction Prevention), which comprised 15,355 patients with ischemic heart disease followed during 22 years, exhibited that HTG is independently associated with more numerous fatalities. Age- and sex-adjusted survival was 41% in the low normal TG group (below 100 mg/dL). With levels of 100-140 mg/dL, 150-199 mg/dL, 200-499 mg/dL, and above 500 mg/dL, survival rates were 37%, 36%, 35%, and 25%, respectively ($p < 0.001$). In the latter group, after 22 years of follow-up, lethal danger worsened by 68% when compared with individuals with low-normal TG ($p < 0.001$).[8]

The PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) analysis of 4,162 ill persons hospitalized after acute coronary syndrome, treated with statins, analyzed the relationship between fasting TG levels and an LDL-c goal below 70 mg/dL, which attained and a 28% reduction in fatalities. Deaths, myocardial infarction (MI), or recurrent CV events occurred in 11.7% of patients with TG below 150 mg/dL, while the rate ascended to 16.5% in those with TG > 150 mg/dL ($p < 0.001$).[9]

Another important aspect of determining the concentration of TG is their non-fasting measurement rather than fasting quantification. Nordestgaard et al. detected a more significant impact as a risk factor with non-fasting TG since they better represent the plasma levels of atherogenic lipoproteins, including both atherogenic lipoproteins of hepatic and intestinal origin. The maximum changes in averages for random non-fasting concentrations versus fasting are +26 mg/dL for TG, -8 mg/dL for TC and low-density lipoprotein, +8 mg/dL for remaining cholesterol, and -8 mg/dL for non-HDL-c.[10] In the Copenhagen City Heart Study and Copenhagen General Population Study, extremely high amounts of non-fasting TG are associated with an increased peril of ASCV and total mortality. For persons with fasting TG fewer than 580 mg/dL versus 70 mg/dL, the probability of MI was 5.1 times greater, 3.2 times for ischemic heart disease and ischemic stroke, and 2.2 times for death by any cause.[4]

GENETIC STUDIES: MENDELIAN RANDOMIZATION

Researches with Mendelian randomization allowed identifying some genetic variants which, alongside lifestyle factors such as atherogenic diet and obesity, raise CV stakes. Specific gene mutations have been found which cause loss of function of lipoprotein lipase (LPL), the primary metabolizing enzyme of TG, which in turn determines the functionality of various proteins, as the enzyme called lipase maturation factor (LMF1), Apo C-II, an apolipoprotein which is an activating cofactor, apolipoprotein A-5 (APOA-5) that stabilizes LPL-1 complexes, and the HDL-binding protein attached to glucosylphosphatidinositol type one (GPIHBP-1), which translocates the LPL-1 to the endothelial surface, and simultaneously anchors the chylomicrons, and whose loss of function variants are also linked to HTG.[11]

On the other hand, mutations in angiopoietin-like proteins three and four (ANGPTL3 and ANGPTL4), endogenous inhibitors of LPL, and apoprotein C-3, an Apo E antagonist, cause a diminution of TG and LDL-c, with a consequent decrease of CVD. In an analysis of 21,980 individuals with CAD and 158,200 control subjects, in whom a gene sequence of ANGPTL3 deficiency was evidenced and compared with those who do not possess it, a decline of 17% of circulating TG and 12% of C-LDL, and 34% of the odds ratio of CAD were noticed.[12]

The impact of TRL was evident in a Mendelian randomization design research conducted in the Copenhagen population of 73,000 citizens, in whom 11,984 had ischemic heart disease. Fifteen genetic variants were selected that affect the residual cholesterol

particles, with and without HDL-c combined, HDL-c alone, and LDL-c as a positive control. It was concluded that the increase in non-fasting remaining cholesterol of one mmol/L (39 mg/dL) is associated with a 2.8-fold causal risk of ischemic heart disease, independent of reduction HDL-c.[13] Mutations with loss of function in APOC3 are linked with minor TRL levels and scant CVD danger. Some papers confirm another relationship of low LDL-c that could explain the reduced threat of CVD in heterozygous with loss of APOC3 function. Therefore, in a meta-analysis, these parameters were independently evaluated. It was decided that the tiny chance of observed events is mainly mediated by the lower concentration of cholesterol-rich lipoproteins and not by LDL-c diminution alone. This conclusion suggests that APOC3 and TRL may be therapeutic targets to reduce cardiovascular hazards.[14]

Another examination of the general population of Copenhagen, which included approximately 100,000 Danes, showed that in addition to LDL-c, cholesterol leftovers are directly responsible for ASCVD, regardless of LDL-c concentrations. In the observational analysis, the hazard rate (HR) of MI per each mmol/L (39 mg/dL) was 1.3 times for LDL-c and 1.4 times for remnants. In genetic studies with Mendelian randomization, HR for MI was 2.1 times for LDL-c, and 1.7 times for remainders.[15]

INTERVENTION STUDIES

Explorations with niacin, fibrates, and omega-3 fatty acids, which reduce plasma TG, have not positively reduced CVD. Notwithstanding, in some trials, subgroup analyses have displayed protective effects in subjects with mild HTG and low HDL-c, particularly fibrates, in the period before statins. So far, just a handful of papers have revealed a significantly beneficial effect on CV outcomes. The REDUCE-IT study, which included diabetic patients or those with CVD and HTG, already treated with statins, documented a relative risk of 32% decrease in the primary endpoint using a dose of omega-3 icosapent ethy of 2 × 2 grams. The JELIS (Japan EPA Lipid Intervention Study), with eicosapentaenoic acid (EPA) 1.8 g/day added to a statin, indicated a 19% reduction in CV events. It has been considered that benefit more than the decline in TG derived by the anti-inflammatory and antithrombotic pleiotropic effects. The lack of positive results in previous reports could be due to inadequate selection of individuals, pre-existing TG quantities, or the wrong type and dose in most omega-3

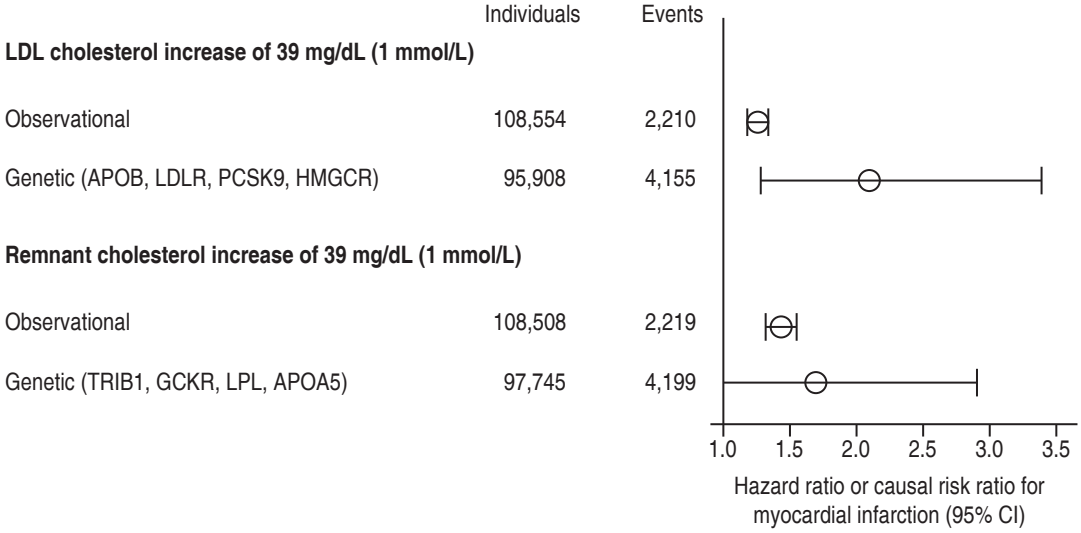


Figure 1: Comparison of risk of myocardial infarction by 1 mmol/L (39 mg/dL) higher levels of low-density lipoprotein (LDL) cholesterol AND remnant-cholesterol from observational and genetic studies, data from individuals in the Copenhagen General Population Study. Adapted from: Handelsman Y et al.[17]

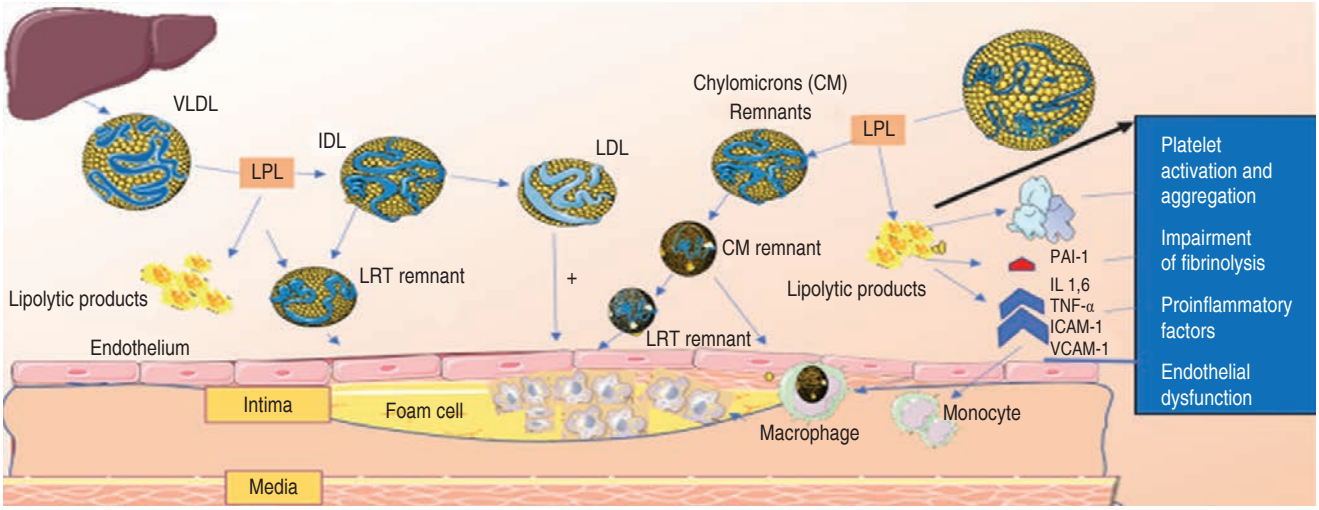


Figure 2: Possible mechanisms of atherogenesis by TRL. These particles also contain cholesterol esters, can penetrate the arterial intima, and are taken up by macrophages, transforming them into foam cells. TRL also promotes endothelial dysfunction through oxidized fatty acids (lipolytic products), by favoring a pro-inflammatory response and activation of prothrombotic factors.

fatty acid assays. In such a way, HTG could be a biomarker of the presence of a more atherogenic lipoprotein particle, such as TRL and the lingering cholesterol *(Figure 1)* .[16,17]

MECHANISM THAT CONDITIONS ATHEROSCLEROSIS

A plausible explanation of the difficulty in establishing a clear causal role of HTG in CVD risk is that the products of TRL lipolysis, rather than the TRL themselves, are the likely mediators of increased CVD danger because they are more atherogenic than large TRL. After all, they penetrate the arterial wall more easily by containing higher cholesterol relative to triglycerides (5 to 20 times), promoting proatherogenic effects in the vascular endothelium. These lithic products, remnant lipoprotein particles (RLP), are estimated to result from the extensive remodeling of chylomicrons, VLDL, and those in intermediate ranges, with a more significant pro-atherogenic effect. Those remainders of TRL are generated by the LPL hydrolysis, resulting in progressively small fragments depleted of TG with an increase in cholesterol content. The lower clearance of RLP may be due to reduced LPL activity or incomplete conversion of LRT to lipoproteins having a greater liver affinity for removal. This fact prolongs the plasma half-life of remaining lipoproteins of different size spectra in the circulation. The smaller size favors its penetration into the arterial wall. Once in the subendothelial space, they are trapped by proteoglycans and can be absorbed by macrophages; such residues without the need to oxidize can quickly form a foaming cell and promote the development of atherosclerosis.[18] HTG is also associated with the increase of small and dense LDL-c elements, which may be more atherogenic; while cutting HDL-c elements. The extended circulation time of LDL-c is derived from lipolysis of various VLDL1 species, facilitating a significant transfer of cholesterol and replaces it with TG donated by the VLDL, which are eventually hydrolyzed by the hepatic lipase, generating smaller units of LDL-c.[2]

In addition, it has been observed that, in the process of TG metabolism, remnants of TRL may favor an infamous response. The resulting lytic products such as oxidized fatty acids, together with the remainders, induces the production of cytokines (TNF-alpha), interleukins and promotes the adhesion of proatherogenic molecules, which facilitates the migration of leukocytes to the site of inflammation; this favors the adhesion of monocytes to the endothelium and the activation of neutrophils. On the other hand, by allowing

the overexpression of the plasminogen-1 inhibitor gene and the plasminogen-1 inhibitor antigen, platelet activation and aggregation processes are facilitated, giving rise to a prothrombotic state *(Figure 2)*. Metabolic effects are summarized below:[18,19]

1. Decrease in HDL-c.
2. Occurrence of TG-rich lipoprotein.
3. Presence of small and dense LDL-c particles.
4. Prothrombotic state.
5. Increased inflammatory response and endothelial dysfunction.

CONCLUSIONS

Epidemiological, genetic, and pharmacological intervention reviews provide increasingly strong evidence that large TRL concentrations are an independent predictive causal risk factor for CVD. Consequently, HTG is more a biomarker of its existence, not only because of its atherogenic potential but also a marker of small and dense LDL-C particles with a higher atherogenic effect. Therefore, they may be a potential target for future therapeutic intervention to reduce the residual lipids hazards and reduce atherosclerotic vascular burden.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139 (25): e1082-e1143.
2. Packard CJ, Boren J, Taskinen MR. Causes and consequences of hypertriglyceridemia. Front Endocrinol (Lausanne). 2020; 11: 252.
3. Hernández-Mijares A, Ascaso JF, Blasco M, Brea A, Díaz A, Mantilla T et al. Residual cardiovascular risk of lipid origin. Components and pathophysiological aspects. Clin Investig Arterioscler. 2019; 31 (2): 75-88.
4. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res. 2016; 118 (4): 547-563.
5. Castelli WP. Epidemiology of triglycerides: a view from Framingham. Am J Cardiol. 1992; 70 (19): 3H-9H.
6. Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol. 1996; 77 (14): 1179-1184.
7. Liu J, Zeng FF, Liu ZM, Zhang CX, Ling WH, Chen YM. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. Lipids Health Dis. 2013; 12: 159.
8. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman E, Kopel E et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the bezafibrate infarction prevention study and registry. Circ Cardiovasc Qual Outcomes. 2016; 9 (2): 100-108.
9. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2008; 51 (7): 724-730.
10. Nordestgaard BG. A test in context: lipid profile, fasting versus nonfasting. J Am Coll Cardiol. 2017; 70 (13): 1637-1646.
11. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020; 41 (1): 99-109c.
12. Stitziel NO, Khera AV, Wang X, Bierhals AJ, Vourakis AC, Sperry AE et al. ANGPTL3 deficiency and protection against coronary artery disease. J Am Coll Cardiol. 2017; 69 (16): 2054-2063.
13. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013; 61 (4): 427-436.
14. Wulff AB, Nordestgaard BG, Tybjærg-Hansen A. APOC3 loss-of-function mutations, remnant cholesterol, low-density lipoprotein cholesterol, and cardiovascular risk: mediation- and meta-analyses of 137 895 individuals. Arterioscler Thromb Vasc Biol. 2018; 38 (3): 660-668.
15. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020; 41 (24): 2313-2330.
16. Patel PN, Patel SM, Bhatt DL. Cardiovascular risk reduction with icosapent ethyl. Curr Opin Cardiol. 2019; 34 (6): 721-727.
17. Handelsman Y, Shapiro MD. Triglycerides, atherosclerosis, and cardiovascular outcome studies: focus on omega-3 fatty acids. Endocr Pract. 2017; 23 (1): 100-112.
18. Basu D, Bornfeldt KE. Hypertriglyceridemia and atherosclerosis: using human research to guide mechanistic studies in animal models. Front Endocrinol (Lausanne). 2020; 11: 504.
19. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev. 2019; 40 (2): 537-557.

Correspondence:
Edith Ruiz-Gastélum, MD, FACC
E-mail: edithdruizg@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100804

Approach to hypertriglyceridemia syndromes: the importance of distinguishing between primary and secondary etiologies

Acercamiento a los síndromes de hipertrigliceridemia: la importancia de distinguir entre etiologías primaria y secundaria

Ivette Cruz-Bautista, MD, BSc*

INTRODUCTION

Hypertriglyceridemia (HTG) is a common clinical problem. Current medical guidelines define normal fasting plasma triglycerides (TG) concentrations as less than 150 mg/dL. According to the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), mild-to-moderate common HTG (CHTG) is defined by TG concentrations between 150-880 mg/dL, and severe HTG refers to ranks higher than 880 mg/dL.[1,2] The prevalence of HTG varies among ethnic groups; it is hugely prevalent in Hispanics. In Mexico, the pervasiveness of mild-to-moderate hypertriglyceridemia is around 31%, with ~5% of the Mexican population showing critical HTG.[3] Standards recommend advising all subjects suffering from HTG on lifestyle modifications. For patients having CHTG, the main goal is to decrease cardiovascular risk by reducing low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) as well as apolipoprotein B levels (apo B). If the patient has dangerous HTG, the chief goal is to reduce the danger of pancreatitis.[4] Recent epidemiologic and genetic studies establish TG-rich lipoproteins (TRL) and their leftovers rich in cholesterol (RCL) as essential contributors to atherosclerotic cardiovascular disease (ASCVD).[5,6] So novel therapies that target TRL and inflammation are in development to reduce residual ASCVD risk.[7] Various methods for measuring residues exist; however, because cholesterol remnants lipoproteins (RLP-c) are heterogeneous populations of different sizes and lipid composition, a direct assay has not yet been developed.[8]

Metabolism of triglycerides and triglyceride-rich remnant lipoproteins

Enzymes such as diacylglycerol acyltransferase are responsible for TG synthesis. They originate in the intestine built from dietary fatty acids or free fatty acids (FFA) extracted from the circulation or are newly synthesized in the liver. Microsomal triglyceride transfer protein (MTTP) unites lipids apolipoprotein B-48 (apo B-48) or apo B 100 in the intestine or liver, respectively, forming chylomicrons (CHY) which enter plasma indirectly through lymphatics, or very-low-density lipoprotein (VLDL) that transport TG, respectively. Hydrolysis of circulating CHY or VLDL particles type one or two by lipoprotein lipase (LPL) releases FFA and produce chylomicron remnant, whose clearance requires apolipoprotein E (apo E), as apo B-48 does not have the low-density lipoprotein receptor-binding domain and VLDL-remnant lipoproteins (intermediate density lipoprotein, IDL), that can bind to low-density lipoprotein receptor-related protein 1

*Unidad de investigación de enfermedades metabólicas, Instituto Nacional de Ciencias Médicas y Nutrición «Salvador Zubirán», Mexico City, Mexico.

Received: 08/07/2021
Accepted: 13/07/2021

How to cite: Cruz-Bautista I. Approach to hypertriglyceridemia syndromes: the importance of distinguishing between primary and secondary etiologies. Cardiovasc Metab Sci. 2021; 32 (s3): s236-s241. https://dx.doi.org/10.35366/100804

(LRP-1) in the liver. In contrast, another part, under the action of hepatic lipase (HL), is transformed into LDL.

Atherobiology of RLP-c lipoproteins

RPL-c elements are partially TG-depleted post lipolytic particles whose cholesterol content is more likely to cause atherosclerosis. Just like LDL, RCL can invade the arterial intima.[6] Once there, fragments could even be trapped preferentially to LDL simply because of affinity to extracellular proteoglycans. In contrast to LDL, apo C3 and apo E-enriched remnants can be directly taken up by macrophages in their native condition, without enzymatic modification or specific receptors, leading to foam cells' formation.[9] Beyond LDL, the RLP-c proteins transport up to 30% of the cholesterol load in postprandial conditions, meaning more cholesterol per particle than LDL does. Increased production and delayed catabolism of TGRL lead to its increase and greater concentrations of RLP-c. APOC3 reduces VLDL and CHY lipolysis by inhibiting LPL and blocking TRL and RLP uptake by hepatic receptors. Thus, HTG results from increased production or decreased catabolism of CHY and VLDL or VLDL alone; has a direct effect on the composition of LDL and high-density lipoprotein (HDL), caused by elevated activity of cholesteryl ester transfer protein that shifts TG from CHT and VLDL to LDL and HDL, in exchange for cholesteryl esters.[10] In a recent study, it is shown that apoB48-containing particles in subjects with HTG are released across the entire chylomicron-VLDL size range. This process persists for many hours, elevating their concentrations and adding to the circulating population of particle remainders.[11]

The five steps for differential diagnosis in clinical practice

1. Syndromic diagnosis. In 1994, the European Consensus[12] established the initial approach to the patient affected by dyslipidemia. The division in lipid phenotypes *(Table 1)* allows elucidating the most frequent primary and secondary causes. However, syndromic judgment has no impact on cardiovascular prevention and may overestimate or underestimate treatment.
2. Family history. Screening closest relatives of patients with primary dyslipidemias (those showing cholesterol or triglycerides levels higher than 300mg/dL, premature coronary heart disease, frequent pancreatitis events, xanthomas, xanthelasmas, etcetera).[13]
3. Search for secondary causes. Environmental origins should be excluded. A variety of lifestyle factors and medical conditions can cause hypertriglyceridemia *(Figure 1)*. Common secondary roots include obesity, uncontrolled diabetes, hypothyroidism,

Table 1: Syndromic diagnosis.

Type	TC	TG	HDL-C
Mixed hyperlipidemia	> 200	> 150	
Hypertriglyceridemia			
Isolated	< 200	> 150	
Severe		> 500	
Hypoalphalipoporteinemia			< 40
Hyperalphalipoproteinemia			> 60
Hypercholesterolemia			
Isolated	> 200	< 150	
Severe	> 300		

TC = total cholesterol, TG = triglycerides, HDL-c = high-density lipoprotein-cholesterol.

smoking, alcohol abuse, endocrinopathies, and various commonly used drugs *(Table 2)*.[14]

4. Etiological diagnosis. Most patients enduring HTG do not have a recognizable genetic cause. Primary severe HTG has both monogenic and polygenic determinants. For example, Familial chylomicronemia syndrome (FCS, type 1), a rare form of monogenic HTG with an estimated one in a million prevalence. Also consider the

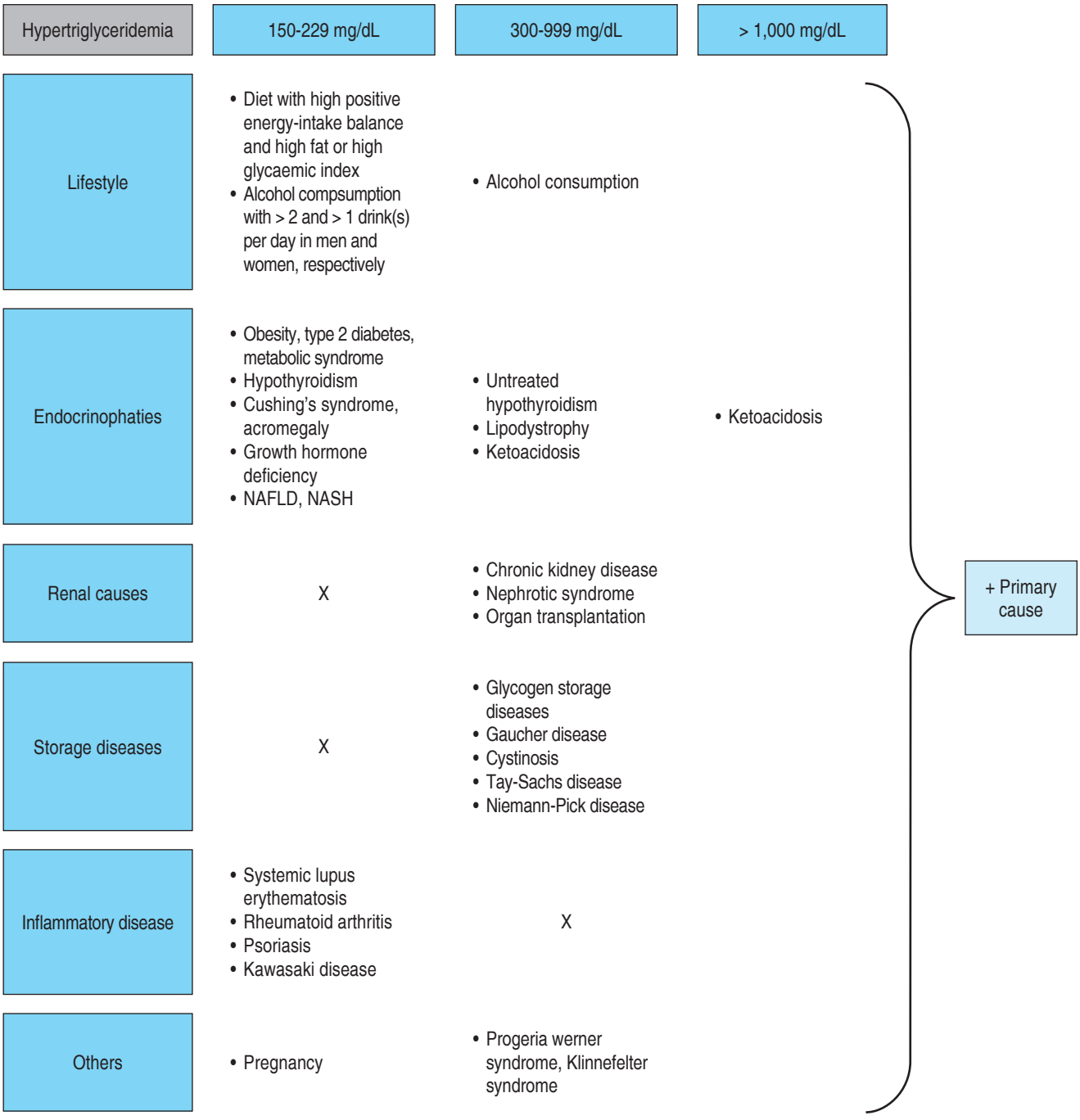


Figure 1: Secondary causes of hypertriglyceridemia.

Table 2: Drugs associated with high triglycerides levels.

Hormonal	• Oral oestrogens (40%) • Selective estrogen receptor modulators (20%) • Steroids • Tamoxifen (20%) • Raloxifen (20%) • Clomiphene (40%) • Growth hormone therapy • Androgen deprivation therapy (15%)
Cardiometabolics	• Non cardioselective beta blockers (20%) • Thiazides (15%) • Diuretics (10%) • Bile acid sequestrants
Immunosuppressants	• Cyclosporine (20%) • Sirolimus (30%) • Tacrolimus (30%) • Interferon alpha (20%)
Anti-cancer therapeutics	• L-asparaginase • Cyclophosphamide • Tyrosin-kinase inhibitors (20-70%)
Others	• Retinoids (40%) • Protease inhibitors (100%), ITRN (50%), ITRNN (40%), INH, INTEG (0%) • Antidepressants y atypical antipsychotics (30%) • Propofol (20%)

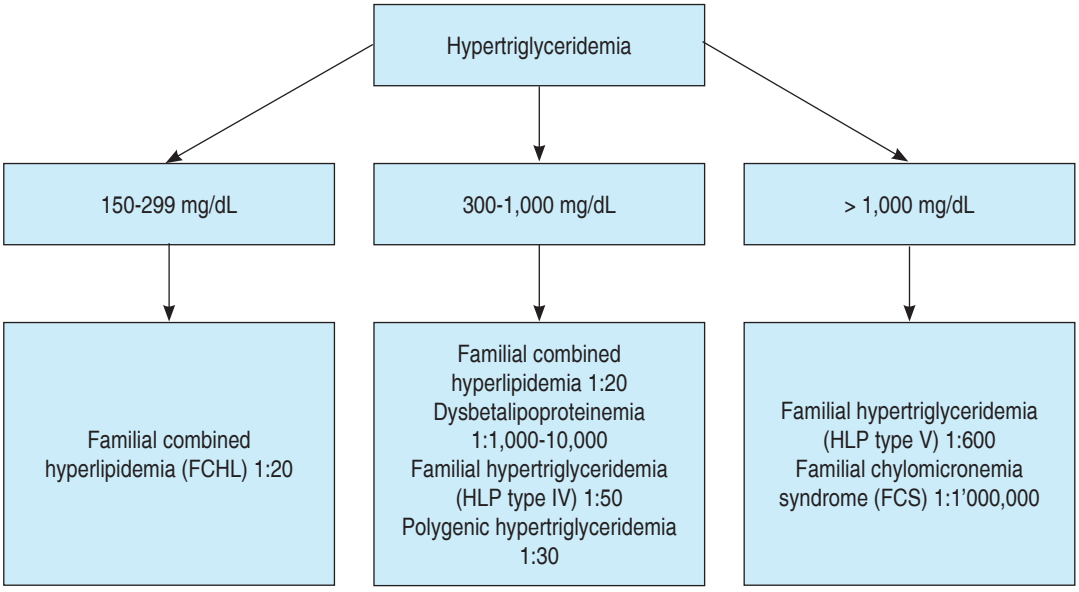


Figure 2: Primary causes of hypertriglyceridemia.

detection of rare, biallelic (homozygous or compound heterozygous) variants in one of six genes: LPL (accounting for 90% of cases), APOC2, APOA5, LMF1, GPIHBP1, ANGPTL3.[13] Familial HTG (gype V) highly oligogenic, could be a cause of critical HTG frequently confused with other primary dyslipidemias.[15] A significant number of conditions *(Figure 2)* that cause mild-to-moderate HTG ought to be excluded.

5. Assessment of cardiovascular risk. All current recommendations on the prevention of ASCVD in clinical practice endorse evaluating the total CVD threat. The Globorisk score[16] in people over 40 is a good tool for assessing cardiovascular hazards in Mexican people. The 2019 ESC/EAS guidelines establish that persons having documented ASCVD, diabetes type one or two, extreme levels of individual danger factors, or chronic kidney disease (CKD) generally have very prominent or high total CV peril. No risk estimation models are needed for such persons.[2]

RECOMMENDATIONS AND CONCLUSIONS

The objective of the differential analysis is to identify dyslipidemias exhibiting atherogenic potential from those without it. One must always search for secondary causes in all scenarios.

1. High-risk primary hyperlipidemias ought to be treated with intensity regardless of the existence of other hazard factors (i.e., familial hypercholesterolemia and familial HTG).
2. Etiological diagnosis is essential to categorize the patient. It must systematize the scrutiny of dyslipidemias and promote inquiry studies in first-degree relatives.
3. Subclinical atherosclerosis should be sought in asymptomatic individuals revealing the most atherogenic primary dyslipidemias.

REFERENCES

1. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2016; 37: 2999-3058.
2. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.
3. Huerta-Chagoya A, Moreno-Macías H, Sevilla-González M, Rodríguez-Guillén R, Ordóñez-Sánchez ML, Gómez-Velasco D et al. Contribution of known genetic risk variants to dyslipidemias and type 2 diabetes in Mexico: a population-based nationwide study. Genes (Basel). 2020; 11: 114.
4. Simha V. Management of hypertriglyceridemia. BMJ. 2020; 371: m3109.
5. Langsted A, Madsen CM, Nordestgaard BG. Contribution of remnant cholesterol to cardiovascular risk. J Intern Med. 2020; 288: 116-127.
6. Salinas CAA, Chapman MJ. Remnant lipoproteins: are they equal to or more atherogenic than LDL? Curr Opin Lipidol. 2020; 31: 132-139.
7. Reeskamp LF, Tromp TR, Stroes ESG. The next generation of triglyceride-lowering drugs: will reducing apolipoprotein C-III or angiopoietin like protein 3 reduce cardiovascular disease? Curr Opin Lipidol. 2020; 31: 140-146.
8. Nordestgaard BG, Langlois MR, Langsted A, Chapman MJ, Aakre KM, Baum HP et al. European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative. Quantifying atherogenic lipoproteins for lipid-lowering strategies: Consensus-based recommendations from EAS and EFL. Atherosclerosis. 2020; 294: 46-61.
9. Duran EK, Pradhan AD. Triglyceride-Rich Lipoprotein remnants and cardiovascular disease. Clin Chem. 2021; 67: 183-196.
10. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020; 41: 2313-2330.
11. Bjornson E, Packard CJ, Adiels M, Andersson L, Matikainen N, Soderlund S et al. Investigation of human apoB48 metabolism using a new, integrated non-steady-state model of apoB48 and apoB100 kinetics. J Intern Med. 2019; 285: 562-577.
12. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. On behalf of the Task Force. Prevention of coronary heart disease in clinical practice: recommendations of the Task Force of the European Society of Cardiology, European. Atherosclerosis Society and European Society of Hypertension. Atherosclerosis. 1994; 110: 121-161.
13. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020; 41: 99-109.
14. Packard CJ, Borén J, Taskinen MR. Causes and consequences of hypertriglyceridemia. Front Endocrinol (Lausanne). 2020; 11: 252.
15. Cruz-Bautista I, Huerta-Chagoya A, Moreno-Macías H, Rodríguez-Guillén R, Ordóñez-Sánchez ML, Segura-Kato Y et al. Familial hypertriglyceridemia:

an entity with distinguishable features from other causes of hypertriglyceridemia. Lipids Health Dis. 2021; 20: 14.
16. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinol. 2015; 3: 339-355.

Correspondence:
Ivette Cruz-Bautista MD, BSc
E-mail: ivette.cruzb@incmnsz.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100805

Current treatment of hypertriglyceridemia

Tratamiento actual de la hipertrigliceridemia

Humberto Álvarez-López, MD* Edith Ruiz-Gastélum, MD‡ Alejo Díaz-Aragón, MD§

INTRODUCTION

Hypertriglyceridemia (HTG) and triglyceride-rich lipoproteins (TRL) such as chylomicrons or very-low-density lipoproteins (VLDL) have been associated with an increased danger of cardiovascular disease (CVD) and remain elevated in up to 25% of patients with established CVD.[1-4] A severe elevation (> 500 mg/dL) of triglycerides (TG) increases the risk of pancreatitis due to the toxic effects of free fatty acids released by pancreatic lipase, requiring reduction through lifestyle changes and pharmacotherapy, in addition to correcting precipitating etiological factors.[1]

Statin medication aims to minimize low-density cholesterol (LDL-c) and has been shown to improve atherosclerotic CVD damage. Despite this, the residual peril of new events persists,[1,2,4] partly attributed to a mild to moderate HTG by several studies, behaving as an independent risk factor for CVD. However, clinical trials data for managing raised triglycerides taking drugs including fibrates, omega-3 fatty acids, and niacin showed no definitive evidence of the reduced danger of new cardiovascular incidents. The purpose of this review is to examine the role that triglycerides play in cardiovascular hazards and their potential drug administration.

Treatment. The goals of this action are to reduce the risk of pancreatitis in sick individuals with severe HTG and to decrease CVD perils in those experiencing mild to moderate HTG.[1,5-7]

Two fundamental parameters will always guide the care of hypertriglyceridemia: the elevation level of triglycerides and the calculated threat of atherosclerotic disease at ten years.[6] In patients enduring mild to moderate hypertriglyceridemia, LDL-c continues to be the primary treatment target in lipid diminution therapy, and secondary targets being non-HDL cholesterol (non-HDL-c), apolipoprotein B (Apo B), and finally, TG reduction. According to medical guidelines, it is always necessary to reach the recommended goals in the described order.[1,7,8]

Lifestyle changes. To begin with, secondary causes of TG elevation should be excluded, and the corrections appropriate to each case must be carried out.[1,5-7,9-11] Once these tasks are accomplished, the central therapeutic intervention for the treatment of increased TG will be lifestyle modifications, for example, reducing overweight or obesity, decreasing carbohydrate intake, limiting alcohol intake, performing regular physical activity, and attaining adequate glucose control in sick individuals suffering type two diabetes *mellitus*.[5,6,11] It is noteworthy that the most significant impact on HTG is achieved via weight loss and limiting alcohol intake. A decrease of TG up to 80% was reported in ill persons with alcohol abuse who can significantly limit alcoholic ingestion *(Table 1)*.[1]

Pharmacological treatment. Once lifestyle adjustments have been attained, medications will be prescribed according to TG blood concentrations and calculated cardiovascular risk category.[6] In *Figure 1*, the authors propose a simplified flowchart for treatment.

* Hospital de Especialidades Puerta de Hierro Andares.
‡ Clinical Hypertension and Cardiovascular Risk Clinic. ISSSTESON Juarez y Aguascalientes.
§ Facultad de Medicina de la Universidad Autónoma Benito Juárez de Oaxaca.

Received:
08/07/2021
Accepted:
19/07/2021

How to cite: Álvarez-López H, Ruiz-Gastélum E, Díaz-Aragón A. Current treatment of hypertriglyceridemia. Cardiovasc Metab Sci. 2021; 32 (s3): s242-s246. https://dx.doi.org/10.35366/100805

Indications:

1. For CVD prevention: patients with triglycerides of 150-499 mg/dL.
   a) **Low risk:** lifestyle changes.
   b) **Intermediate risk:** assessing statin use.
   c) **High risk or with established CVD:** use high potency statin until reaching the LDL-c target. If raised TH concentrations persist, preferably assess the use of either or both icosapent ethyl and fibrates.
   d) **For the avoidance of pancreatitis: triglycerides > 500 mg/dL:** coupled to lifestyle alterations, pharmacologic approach with fibrates, niacin, and omega-3 fatty acids should be initiated. In case the patient has cardiovascular disease, these drugs ought to be added to statin therapy.

DRUGS FOR THE TREATMENT OF HTG

1. **Statins, ezetimibe, and PCSK9 inhibitors:** mainly decreasing C-LDL and additionally slightly lessening the TG concentration about 5-15%, but having a significant impact on reducing cardiovascular events.[1,6]
2. **Fibrates, niacin, and omega-3 fatty acids**: achieve a triglyceride reduction of 25-50%, but the impact on reducing cardiovascular incidents is still questioned *(Table 2)*.[1,6]
   Fibrates: these drugs act as binders for the regulator of the nuclear transcription of the alpha receptor activated by proliferated peroxisome (α-PPAR), causing an increase in the synthesis of the enzyme lipoprotein-lipase (LPL), which is responsible for the catabolism of VDLD and chylomicrons (molecules composed primarily of TG). The released free fatty acids (FFA) are the main fuels for every tissue except neurons and blood red cells. The FFA not used for internal combustion, mainly by the striated skeletal muscle, are stored in adipose tissue and the liver, in the form of TG (lipogenesis). They are metabolized by cytochrome P450 isoenzyme 2C9 (CYP2C9) and are excreted via the kidneys.[12]
   Niacin: inhibits the synthesis and esterification of fatty acids by shrinking TG production and also stimulating LPL, so increasing TG cleavage from chylomicrons and VLDL in a way such that it modifies the endogenous and exogenous metabolism of lipids.
   Omega-3 fatty acids: diminish serum TG by decreasing VLDL synthesis through various mechanisms, including changes in the n-6/n-3 ratio of fatty acids, incrementing β-oxidation, lowering hepatic lipogenesis, and increasing degradation of intracellular apolipoprotein B.
3. **Others:** epanova, pemafibrate, evinacumab, volanesorsen, AKSEA APO CIII (apolipoprotein C III), alipogene, ionis angptl3-Lrx.[12-14]

CLINICAL EFFICACY

Statins

There is excellent scientific evidence about the use of statins in both primary and secondary prevention. This approach would need to be started in all patients exhibiting HTG and great cardiovascular danger of CVD.[1-3] Therefore, the authors certainly need to insist, high potency statins will always be the first-line therapy in HTG to reach the goal of LDL-c, non-HDL-c, and Apo B.

Once the goals have been achieved, if the elevation of TG persists, the use of specific medication with fibrates, omega-3 fatty acids, niacin, icosapent ethyl, or biological agents in the research phase will be assessed.[6]

Table 1: Lifestyle changes suggested for hypertriglyceridemia.

Losing excess weight
Decrease carbohydrate intake
Decrease or avoid alcohol consumption
Increased consumption of polyunsaturated and monounsaturated fat
Increased consumption of omega-3 fatty acids in foods (fish as salmon)
Exercise
Adequate glucose control in patients with diabetes

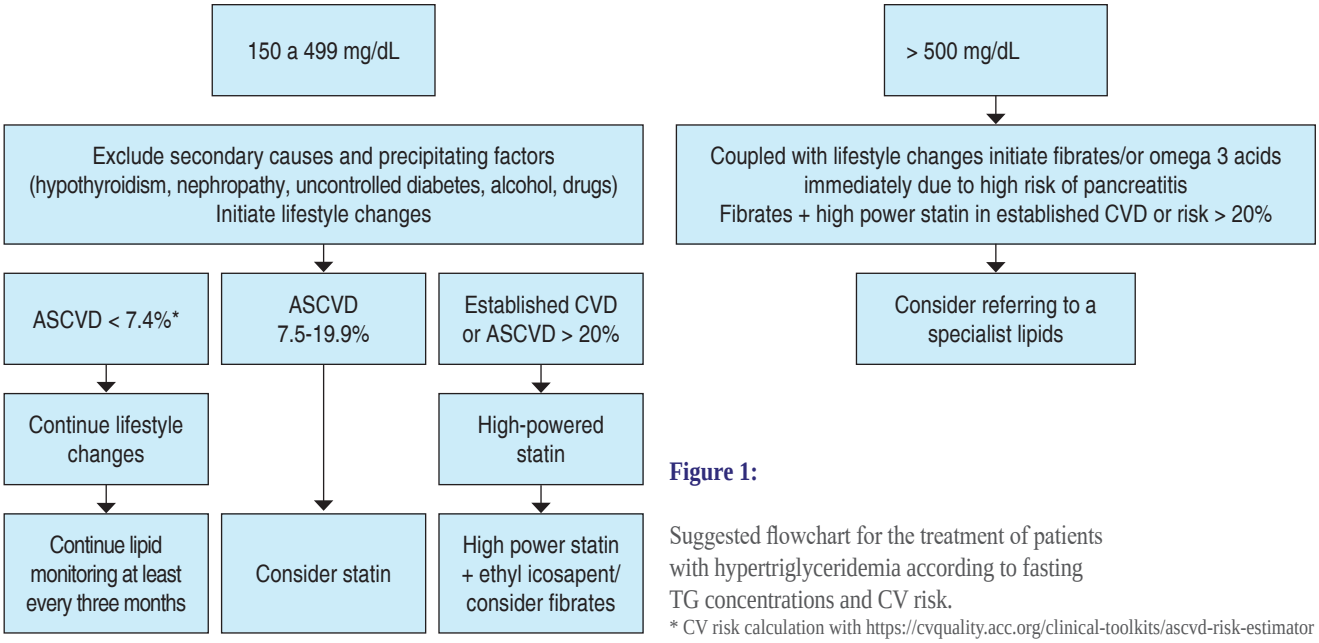


Figure 1:

Suggested flowchart for the treatment of patients with hypertriglyceridemia according to fasting TG concentrations and CV risk.

* CV risk calculation with https://cvquality.acc.org/clinical-toolkits/ascvd-risk-estimator

Fibrates and niacin. Although fibrates and niacin have been the traditional treatment used to lower TG levels in those affected by severe elevation and critical hazard of pancreatitis, it is unclear from what level management should be initiated in primary and secondary prevention and whether it would be sufficient together with the adoption of lifestyle changes.[5,15]

Although multiple studies have been conducted with fibrates, there is not enough evidence to support its use in reducing cardiovascular events.[16] With niacin studies like CDP, AIM HIGH, and HPS2 THRIVE failing to demonstrate effectiveness in lowering occurrences,[5,6] if a fibrate is indicated, the most recommended is fenofibrate.

Omega-3 fatty acids. Pharmacological interest in omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the deterrence of CVD is due to a lower incidence of CVD seen in populations consuming large amounts of fish oil. Short-term studies have revealed how omega-3 fatty acids (2-4 g/day) can reduce TG levels.

Omega-3 EPA fatty acids (without DHA) improve lipid levels beyond the lessening of TG, and in addition diminish non-HDL-c, Apo B, LDL-c, and the number of atherogenic particles. In addition to atherogenic control, EPA improves inflammation, as manifested by a lower C-reactive protein activity and greater concentration of adiponectin.[5,6] Regression of the atheromatous plaque and improvement of endothelial dysfunction has also been demonstrated. However, in systematic reviews, none of the omega-3 fatty acids have been shown to decrease cardiovascular incidents consistently, so its use in the primary prevention of cardiovascular disease is not recommended.[5] The recent STRENGTH study, which included 13,078 persons with omega-3 fatty acid supplementation in HTG patients, was prematurely discontinued because the formulation did not decrease major cardiovascular events in diseased persons at notorious cardiovascular risk.[17-19] The exception is icosapent ethyl in the REDUCE-IT study, which included those with elevated TG concentrations and a high cardiovascular threat or with proven CVD. Oral administration of four grams daily of this drug demonstrated a 25% reduction in CVD.[20-22] Decreased revascularizations have also become evident in ill people treated with this drug.[4] However, estimating a cost-benefit ratio with this substance is necessary to evaluate whether the intervention is cost-effective.[6]

Emerging therapies: omega-3-carboxylic acid, pemafibrate, AKSEA, APO CIII inhibitors such as volanesorsen, alipogene to treat lipoprotein lipase deficit, ANGPTL3 inhibitor antibody (evinacumab), ANGPTL4 inhibitors, and ANGPTL8 inhibitors-1.[1,13,14,23]

What do dyslipidemia treatment guidelines recommend? US American and European guidelines suggest that first-line therapy promotes statins in people with moderate to severe hypertriglyceridemia. These guidelines consider adding ethyl of icosapent or fibrates in those with TG > 500 mg/dL or high VLDL or chylomicrons. Contrariwise, European guidelines consider icosapent ethyl in TG > 135 mg/dL despite treatment with statins in subjects at significant cardiovascular risk. Fibrates are not recommended in primary prevention.[4,8,22,23]

Managing hypertriglyceridemia in the COVID-19 pandemic. Significant elevations of TG have been reported in sick ones treated with tocilizumab. No interactions of statins, fibrates, or omega-3 fatty acids were publicized in clinical trials for the therapy of COVID-19, so they must be continued unless there is a specific contraindication for administration.[24]

Discussion and conclusions. In patients suffering verified CVD, a residual risk of new episodes persists. In the case of having a high TG serum concentration, it is proposed that once optimized, the management with statin and the control of LDL-c are attained. Here is an area of opportunity managing TRL with new potential remedies. The main objective of HTG care is to reduce cardiovascular risk and the onset of pancreatitis. However, to date, there is little evidence that the addition of fibrates, omega-3 fatty acids, or niacin to a prescription decreases said events. There is also no convincing evidence of lipid-reducing treatment diminishing the risk of pancreatitis.

The REDUCE-IT study showed that in those at lifted cardiovascular risk who show elevated triglycerides despite statin use and adequate levels of LDL-c, icosapent ethyl at a dose of four grams daily reduces cardiovascular instances, so its use should be considered in this type of patients. Several emerging therapies are currently under study.

Table 2: Hypertriglyceridemia treatment: key messages.

The use of omega-3 fatty acids, niacin and fibrates for cardiovascular disease prevention is not supported
In patients with established or high cardiovascular risk CVD consider adding to statin therapy, icosapent ethyl at a dose of 4 g daily
In patients with severe HTG and high risk of pancreatitis consider fibrates, niacin, and omega-3 fatty acids at a dose of 2 to 4 g daily
For patients with pancreatitis, hypertriglyceridemia > 1,000 mg/dL and hyperglycaemia consider insulin and plasmapheresis infusion, in addition to fibrates, niacin, and omega-3 fatty acids

REFERENCES

1. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 2020; 41 (1): 99-109c.
2. Collins R, Armitage J, Parish S, Sleigh P, Peto R. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet. 2003; 361 (9374): 2005-2016.
3. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004; 364 (9435): 685-696.
4. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-188.
5. Toth PP, Shah PK, Lepor NE. Targeting hypertriglyceridemia to mitigate cardiovascular risk: A review. Am J Prev Cardiol. 2020; 3: 100086.
6. Iqbal Z, Ho JH, Adam S, France M, Syed A, Neely D et al. Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: An expert panel position statement from HEART UK. Atherosclerosis. 2020; 313: 126-136.
7. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls S, et al. Perkovic, V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010; 375 (9729): 1875-1884.
8. Ray KK, Corral P, Morales E, Nicholls SJ. Pharmacological lipid-modification therapies for prevention of ischaemic heart disease: current and future options. Lancet. 2019; 394 (10199): 697-708.
9. Mauri M, Calmarza P, Ibarretxe D. Dyslipemias and pregnancy, an update. Clin Investig Arterioscler. 2021; 33 (1): 41-52.

10. Simha V. Management of hypertriglyceridemia. BMJ. 2020; 371: m3109.
11. Oh RC, Trivette ET and Westerfield KL. Management of hypertriglyceridemia: common question and answers. Am Fam Physician. 2020; 102 (6): 347-354.
12. Santos-Baez LS and Ginsberg HN (2020) Hypertriglyceridemia-Causes, Significance, and Approaches to Therapy. Front. Endocrinol. 11:616. NICE Clinical Guideline CG 181 (2014) Cardiovascular disease: risk assessment and reduction, including lipid modification. Available in: https://www.nice.org.uk/guidance/cg181
13. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with Diabetes (PROMINENT) study. Am Heart J. 2018; 206: 80-93.
14. Skulas-Ray A, Wilson P, Harris W, Brinton E, Kris-Etherton P, Richter C et al. Omega-3 fatty acids for the management of hypertriglyceridemia. A science advisory from the American Heart Association. Circulation. 2019; 140: e673-e691.
15. Araki E, Yamashita S, Arai H, Yokote K, Satoh J, Inoguchi T et al. Effects of pemafibrate, a novel selective PPARα Modulator, on lipid and glucose metabolism in patients with type 2 diabetes and hypertriglyceridemia: a randomized, double-blind, placebo-controlled, Phase 3 Trial. Diabetes Care. 2018; 41 (3): 538-546.
16. Schandelmaier S, Briel M, Saccilotto R, Olu KK, Arpagaus A, Hemkens LG, Nordmann AJ. Niacin for primary and secondary prevention of cardiovascular events. Cochrane Database Syst Rev. 2017; (6): CD009744.
17. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L et al. Omega-3 treatment trialists' collaboration. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals. JAMA Cardiol. 2018; 3 (3): 225-234.
18. Khan MS, Ishaq M, Ayub MT, Rehman AU, Hayes JJ, Mortada M, Biederman RW. The novelty of icosapent ethyl in the management of hypertriglyceridemia and alleviating cardiovascular risk. J Lipids. 2021; 2021: 6696915.
19. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB et al. REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019; 380 (1): 11-22.
20. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ et al. Effect of high-dose omega-3 fatty acids vs. corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. JAMA. 2020; 324 (22): 2268-2280.
21. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 73 (24): 3168-3209.
22. Peterson BE, Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA et al. REDUCE-IT Investigators. Reduction in revascularization with icosapent ethyl: insights from REDUCE-IT revascularization analyses. Circulation. 2021: 143 (1): 33-44.
23. Patel PN, Patel SM, Bhatt DL. Cardiovascular risk reduction with icosapent ethyl. Curr Opin Cardiol. 2019; 34 (6): 721-727.
24. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97 (9): 2969-2989.

Correspondence:
Humberto Álvarez-López, MD
E-mail: beto66_mx@yahoo.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100806

Myocardial infarction as a consequence of atherosclerosis

Infarto de miocardio como consecuencia de aterosclerosis

Rafael Moguel-Ancheita, MD* Virginia Samaniego, MD‡

INTRODUCTION

Atherosclerosis is a main cause of myocardial infarction (MI), establishing a vicious circle that increases atherosclerosis and risk of more infarctions.[1] There are many ancient descriptions and recent discoveries of myocardial infarction and coronary calcification on ancient mommies. One of the first findings on sudden death, came from the Danish sculptor's autopsy Bertel Thorvaldsen in 1844, where an ulcerated coronary atherosclerotic plaque exposing subendothelial components was shown.[1]

The current knowledge about atherothrombosis causing myocardial infarction evolved through the last three centuries. The present chapter describes the atheroma events causing MI and the process of myocardial necrosis.

THE VULNERABLE PLAQUE

The atherosclerotic plaque starts very early in life, and later progresses towards a lesion which is a potential cause of ischemic heart syndromes: angina or equivalent, myocardial infarction, and sudden death. In 1858, Rudolf Virchow published a book containing his lectures in the Pathological Institute of Berlin. Lecture XVI described the pathology and histology of «fatty metamorphosis». He described the atheromatous process in arteries, as it is currently explained, stating that the plaque contained a fat core with muscular layer's involvement, identifying fat granules containing cells, and evidence of inflammation. Virchow interprets the atheroma as a dermal cyst,[2] similarly to an abscess contained into its capsule, that could eventually break.

The plaque involves several anatomic, histological, mechanical, and chemical properties that interact with other environmental factors that include several physical forces. The plaque becomes vulnerable when it is prone to rupture and causing thrombosis.[3] However, a significant proportion (40%) of complicated plaques do not provoke thrombosis,[4] and half of them do not cause severe stenosis. The vulnerability is expressed when the cover atheromatous cap is less than 65 µm –the thin fibrous cap–,[5] there is loss of smooth muscle cells, increased components of extracellular matrix, inflammatory infiltrate, high-volume necrotic core, intra-plaque hemorrhage, calcification, and numerous vasa vasora.[6,7]

Rupture or erosion may be the main vulnerable plaque complication. The first one consists of the loss of continuity of an area of the fibrous cap covering a large necrotic core plaque, macrophage and lymphocytic infiltration, and thrombi. The ruptured plaque is a major cause for sudden death in men under 50 and women over 50 years old, with a significant correlation with high total cholesterol/HDL-cholesterol ratio and major thrombosis particularly in smokers.[8,9] Nonetheless, the ruptured plaque is not always associated with sudden death. Farb et al., found proteoglycan and smooth muscle cell-enrich plaques denuded from the endothelium,

* Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular (COMECITE), México.
‡ The Clinics of the Heart, Cozumel, Q. Roo, Mexico.

Received:
28/06/2021
Accepted:
08/07/2021

How to cite: Moguel-Ancheita R, Samaniego V. Myocardial infarction as a consequence of atherosclerosis. Cardiovasc Metab Sci. 2021; 32 (s3): s247-s252. https://dx.doi.org/10.35366/100806

without rupture, in 44% of autopsy specimens, with several differences between ruptured and eroded plaques. The latter were more frequent in younger subjects and women, originating less stenosis, with less macrophages and T cells infiltration, more frequent smooth muscle cells clusters adjacent to thrombi, and less expression of human leukocyte antigen-DR isotype (HLA-DR).[5]

In both rupture and erosion, the presence of macrophages, T cells, and HLA-DR antigens on these cells and on adjacent smooth myocytes is consistent with the concept of inflammation, destabilizing the fibrous cap and enhancing the risk of coronary thrombosis.[4]

On the other hand, almost half of cases of sudden death result from plaque's erosion characterized by endothelium absence with exposure of smooth muscle and proteoglycans, less necrotic core and inflammatory cells than ruptured plaques. This event is more frequent in 50 years old or younger men and women. Plaque rupture and erosion may coexist in a single event.[10]

Calcified nodules may complicate plaques causing disruption and thrombosis. These complications may result from the action of torsion forces and mechanical lesion of the plaque by the hard calcified nodule, especially in the mid-segment of the right coronary artery.[11] Interestingly, approximately one-fourth of sudden death cases may show intact plaques, but significant stenosis and myocardial scars from old infarctions. Other cases present plaque fissuring with hemorrhage and fibrin inside the necrotic core. These fissures possibly result from vasa vasora rupture and are possible precursors of ruptures. Fissures may be incidental findings in non-cardiovascular deaths.[11] The complicated plaque sometimes heals when new synthesis of type-III collagen cover the disrupted fibrous, with a matrix composed of proteoglycan-enrich mass or collagen-enrich scar. These healed events may contribute towards more lumen occlusive plaques.[12]

Another significant component for plaque's vulnerability is the vasa vasorum developed from the adventitia, which is a stem cell reservoir. The vessel wall injury stimulates angiogenesis and immature vessels penetrate the plaque favoring plaque growth and hemorrhage. The vasa vasora may be the conduit of inflammatory cells arriving into the plaque, and the initial factor for instability.[13,14]

Inflammation is involved in atherogenesis, atheroma development, and partly responsible for plaque complications. The phagocytes, mainly macrophages, produce proteolytic enzymes, particularly collagenases, members of the matrix metalloproteinases family, that could damage the biomechanical stability of the fibrous plaque.[15]

Several substances activate focal and global inflammation and may constitute clinical markers for major cardiovascular events prediction and prognosis. The C-reactive protein is the current dominant marker. It participates in plaque formation, stimulates monocytes and macrophages to synthesize interleukins 6 and 1β, tumor necrosis factor-α, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1, and opsonizes the low-density lipoprotein, favoring macrophage's uptake. Other inflammation related substances present are pregnancy associated plasma protein, soluble P-selectin.[16]

Inflammation may involve infections and immunity, increasing local thermal activity, energy production uncoupling, exothermic chemical reactions, blood friction over the wall, turbulent flow, blood viscosity and red cell aggregation.

Oxidized low-density lipoprotein and lipoprotein (a) not only produce plaque growth but induce more inflammation, necroptosis, thrombosis, cholesterol delivery to atheroma, and smooth muscle cell proliferation and together with the formation of cholesterol crystals may damage the plaque from inside, establishing a continuous event that weakens the plaque's fibrous cap and extracellular matrix.[17]

The plaque stability or instability relate to external mechanical and hydraulic forces

1. The Laplace's stress, which is directly proportional to the vessel's ratio and the blood pressure and indirectly proportional to the wall thickness, is higher in the plaque edges because of the major ratio and thinner wall.

2. Shear, which is the blood's force over the vessel wall as it flows over it.
3. The turbulent flow that causes areas with less shear and continuous particle interaction with the wall.
4. The torsion of the vessel during the heart movement.

Unstable plaque presence can be associated with acute coronary syndromes, although controversy exists due to the coexistence of unstable and stable plaques and because the relationship of either one to specific events is not linear.[18]

Several diagnostic tools, aimed to visualize the anatomical aspects of the atherosclerotic plaque *in vivo*, such as the optical coherence tomography (OCT) obtained during cardiac catheterization have been recently developed. This imaging tool can distinguish the coronary arteries' layers with high resolution, well beyond the intravascular ultrasound. The sensitivity and specificity may reach over 90% for detecting fibrous plaque, fibroatheroma, and fibrocalcific plaque. It may detect very small processes such as microthrombi, erosion, ulcers, macrophage aggregates, calcific nodules, lipid core, thin cap, vasa vasora, microdissections, and intra-plaque hemorrhage.[19] Some examples of images obtained in our catheterization laboratory show some of the aspects described above *(Figure 1)*.

Apart from the vulnerable plaque, we must consider the relevant role of blood in the process. The thrombogenic blood status can be established by the presence of several markers of hypercoagulability (fibrinogen, D-dimer, factor V Leiden), increased platelet aggregation, increased coagulation factors, decreased anticoagulation factors, decreased endogenous fibrinolysis, prothrombin mutation, increased viscosity, and transient hypercoagulability.

The possibility of an acute coronary syndrome and its magnitude is also related to factors beyond the vulnerable plaque and blood, yielding to the concept of the vulnerable patient and vulnerable myocardium. This includes metabolic syndrome, inflammation, gut microbiome, smoking, diet, physical activity, psychosocial stress, and socioeconomic status. The vulnerable myocardium includes sympathetic activity, autonomic reactivity, hypertrophy, cardiomyopathy, valvulopathy, commotio cordis, anomalous coronary origin, myocarditis, myocardial bridging, and electrophysiological disorders.[20,21]

THROMBOSIS

Virchow, in 1848, coined the terms thrombosis and embolus that meant the same as today. In the same year, he described the triad of vascular lumen irregularity, damaged blood flow, and increased coagulability. Virchow's work in the vascular area was continued and crowned by his remarkable student Julius Cohnheim who injected wax emboli into the frog's tongue and demonstrated the lesions that a hundred years later would be called ischemic necrosis and hemorrhagic infarction.[2]

The coronary thrombosis is finally a continuum of the complicated plaque. Either rupture or erosion, going from microthrombi to complete thrombotic occlusion, related to the same plaque, blood, and patient's risk factors. It is a major cause of death in developed and developing countries.[22]

The endothelial layer is composed by a unique cell type compatible with blood without causing coagulation activation. When the endothelium loses its integrity, subendothelial components contact circulating platelets that activate and aggregate them, later releasing serotonin, adenosine diphosphate, thromboxane A2, endothelin, and other vasoconstrictors.

The subendothelial matrix releases tissue factor and activates the extrinsic coagulation cascade leading to fibrin accumulation, thrombus formation, acute occlusion, interruption of blood flow, and further ischemic complications. The thrombus composition includes platelets conglomerates, erythrocytes, vasoconstrictors, thrombin, and other procoagulants in a net of two different fibrin fibers, thin and thick; the first ones resistant to mechanical forces and fibrinolysis.[23]

Other fact that participates in atherosclerotic-related processes is the ectopic fat (visceral, intrahepatic, pericardial, and perivascular) since it causes direct lipotoxicity, local and systemic pro-inflammatory effects, dysregulating cytokines and adipokines, finally

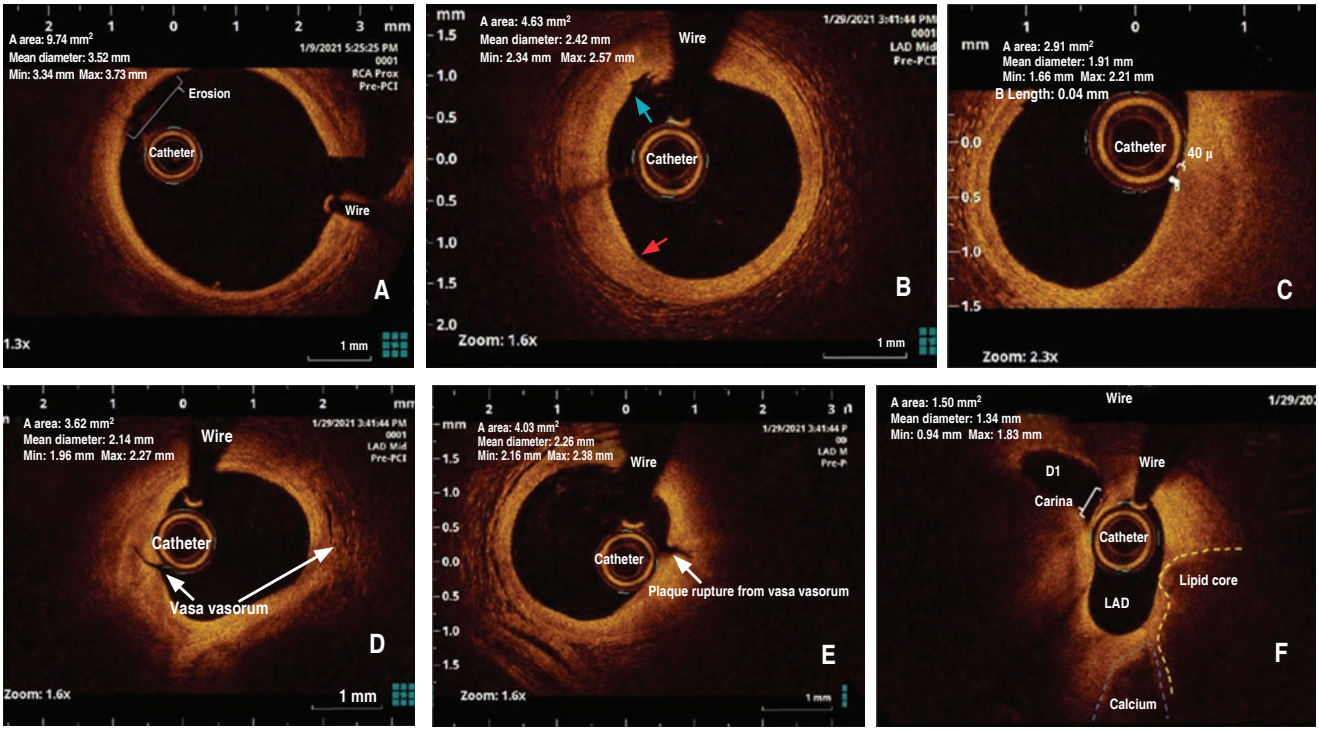


Figure 1: A) Shows endothelial denudation, microdissection, microthrombi, and macrophage aggregates. **B)** Shows an ulcer and microthrombi. **C)** Shows a typical thin cap fibroatheroma with a large lipid core and macrophage aggregates. **D)** Shows vasa vasorum with a dissection. **E)** Shows a ruptured plaque from the vasa vasorum. **F)** Shows mixed plaque containing a large necrotic core and a calcific nodule. The carina between the left anterior descendent coronary (LAD) and the first diagonal (D1) branch is free from atheroma.

causing inflammation, endothelial dysfunction, atherogenesis progression, and pro-thrombotic milieu. The thrombus formation results from the interaction of blood cells, complement, myeloid cell tissue factor, and coagulation proteases.[24] The early detection of risk factors, including ectopic fat and inflammation markers, raises the possibility for opportune secondary prevention.[25,26]

Interestingly, if thrombosis develops, the color of the thrombus, white or red, is important not only for the histological (more fibrin and fewer cells in the white) differences but several features that finally give the latter a better prognosis and response to treatment. The white thrombus is smaller than the red, occurs in smaller vessels, and associates with smaller thrombus burden, lower creatine kinase-MB and troponin, higher post-procedural TIMI-3 flow and blush grade, and lower ischemic time. One-third of myocardial infarctions display white thrombi.[27] The OCT detects very small thrombi and can differentiate white from red. The white one is low-backscattering projections within the lumen, and the red is a high-backscattering mass protruding into the artery lumen, with signal-free shadowing *(Figure 2)*.[28]

MYOCARDIAL INFARCTION AND SUDDEN DEATH

Unfortunately, the myocardial infarction and sudden death are dramatic events present in history for thousands of years, from the Ebers papyrus, dating more than three thousand years, the sudden death of Horemkenesi, priest of Ammon, and the Hippocratic descriptions. Later, da Vinci's first necropsy performance after a coronary death in 1506, Lancisi's book «De subitaneis mortibus», Dr. John Hunter's sudden death 1793, and the case of the sculptor Bertel Thorvaldsen, already described above.[2]

Irreversible myocardial injury takes place after more than 20 minutes from coronary

occlusion. The lesion size depends on the occlusion characteristics, the extent of collateral circulation, myocardial preconditioning, and reperfusion.

During the first day of the non-reperfused infarction, early signs of coagulation necrosis start, with sarcoplasmic hypereosinophilia and initial nuclei chromatin condensation, followed by neutrophil infiltration in the ischemic edges and complete coagulation necrosis with sarcomere elongation. During the first week, the infarction center reveals loss of myocyte nuclei and striations with later inflammatory cellular infiltrations that decline giving place to granulation, neocapillarity, and appearance of lymphocytes and plasma cells. After two weeks, there is a prominent fibroblast activity, removing necrotic myocytes, and healing process with collagen production and angiogenesis leading to a chronic scar after one to two months.

If reperfusion was possible, a different histological behavior is present, with in-infarction hemorrhage in the first four to six hours, followed by neutrophil infiltration and necrosis interdigitation with normal myocardium. The next five days show macrophages, stromal cells, neutrophil debris, and fibroblasts. After one week, the tissue shows collagen deposition, macrophages containing ingested myocytes, lymphocytes, and angiogenesis, for a complete heal after two to three weeks.[29]

The topography of the infarction is frequently regional along with the distribution of the occluded coronary artery, but the early reperfusion can interrupt the wave front of necrosis, limiting the irreversible damage to the subendocardium. The presence of collaterals can cause a less defined section of infarction. Hypotension on the multivessel coronary disease can cause a circumferential infarction usually involving the entire subendocardium (be aware of rapid blood pressure reduction in the hypertensive patient). Other topographic localizations include regional subendocardial and diffuse multifocal infarctions. The myocardial infarction may complicate with pulmonary edema causing a 20-40% 30-day death rate. Heart rupture is rare after reperfusion, but it can involve left ventricle free-wall, interventricular septum, and papillary muscle.[30]

Other anatomical complications are left ventricular aneurysms and pseudoaneurysms, mitral valve insufficiency, and pericarditis.[31]

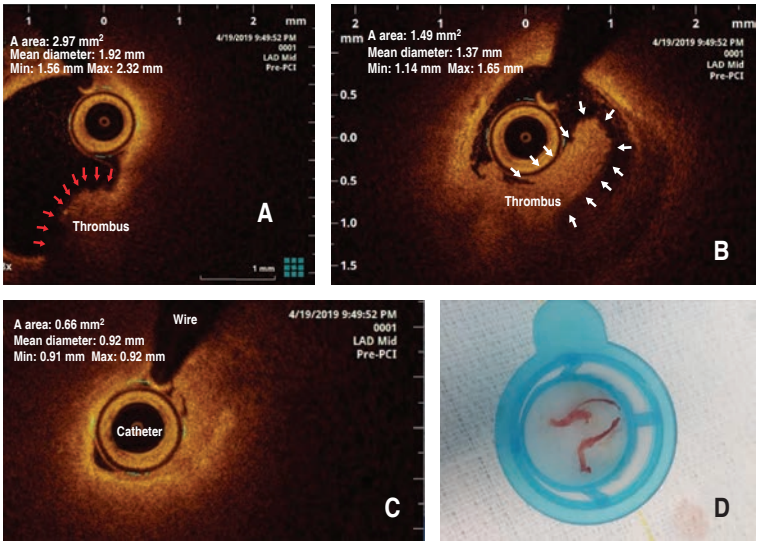


Figure 2: OCT from our catheterization laboratory. **(A)** Shows a ruptured plaque with subendothelial exposure and red thrombus, **(B)** shows a large white thrombus, completely occluding the coronary artery in **(C)**; **(D)** shows the retrieved white thrombus.

CONCLUSIONS

This chapter stresses the importance of the knowledge of the process that finally leads to myocardial infarction. Understanding the characteristics of the unstable plaque interaction with hydraulic and mechanic forces and other susceptibility factors in the blood, the patient, and the myocardium should contribute towards a more efficient diagnosis and treatment.

The present approach allows for distinguishing patients prone to myocardial infarction, using non-invasive and invasive diagnostic tools, favoring more effective secondary prevention.

REFERENCES

1. Moguel R, Cabrera C. A minimal tour towards the history of the myocardial infarction. Cardiovasc Metab Sci. 2020; 31 (3): 104-108.
2. Virchow R, Chance F. Cellular pathology as based upon physiological and pathological histology: twenty lectures delivered in the Pathological Institute of Berlin during the months of February, March, and April, 1858. London: John Churchill; 1860.

3. Yonetsu T, Jang IK. Advances in intravascular imaging: new insights into the vulnerable plaque from imaging studies. Korean Circ J. 2018; 48 (1): 1-15.
4. Van der Wal AC, Becker AE, Van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994; 89: 36-44.
5. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. Circulation. 1996; 93: 1354-1363.
6. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997; 336: 1276-1282.
7. Davies MJ, Woolf N, Rowles PM, Pepper J. Morphology of the endothelium over atherosclerotic plaques in human coronary arteries. Br Heart J. 1988; 60 (6): 459-464.
8. Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med. 1997; 336: 1276-1282.
9. Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation. 1998; 97: 2110-2116.
10. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 2000; 20: 1262-1275.
11. Davies MJ. Anatomic features in victims of sudden coronary death: coronary artery pathology. Circulation. 1992; 85: 119-124.
12. Davies MJ. Stability and instability: two faces of coronary atherosclerosis: the Paul Dudley White Lecture, 1995. Circulation. 1996; 94: 2013-2020.
13. Kawabe J, Hasebe N. Role of the vasa vasorum and vascular resident stem cells in atherosclerosis. Biomed Res Int. 2014; 2014: 701571.
14. Ito H, Wakatsuki T, Yamaguchi K, Fukuda D, Kawabata Y, Matsuura T et al. Atherosclerotic coronary plaque is associated with adventitial vasa vasorum and local inflammation in adjacent epicardial adipose tissue in fresh cadavers. Circ J. 2020; 84 (5): 769-775.
15. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012; 32 (9): 2045-2051.
16. Schwartz RS, Bayes-Genis A, Lesser JR, Sangiorgi M, Henry TD, Conover CA. Detecting vulnerable plaque using peripheral blood: inflammatory and cellular markers. J Interv Cardiol. 2003; 16 (3): 231-242.
17. Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary atherosclerotic vulnerable plaque: current perspectives. J Am Heart Assoc. 2017; 6 (3): e005543.
18. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. Eur Heart J. 2015; 36 (43): 2984-2987.
19. Toutouzas K, Karanasos A, Tousoulis D. Optical coherence tomography for the detection of the vulnerable plaque. ECR. 2016; 11 (2): 90-95.
20. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation. 2003; 108 (15): 1772-1778.
21. Tomaniak M, Katagiri Y, Modolo R, De-Silva R. Vulnerable plaques and patients: state-of-the-art. Eur Heart J. 2020; 41 (31): 2997-3004.
22. Mahajan K, Negi PC, Merwaha R, Mahajan N, Chauhan V, Asotra S. Gender differences in the management of acute coronary syndrome patients: One year results from HPIAR (HP-India ACS Registry). Int J Cardiol. 2017; 248: 1-6.
23. Adnan G, Singh DP, Mahajan K. Coronary artery thrombus [Updated 2020 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available in: https://www.ncbi.nlm.nih.gov/books/NBK534808/
24. Spronk HMH, Padro T, Siland JE, Prochaska JH, Winters J, van der Wal AC et al. Atherothrombosis and thromboembolism: position paper from the second maastricht consensus conference on thrombosis. Thromb Haemost. 2018; 118 (2): 229-250.
25. Libby P, Loscalzo J, Ridker PM, Farkouh ME, Hsue PY, Fuster V et al. Inflammation, immunity, and infection in atherothrombosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2018; 72 (17): 2071-2081.
26. Olie RH, van der Meijden PEJ, Ten Cate H. The coagulation system in atherothrombosis: Implications for new therapeutic strategies. Res Pract Thromb Haemost. 2018; 2 (2): 188-198.
27. Quadros AS, Cambruzzi E, Sebben J, David RB, Abelin A, Welter D et al. Red versus white thrombi in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: clinical and angiographic outcomes. Am Heart J. 2012; 164 (4): 553-560.
28. Kubo T, Yamano T, Masyo T, Takarada S, Imanishi T, Tomobuchi Y et al. Abstract 3060: assessment of coronary red and white thrombus by optical coherence tomography. Circulation. 2006; 114: II_645.
29. Romero ME, Fernández-Jiménez R, Ladich E, Fuster V et al. Chapter 37: Pathology of myocardial infarction and sudden death. In: Fuster V, Harrington RA, Narula J, Eapen ZJ, eds. Hurst's the heart. 14 edition. New York, NY: McGraw-Hill Education; 2017.
30. Michaud K, Basso C, d'Amati G, Giordano C, Kholová I, Preston SD et al. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. Virchows Arch. 2020; 476 (2): 179-194.
31. Pasotti M, Prati F, Arbustini E. The pathology of myocardial infarction in the pre- and post-interventional era. Heart. 2006; 92 (11): 1552-1556.

Correspondence:
Rafael Moguel-Ancheita, MD
E-mail: cathboss@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100807

Coronary atherosclerosis diagnosis by non-invasive studies: echocardiography, computed tomography

Diagnóstico de aterosclerosis coronaria mediante estudios no invasivos: ecocardiografía, tomografía computarizada

Pedro Gutiérrez-Fajardo, MD, PhD* Lilia M Sierra-Galán, MD‡

INTRODUCTION

Coronary artery disease (CAD) represents an important cause of morbidity and mortality worldwide.[1] Noninvasive cardiac imaging studies (NICIS) are fundamental for appraisal. Choosing a cardiac imaging test demands knowledge and understanding of diagnostic and prognostic accuracy, advantages and drawbacks. Establishing presence of CAD will determine the implementation of measures to avoid an acute coronary event as well as secondary prevention. In the event that CAD is ruled out, will allow reinforcing adherence to primary prevention.[2]

Patients are referred to a NICIS due to the presence of different both; typical and atypical symptoms. There is no enough evidence in open population demonstrating that a test is significantly better than any other for CAD diagnosis. Appropriate criteria, pretest probability, availability, accessibility, center expertise and cost, will facilitate clinicians´ decision for the use of a specific imaging modality.[2] For the purpose of this section, only stress echocardiography (SE) and computed tomography will be considered.

STRESS ECHOCARDIOGRAPHY

Background. Due to its versatility, technological advances in acquiring images, echo borders enhancement agents, lack of radiation and diagnostic accuracy, SE has become a reliable tool in CAD diagnosis and stratification. It is also indicated in preoperative risk assessment, evaluation of exertional dyspnea, after revascularization and for ischemia localization. It is an operator-dependent technique and a high level of training is needed to adequately perform and interpret results.[3]

Technical principles. The detection of wall motion abnormalities (WMA) is the core of SE. For didactic purposes, it is considered that WMA appear before symptoms and electrocardiographic (EKG) changes, and after perfusion abnormalities.[4] The protocol consists in acquiring base, low dose, peak dose and recovery phases images in four-screen setup. Either exercise (treadmill or bicycle) or pharmacologically (dobutamine or dipyridamole) SE can be used, the target heart rate will be at least 85% of the age-predicted heart rate. Eventually, atropine and/or handgrip strength can be used to enhance chronotropic response.

The left ventricle is divided in 17 segments. Basal wall motion is compared with intermediate and mainly with peak stress. Rationale of this test is inducing a chronotropic and inotropic response to induce myocardial ischemia. Normal segments will present hypercontractile responses while ischemic segments will become hypo-contractile. A necrotic segment has dysfunction at rest and remains fixed during stress. A hypokinetic segment may show either improvement during stress indicating a stunned myocardium or improve during early stress and later deterioration with peak stimulation

* Cardiotest, Laboratorio de Ecocardiografía. Hospital de Especialidades San Francisco de Asís. Guadalajara, Jal., Mexico.
‡ American British Cowdray Medical Center, Mexico City, Mexico.

Received:
01/07/2021
Accepted:
09/07/2021

How to cite: Gutiérrez-Fajardo P, Sierra-Galán LM. Coronary atherosclerosis diagnosis by non-invasive studies: echocardiography, computed tomography. Cardiovasc Metab Sci. 2021; 32 (s3): s253-s257. https://dx.doi.org/10.35366/100807

(biphasic response) suggesting viability and ischemia. During the test, EKG, blood pressure, oxygen saturation and symptoms are monitored. Indications for stopping SE protocol are presence of new or worsening of WMA, significant rhythm abnormalities, hypertensive response, significant hypotension and intolerable symptoms.[5]

Diagnostic accuracy and prognostic information. Accuracy of SE refers to detection of coronary artery disease and myocardial viability. Different stressors such as exercise (ES), dobutamine (DBS) and dipyridamole (DYS), have similar accuracies and sensitivities for CAD and results will be related to percentage of coronary stenosis. The more stenotic and greater number of affected coronary arteries, the more probability to provoke wall motion abnormalities. In general, sensitivity and specificity for ES, DBS and DYS are 85% and 77%, 80% and 86%, and 78% and 91%, respectively. On the other hand, a normal SE has been associated with a good prognosis with an event rate for cardiac events less than 1% per year. In terms of myocardial viability detection, DBS is widely used for assessing contractile reserve.[5]

Advantages and disadvantages

Due to its versatility, echocardiography represents the first imaging technique to approach different clinical scenarios. SE maintains these advantages: availability, accessibility, portability, reproducibility, low cost, no radiation, border enhancement agents, rational time protocol and immediate results. Main disadvantages are related with both; patient (poor acoustic window due to thinness, obesity, thorax over distention in some pulmonary diseases and exercise capacity) and operator (level of expertise, left ventricle foreshortening).

Highlights

SE is a reliable NICIS for risk stratification and diagnosis of CAD.

Normal wall motion does not rule out significant CAD.

Abnormal wall motion could be secondary to ischemic or non-ischemic origin.

Negative SE in a high probability pretest patient could be associated to circumflex disease, two non-significant vessel disease or small vessel disease.

CONCLUSIONS

SE remains as a robust NICIS, either with exercise or with a pharmacological agent, allowing the assessment and stratification of patients with diagnosed or suspected CAD. Also, can be used to detect functional viable myocardium.

COMPUTED TOMOGRAPHY

Background. There are mainly two different types of atherosclerotic coronary artery disease (CAD) that can cause acute coronary syndromes (ACS), the obstructive CAD (OCAD) and non-obstructive CAD (NObCAD). OCAD is traditionally clinically recognized by causing a ST-segment elevation during myocardial infarction, by sensitive biomarkers, by high-grade coronary stenosis in coronary computed tomography angiography (CCTA), and by the luminography of the invasive coronary angiography (ICA). However, the identification of NObCAD remains challenging if we study the patients only with «standard imaging modalities» and criteria. It is imperative to learn how to recognize the NObCAD since it contributes to the burden of atherosclerosis. In some groups, such as young women, it represents the majority of cases of ACS. NObCAD causes ACS with significantly lower cardiovascular risk at baseline in those patients, typically categorized as low-risk patients, and a subsequently lower likelihood of death or MACE. However, they are still at high risk for cardiovascular mortality and morbidity based on their underdiagnoses and undertreatment.[6]

Some of these cases are currently included as MINOCA or INOCA syndromes, which include several pathophysiological entities beyond the scope of this text.

Technical principles. The non-invasive evaluation of OCAD and NObCAD relies upon the decision to investigate anatomy vs function. If we decide to investigate CAD functionally, we have to use techniques that look for myocardial perfusion or function at stress, such as echocardiography, nuclear –SPECT

and PET– computed tomography perfusion, and cardiovascular magnetic resonance. If we opt to investigate CAD anatomically, we have to look inside the vessels; the more common, widely available, and reproducible method for that purpose is CCTA.

CCTA is performed in a multidetector CT scanner with the possibility of at least 64 slices. A lower number of detectors is feasible, but the image quality and the amount and type of artifacts refrain from widely used and recommended. The main requirements of this study from the technical point of view are; 1) the intravenous access, it is crucial to have good access to allow a high pressure of a rapid bolus of a considerable amount of viscous iodine contrast media, 2) heart rate control, around 60 bpm, in scanners with a higher number of detectors this requirement is less crucial and even could not be necessary, 3) good patient cooperation with breath-holding during images acquisition.

The presence of arrhythmias and some intravascular-intracardiac devices limits the acquisition, produces several artifacts and reduces image quality; however, it is challenging but feasible in experienced hands.[7]

Radiation dose is important however, we cannot see it, and some personnel is not aware of the risks of the radiation to the patients. We should scan patients having the ALARA principle[8] (as low as reasonably achievable) in mind. Specific data about radiation dose reduction protocols used worldwide and the information from Latin America is shown in detail in the PROTECTION VI study.[9]

Diagnostic accuracy and prognostic information for OCAD *(Figure 1A)*, in the real world, as demonstrated by the PICTURE study, without the bias of patients with a high

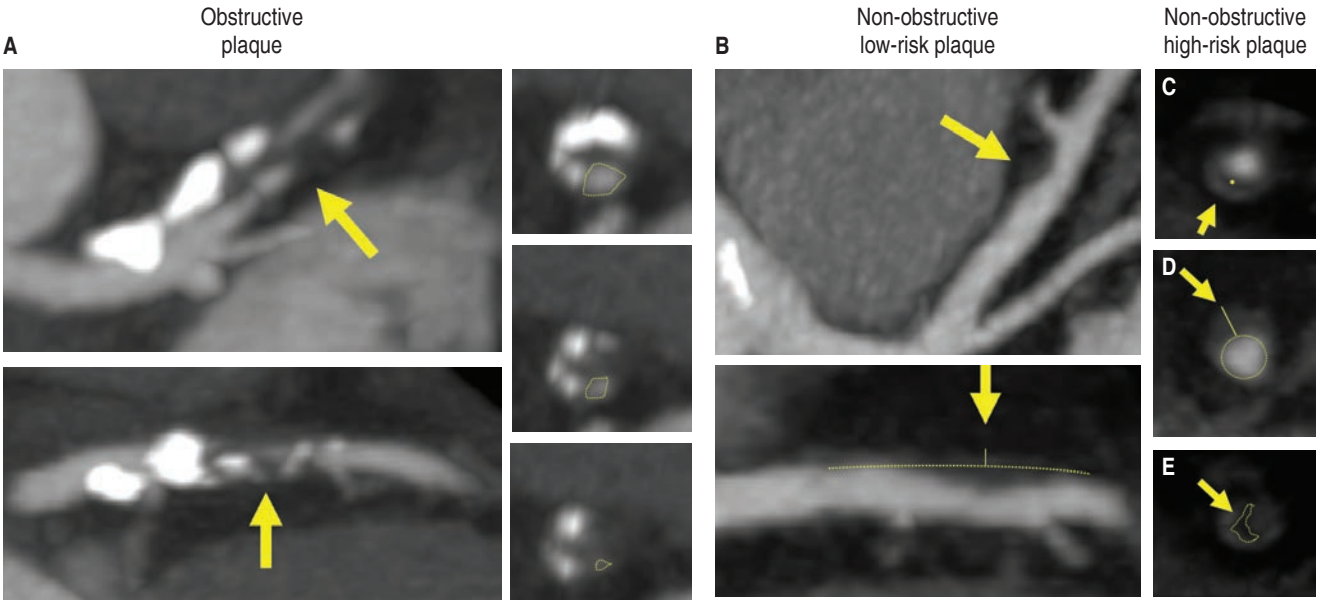


Figure 1: A) The left panel shows high-grade stenosis of the proximal LAD, with stable characteristics such as intense focal calcification, absence of significant positive remodeling, progressive reduction of the lumen, absence of areas of plaque rupture, and napkin ring sign. The right panel shows two different types of non-obstructive plaques. **B)** Shows two orthogonal MPR projections of the proximal LAD. The superior image shows the non-obstructive non-calcified plaque. The lower image shows its positive remodeling (a dashed thin line highlighted the border of the «normal» arterial wall, and the small vertical line marked with the arrow indicates the volume of the non-calcified plaque that expands outwards from the external wall of the artery, representing the positive remodeling. **C-E)** Shows thin axial MPR of the artery with a non-obstructive plaque and different high-risk features. **C)** Shows a plaque that has the napkin ring sing (marked with the tiny asterisk). **D)** Shows a plaque that significant positive remodeling marked with the slim perpendicular line above the lumen (circle). **E)** Shows a low-attenuation plaque of 40 HU delineated and marked with the arrow.
LAD = left descending coronary artery; MPR = multiplanar reconstruction; HU = Hounsfield.

prevalence of the disease, in a prevalence of 52% with a stenosis ≥ 50% by ICA, CCTA has a sensitivity of 92%, and a specificity of 87%. If the stenosis is defined as ≥ 70% by ICA, CCTA has a sensitivity of 93% and a specificity of 89%.[10] The main strength of CCTA is its negative predictive value of 99%, as shown in the ACCURACY trial,[11] giving the ability to discard with confidence and with no additional risk to the patient for future events after an episode of chest pain even from the Emergency Department.[12]

NObCAD *(Figure 1B)* remains challenging since those are the type of lesions that could produce an ACS without being rule out by myocardial perfusion studies and by calling «non-significant» lesions in the CCTA. However, some key features of those lesions have an excellent prognostic value by being associated with the future development of ACS.[13,14] Those features allow to call an atherosclerotic lesion a high-risk plaque and are the equivalent of the histological characteristics of a vulnerable plaque, such as the «napkin ring sing» *(Figure 1C)* that is defined as the presence of a ring of high attenuation around certain coronary artery plaques; and attenuation of the ring presenting higher than those of the adjacent plaque and no > 130 Hounsfield units.[15] This sign has a specificity of 97%, a negative predictive value for future ACS of 99%, and a hazard ratio of 5.55. Therefore, it has significant prognostic importance for ACS. It is independent of other CCTA features such as positive remodeling *(Figure 1D)* and low-attenuation plaque *(Figure 1E)*, which has a hazard ratio of 5.25 and 3.75, respectively; even higher than the presence of an obstructive plaque that has a hazard ratio of 1.62.[14] This information gives us a clue if we do not identify OCAD and the suspicion remains high for ischemic heart disease, the possibility is the presence of one or more features of NObCAD as a surrogate of the presence of an unstable, vulnerable atherosclerotic plaque.

Advantages and disadvantages

The main benefits of CCTA are the ability to evaluate the coronary anatomy non-invasively, its high negative predictive value,[15] and the possibility to identify high-risk plaques with certainty. The main disadvantages are its low positive predictive value, the prompts to further test if the clinical suspicion remains high, and the absence of functional information[15] if following the ALARA principle's current recommendations.

Highlights

CAD, obstructive, or non-obstructive can cause ACS.

There are currently imaging modalities that allow non-invasively the proper identification of each one.

CCTA implies radiation and should be considered when order one to a patient, balancing the benefit to the risk, and using the ALARA principle at all times.

CONCLUSIONS

CCTA should be part of the diagnostic algorithm for patients with dyslipidemia, in intermedia risk[16] and with chest pain, using the ALARA principle in the setting of stable ischemic heart disease and also in the Emergency Department, always taking advantage of its main strength, the negative predictive value to rule out obstructive lesions, and the characterization of vulnerable, non-obstructive plaques.

REFERENCES

1. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJL et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010. The global burden of disease 2010 study. Circulation. 2014; 129: 1483-1492.
2. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, American College of Cardiology Foundation Appropriate Use Criteria Task Force, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013. multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014; 63: 380-406.
3. Marwick TH. Stress echocardiography. Heart. 2003; 89: 113-118.
4. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic,

electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol. 1987; 59: 23C-30C.
5. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. J Am Soc Echocardiogr. 2020; 33 (1): 1-41.e8.
6. Pizzi C, Xhyheri B, Costa GM, Faustino M, Flacco ME, Gualano MR et al. Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis. J Am Heart Assoc. 2016; 5 (12): e004185.
7. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr. 2016; 10 (6): 435-449.
8. Kennington E. Reducing radiation in CT angiography. Nat Rev Cardiol. 2009; 6 (5): 325.
9. Heckner M, Deseive S, Massberg S, Stocker TJ, Hausleiter J, Lesser J et al. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the PROspective multicenter registry on radiation dose estimates of cardiac CT angiography in daily practice in 2017 (PROTECTION VI). Eur Heart J. 2018; 39 (41): 3715-3723.
10. Budoff MJ, Li D, Kazerooni EA, Thomas GS, Mieres JH, Shaw LJ. Diagnostic accuracy of noninvasive 64-row computed tomographic coronary angiography (CCTA) compared with myocardial perfusion imaging (MPI): the PICTURE study, a prospective multicenter trial. Acad Radiol. 2017; 24 (1): 22-29.
11. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008; 52 (21): 1724-1732.
12. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. J Am Coll Cardiol. 2009; 53 (18):1642-1650.
13. Sun Z, Xu L. Coronary CT angiography in the quantitative assessment of coronary plaques. Biomed Res Int. 2014; 2014: 346380.
14. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. JACC Cardiovasc Imaging. 2013; 6 (4): 448-457.
15. Lee JH, Han D, Danad I, Hartaigh BO, Lin FY, Min JK. Multimodality imaging in coronary artery disease: focus on computed tomography. J Cardiovasc Ultrasound. 2016; 24 (1): 7-17.
16. Kramer CM, Taylor AJ, Liaison WG, Mcgann C, Rosenberg A, Schwartz R et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. J Cardiovasc Comput Tomogr. 2010; 4 (6): 407.e1-407.e33.

Correspondence:
Pedro Gutiérrez-Fajardo, MD, PhD
E-mail: drpedrogutierrez@yahoo.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100808

Coronary atherosclerotic disease evaluation by nuclear cardiology procedures: Gate-SPECT and PET myocardial perfusion imaging

Evaluación de la enfermedad aterosclerótica coronaria mediante procedimientos de cardiología nuclear: Gate-SPECT y PET de perfusión miocárdica

Adriana Puente-Barragán, MD*

INTRODUCTION

Atherosclerotic disease is the main cause of coronary obstruction, and its fearsome consequences: myocardial ischemia and infarction (MI). Significant atherosclerotic obstructions of the coronary lumen frequently produce a reduction of coronary blood flow, one of the main pathophysiologic determinants of ischemia.[1,2] The most available techniques to evaluating functional ischemia by nuclear cardiology procedures includes myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT), and positron emission tomography (PET). Both are effective and accurate non-invasive methods, useful not only as a diagnostic tool, but also to establish risk stratification, allowing the appropriate therapeutic decisions, regarding the need of revascularization in patients with coronary artery disease (CAD). According to the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of chronic coronary syndromes,[3] it is advisable to perform a noninvasive cardiovascular imaging diagnosis functional test, with ischemic induction, in symptomatic patients with an intermediate likelihood of disease (> 15-85%), in whom obstructive CAD cannot be excluded by clinical assessment alone, and when computed tomography angiography (CTA) has shown coronary lesions of uncertain functional significance or when this latter test is not diagnostic according to the available expert specialists.

GATED-SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (GATED-SPECT)

Diagnosis of CAD. Gated-SPECT (Tc99m Sestamibi or tetrofosmin and Thallium-201 radiotracers), is useful in the assessment of physiological significance of anatomical coronary stenosis. In the presence of a significant coronary stenosis (≥ 50%), the sensitivity and specificity of rest/stress (stress provoked with physical exercise, drugs or both, combined) analyzed by SPECT MPI (radiation exposure 8-10 mSv with Tc and 10-12 mSv Tl-201) are 87-89% and 73-75%, with a high normalcy rate of 91%, which signals it as a good diagnostic test. Recently, novel technologies with new cardiac-dedicated ultrafast SPECT gamma cameras for MPI have been developed. The special technology with Cadmium-Zinc-Telluride (CZT) detectors have greatly improved MPI diagnosis and prognosis, enhancing imaging resolution, and decreasing time of imaging acquisition, and/or radiation exposure (5-6 mSv). Sensitivity, specificity, and diagnostic accuracy of MPI for detection of significant and functional CAD are 92.8, 69.2, and 81.4%.[4-6]

Gated-SPECT prognostic value. Simultaneous acquisition of data for the evaluation of left ventricular function (LVF),

* Centro Médico Nacional «20 de Noviembre», ISSSTE, Mexico City.

Received:
14/06/2021
Accepted:
23/06/2021

How to cite: Puente-Barragán A. Coronary atherosclerotic disease evaluation by nuclear cardiology procedures: Gate-SPECT and PET myocardial perfusion imaging. Cardiovasc Metab Sci. 2021; 32 (s3): s258-s262. https://dx.doi.org/10.35366/100808

allows estimation of left ventricular volumes (left ventricular end systolic volume: LVESV, left ventricular end diastolic volume: LVEDV), left ventricular ejection fraction (LVEF), the assessment of the left ventricular wall movement, and wall thickness. In MPI, the size, severity, and reversibility of the defect implies the extent of risk, or the «total ischemic burden».[7] Evaluation of MPI is done following the recommendation of the American Society of Nuclear Cardiology (ASNC) SPECT Imaging Guidelines,[8] using a semi-quantitative evaluation of 17 anatomical segments[9] *(Figure 1)*. ASNC SPECT Imaging Guidelines,[8] recommend the classification of the perfusion defect severity as mild, moderate, or severe, and the extension as small, medium, or large. Also, perfusion can be classified according to the behavior of the images in rest and effort as following: 1) «fixed or nonreversible defects», refers to defects that do not change between stress and rest images 2) «reversible defects», on the contrary, are more severe and/or extensive perfusion defects on stress imaging compared to rest images. ASNC SPECT Imaging Guidelines,[8] also suggests classifying the severity of perfusion defect with a semi-quantitative evaluation, using a 0-4 score according to radiotracer uptake as normal (100% uptake), mild (10 to < 25% reduction in counts), moderate (25 to < 50% reduction), severe (≥ 50% reduction) or absent uptake. In the same way and according to the involvement of the LV mass, perfusion defects extension can be classified as a small, medium, or large defects, if respectively involves < 10, 10 to 20%, and ≥ 20% of the LV mass. Quantitative scores can be obtained, comparing the score between rest and stress in the polar maps, and can be classified in summed stress score (SSS) that results of the sum of the stress scores in all the 21 segments, summed rest score (SRS) the sum of the resting scores, and the summed difference score (SDS), which corresponds to the result of the difference obtained from the SSS and SRS (SDS = SSS-SRS). This SDS equals or corresponds to the measure of reversibility (inducible ischemia) and have shown to have a high prognostic value. Another parameter is transient cavity dilation (TID), that describes a modification if the of left ventricle (LV) cavity size, that increases on post-stress images, and it is considered abnormal with a value above 1.2. This abnormal value traduces sub-endo-cardial hypo-perfusion and it is associated with greater ischemic burden and severe and/or multivessel CAD. Lung uptake of thallium-201 in post-stress images, indicates the use of lung-heart ratio (LHR) as a prognostic indicator (> 0.55).[8] Bajaj et al. have stated that a higher pulmonary capillary wedge pressure (due to elevated LV end diastolic pressure) can lead to a slower pulmonary transit of the radioisotope and increases its extraction by pulmonary tissues. The increase of LHR represents an important marker of underlying diastolic dysfunction

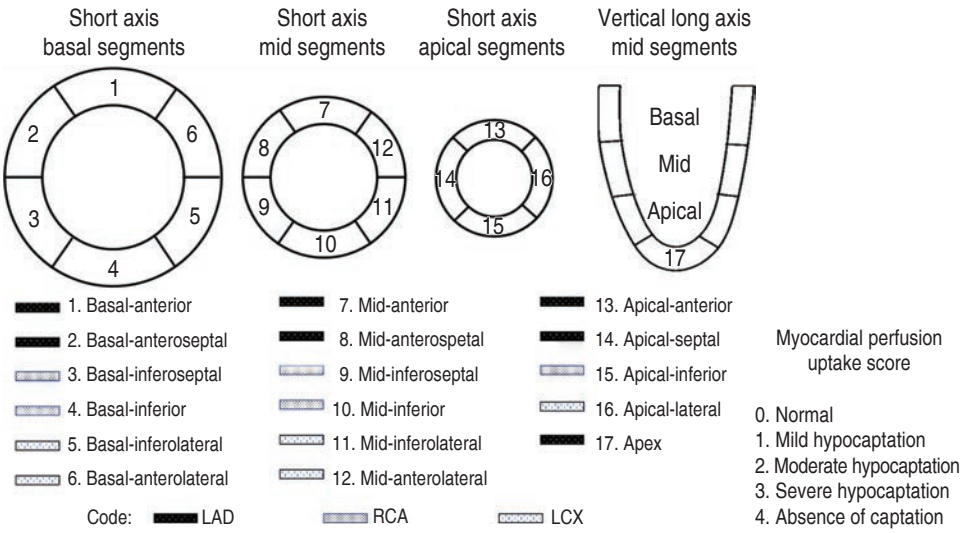


Figure 1:

Evaluation of MPI by a semiquantitative evaluation of 17 anatomical segments. MPI = myocardial perfusion imaging. Modified from: Hansen CL et al.[9]

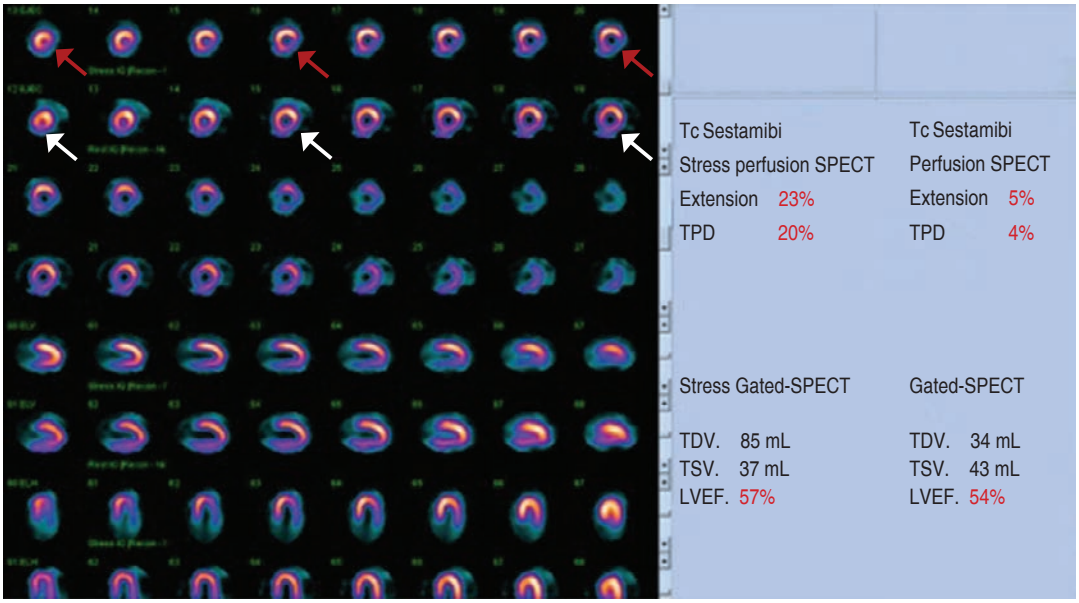


Figure 2: High risk Tc Sestamibi rest/stress Gated-SPECT. Rest image shows an extensive and moderate perfusion defect (white arrows) in the entire inferolateral wall, stress image shows moderate to severe reversibility (red arrows), equivalent to a non-transmural inferolateral infarction with moderate to severe ischemia.
SSS = summed stress score, SRS = summed rest score, SDS = summed differential score, TPD = total perfusion defect, TDV = total diastolic volume, TSV = total systolic volume, LVEF = left ventricular ejection fraction. Contribution from Nuclear Medicine Department, National Medical Center «20 de Noviembre», ISSSTE, Mexico City.

and severe CAD.[10] Quantitative perfusion and LVF evaluation, results in some independent prognostic variables associated with a high risk of mayor adverse cardiovascular events (MACE) rate. A normal Gated-SPECT MPI has an annual MACE (non-fatal myocardial infarction or cardiac death) < 1%; in the other side, a high risk MPI is accompanied by a high MACE rate (≥ 5%). The burden of ischemia guides revascularization treatment decisions. Those patients with an evidence of greater extension of ischemia (> 10-12.5%), benefit from an early revascularization, compared with those with mild degrees of ischemia who benefit better from medical therapy[10] *(Figure 2)*.

POSITRON EMISSION TOMOGRAPHY (PET)

Diagnostic and prognostic value of Stress MPI with Gated-PET. PET allows quantification of *in vivo* physiological processes of the heart. The principal characteristic of PET is its higher spatial resolution and the ability to correct scatter and soft-tissue attenuation. Also, non-invasive PET imaging technique as it has better image quality and higher interpretive accuracy, has greater sensitivity and specificity for detection of obstructive CAD than SPECT. The sensitivity of PET is around of 94-98% with a specificity of 80-89%, and an overall diagnosis accuracy of 92-100% to CAD detection.[4,5] Rest/stress PET with vasodilator (adenosine), exposes patients to significantly lower radiation dose (2.5-3 mSv) due to the nature of the radiotracers used, characterized by high energy and a very short half-life. The most common tracers used for evaluation of ischemia are Rubidium-82 (82Rb; T½ 75 sec) and Nitrogen-13-Ammonia (13 NH3; T½ 10 min). Simultaneous evaluation of coronary anatomy can be done adding computed tomography (CT) through hybrid equipment (Hybrid PET/CT), which improves the positive predictive value (PPV) and negative predictive value (NPV) of PET/CT (90 and 96% respectively) at the cost of higher exposure radiation dose (12-14 mSv).[11] ECG-gated PET (simultaneously evaluating LVF) can be done in real time at rest and during peak stress (in a

different way to post-stress imaging with gated-SPECT).The evaluation of risk stratification and functional reserve are similar. Normally, LVEF increases from baseline (rest) to peak stress. This increment is named LVEF reserve or contractile reserve. When CAD is present, inversely changes in LVEF exist (decrease from rest to stress), and it is related to the magnitude of stress perfusion abnormalities (ischemic myocardium at risk), severity, and extension of CAD. Decreases of LVEF during peak stress comparing with rest, (≤ 5%), even in the absence of apparent perfusion abnormalities, reveals the existence of three-vessel disease or left main CAD. In patients with non-significant CAD obstructions or with 1-vessel disease, LVEF shows a normal contractile reserve with an increase of LVEF ≥ 5%. The NPV of an increase in the difference of LVEF from rest to peak stress with values ≥ 5%, to exclude the presence 3-vessel disease or left main CAD, is 97%. Gated-PET adds prognostic value related to a major extent and severity of perfusion defects in stress imaging (ischemia), that are associated with increasing frequency (≥ 7%) of MACE. In another way, with normal stress imaging, MACE incidence is only about 0.4%. Therefore, mortality is inversely related to LVEF. PET myocardial perfusion imaging added incremental value to LVEF (at any LVEF level, the presence of a higher summed stress score means greater risk) and in an oppositive way, LVEF added incremental value to myocardial perfusion imaging (at any summed stress score, a lower LVEF represent greater risk). PET/CT complements the anatomic information (CAD stenoses) by providing the physiologic (ischemic burden) implications[11-13] *(Figure 3)*.

Quantification of PET myocardial blood flow. PET allows the non-invasive, absolute, and dynamic global and regional quantification of myocardial blood flow (MBF) at rest (MBFR) and peak stress (MBFS), From these data,

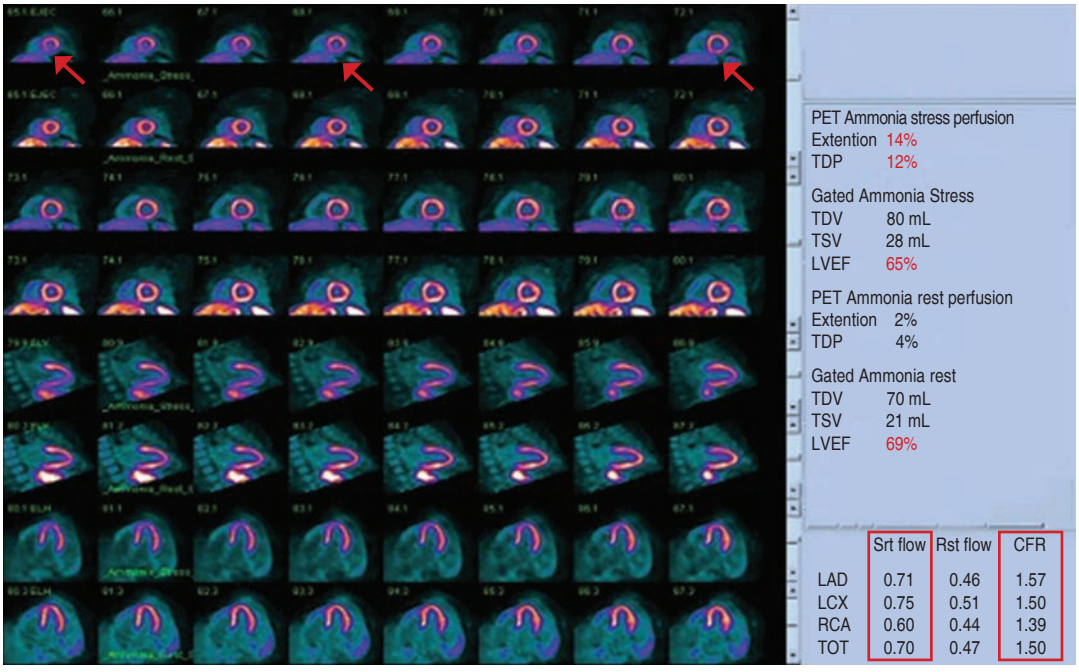


Figure 3: High risk Ammonia rest/stress Gated-PET. Rest mage with normal perfusion; stress image shows extensive moderate reversibility (red arrows) at inferolateral and inferoseptal localization in apical, mild and basal segments, equivalent to moderate ischemia. Gated images demonstrate a fall in stress LVEF > 5% (6%). MBF quantification are decreased in all coronary territories and total CFR is < 2.0 mL/g/min.
SSS = summed stress score, SRS = summed rest score, SDS = summed differential score, TDV = total diastolic volume, TSV = total systolic volume, LVEF = left ventricular ejection fraction, MBF = myocardial blood flow, CFR = coronary flow reserve. Contribution from PET-CT Unit, Medicine/Faculty, National Autonomous University of Mexico, Mexico City.

myocardial flow reserve (MFR) can be assessed (MFR = MBFS/MBFR), expressed in mL/min/g of myocardium. Blood flow quantification reflects the heart's ability to regulate coronary blood flow to the different areas of the myocardium, to reach metabolic demands, modifying the vascular tone in epicardial and small vessels. When severe multivessel CAD exist, the inability to increase flow during stress in all anatomic territories, results in a diffuse (balanced) or apparent normal myocardial perfusion, that could be accompanied with a reduction of global MBF during stress and a diminishing of MFR. A severe reduction of stress MBF (< 1.5 mL/g/min) and MFR (< 1.5) is associated with a higher risk of MACE, while a normal or preserved MFR with a value of ≥ 2.0, is associated with an excellent prognosis and better outcomes. MBF and MFR might be reduced in ischemic patients (epicardial disease), and in other special populations with endothelial dysfunction and microvascular disease, for example, women, patients with hypertrophic cardiomyopathy, diabetes, chronic kidney disease, and obesity. In the follow-up of heart transplant, these variables can signal the existence of cardiac allograft vasculopathy, characterized by intimal hyperplasia rather than CAD. In all this conditions PET MBF provides an additional incremental diagnostic and prognostic value[14,15] *(Figure 3)*.

CONCLUSIONS

Nuclear MPI with SPECT and PET, are effective and accurate non-invasive tools useful in both diagnosis and risk stratification, guiding therapeutic decisions in patients with proved or suspected atherosclerotic CAD. PET is nowadays considered the gold standard technique for non-invasive assessment of MBF. MBF quantification, allows a better assessment of MPI to detect significant epicardial CAD and it is very useful in the evaluation of coronary microvascular endothelial dysfunction, in both ischemic and non-ischemic cardiomyopathies.

REFERENCES

1. Libby P. Mechanisms of acute coronary syndromes and their Implications for therapy. N Engl J Med. 2013; 368: 2004-2013.
2. Marzilli M. Coronary atherosclerosis and myocardial ischemia. Rev Fed Arg Cardiol. 2020; 49: 43-44.
3. Saraste A, Knuuti J. ESC 2019 guidelines for the diagnosis and management of chronic coronary syndromes. Recommendations for cardiovascular imaging. Herz. 2020; 45: 409-420.
4. Al Moudi M, Sun Z, Lenzo N. Diagnostic value of SPECT, PET and PET/CT in the diagnosis of coronary artery disease: A systematic review. Biomed Imaging Interv J. 2011; 7 (2): e9.
5. Al Badarin F, Malhotra S. Diagnosis and prognosis of coronary artery disease with SPECT and PET. Curr Cardiol Rep. 2019; 21: 57-68.
6. Hage FG, AlJaroudi WA. Review of cardiovascular imaging in the Journal of Nuclear Cardiology 2019: single-photon emission computed tomography. J Nucl Cardiol. 2020; 27: 1171-1179.
7. Sabharwal N, Lahiri A. Role of myocardial perfusion imaging for risk stratification in suspected or known coronary artery disease. Heart. 2003; 89: 1291-1297.
8. Dorbala S, Ananthasubramaniam K, Armstrong I, Panithaya C, DePuey G, Einstein A et al. Single iphoton emission computed tomography (SPECT) myocardial perfusion imaging guidelines: Instrumentation, acquisition, processing, and interpretation. J Nucl Cardiol. 2018; 25: 1784-1846.
9. Hansen CL, Goldstein RA, Akinboboye OO, Berman DS, Botvinick EH, Churchwell KB et al. Myocardial perfusion and function: single photon emission computed tomography. J Nucl Cardiol. 2007; 14: e39-60.
10. Bajaj N, Singh S, Farag A, EL-Hajj S, Heo J, Iskandrian E et al. The prognostic value of non-perfusion variables obtained during vasodilator stress myocardial perfusion imaging. J Nucl Cardiol. 2016; 23: 390-413.
11. Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC. Clinical myocardial perfusion PET/CT. J Nucl Med. 2007; 48: 783-793.
12. Dilsizian V, Bacharach S, Beanlands R, Bergmann S, Delbeke D, Dorbala S et al. ASNC imaging guidelines/ SNMMI procedure standard for positron emission tomography. (PET) nuclear cardiology procedures. J Nucl Cardiol. 2016; 23: 1187-1226.
13. Dorbala S, Di Carl M, Beanlands R, Merhige M, Williams B, Veledar E et al. Prognostic value of stress myocardial perfusion positron emission tomography. Results from a multicenter observational registry. J Am Coll Cardiol. 2013; 61: 176-184.
14. Pelletier-Galarneau M, Martineau P and El Fakhri F. Quantification of PET myocardial blood flow. Curr Cardiol Rep. 2019; 21: 11-22.
15. Ziadi M, deKemp R, Williams K, Guo A, ENG M, Chow B et al. Impaired myocardial flow reserve on rubidium-82 positron emission tomography Imaging predicts adverse outcomes in patients assessed for myocardial ischemia. J Am Coll Cardiol. 201; 58: 740-748.

Correspondence:
Adriana Puente-Barragán, MD
E-mail: adripuente@yahoo.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100809

Diagnostic approach of coronary atherosclerosis through invasive procedures: indications and applications of coronary angiography

Abordaje diagnóstico de la aterosclerosis coronaria mediante procedimientos invasivos: indicaciones y aplicaciones de la angiografía coronaria

Xavier Escudero, MD, FACC, FSCAI*,‡ Mara Escudero-Salamanca, MD‡ Manuel Portillo-Villaseñor, MD§

The cardiac catheter was… the key in the lock.
André F. Cournand
1956 Lecture Nobel Prize for Medicine

INTRODUCTION

Coronary angiography is understood as the visualization of the coronary arteries through the injection of a radiopaque contrast material and recorded in radiographic images in digital form. This technique is now the most reliable way to identify coronary anatomy and pathology for therapeutic decision making in patients with myocardial ischemia. Over the next chapter we shall review the most important aspects about its indications and clinical applications in diagnosis and therapeutics for coronary heart disease.

THE PROCEDURE

The pioneering studies in cardiac catheterization by Forssmann, Cournand, and Richards, earned them the Nobel Prize in Physiology or Medicine in 1956. A few years later, Mason Sones performed an aortography by injection in which the catheter accidentally slipped into the right coronary artery, thus giving the first direct angiographic image of a coronary artery in a live patient. The technique was then methodically developed by Sones himself through brachial dissection and later through percutaneous femoral approach by Melvin Judkins.[1] From then on, important breakthroughs in the methodology, mainly the radial artery approach, and the technological advances in guidewire and high flow catheters, as well as digital imaging techniques have made the coronary angiography one of the most used clinical methods in ischemic heart disease. This procedure is safe, very well tolerated and it usually takes between 20 to 40 minutes to be done. In brief, using local anesthesia, a vascular catheter is inserted through the radial or femoral artery employing a percutaneous technique and a 2 mm vascular introducer. With preformed catheters coronary arteries can be easily engaged and images are obtained using a contrast agent. Patients could be sedated, if necessary, pre-treated with heparin 50-100 U/kg and intracoronary nitroglycerin as needed. Images of both coronary arteries in different angles are recorded in a digital radiographic system. At the end of the procedure or intervention, the catheters and introducers are removed, and external arterial compression is applied, preferably with pneumatic compressors. Cardiac complications in a diagnostic procedure are infrequent and they occur in less than 1% of all cases, including acute myocardial infarction, unscheduled revascularization, stroke, coronary dissection,

* Governor of the American College of Cardiology, Mexico Chapter.
‡ Hospital Médica Sur. Mexico City. Mexico.
§ National Institute of Respiratory Diseases «Ismael Cosio Villegas». Mexico City, Mexico.

Received:
06/07/2021
Accepted:
14/07/2021

How to cite: Escudero X, Escudero-Salamanca M, Portillo-Villaseñor M. Diagnostic approach of coronary atherosclerosis through invasive procedures: indications and applications of coronary angiography. Cardiovasc Metab Sci. 2021; 32 (s3): s263-s268. https://dx.doi.org/10.35366/100809

pericardial effusion or even death (0.01%).[2] Major hemorrhage occurs, including subjects undergoing coronary intervention, in 1.3% of patients with a radial approach and 2.5% with a femoral one.[3] The patient usually remains under hospital surveillance until the next day, but in low-risk patients without complications from the procedure, an «outpatient» protocol with early discharge within 24 hours may be considered. It is concluded that diagnostic coronary angiography is a safe and well-tolerated procedure with a very low incidence of complications and short hospital stay.

ANGIOGRAPHIC EVALUATION OF CORONARY ATHEROSCLEROSIS

The images obtained of the coronary arteries by angiography only show the vascular lumen, seen in a two-plane projection. This allows the cardiologist to assess and measure the magnitude of the coronary lesions according to the degree of stenosis of the vascular lumen in relation to the «healthy» reference segments *(Figure 1A)*.

Therefore, it is not possible to visualize the arterial wall, the degree of vascular remodeling, and the characteristics and volume of the plaque. Furthermore, it is necessary to obtain images in complementary projections to visually «reconstruct» the lesions when these are asymmetrical or eccentric. A stenosis is considered «significant» when it is > 50% of the visible diameter or if it obstructs > 75% of the vascular lumen area. Greater obstructions above these percentages have shown a reduction of the distal and reserve flow, as well as a high clinical correlation and with non-invasive ischemia stimulation studies.[4] The direct subjective assessment of the occlusion magnitude will depend on the characteristics of the lesion, the quality of the radiographic images, angulation or the presence of secondary vessel branches or bifurcation. All this factors explain that a great intra and inter-observer variations could exist. The use of quantitative coronary angiography or coronary intravascular ultrasound may be necessary for a more precise characterization and evaluation of the plaque, especially in borderline, complex or difficult to assess lesions *(Figure 1B)*. Even more, it would be ideal whenever possible, the use of functional tests such as the measurement of the pressure differences across a coronary artery stenosis through the «fractional flow reserve» (or FFR) with or without pharmacological therapy to evaluate the significance of the obstruction. This has proven not only to be a better form of identification of the repercussion of coronary stenosis, but also may establish therapeutic indication and prognosis in a more precise way. The cost and time of the procedure, however, has made its use infrequent in routine practice.

In addition to the magnitude and degree of stenosis, the coronary angiography allows to establish various aspects of the morphology and complexity of the plaques. The length of the lesion, its relationship with other vessel branches, eccentricity, ulceration, areas of calcification, dissection or thrombus, should always be considered. In case of total occlusion, it is important to evaluate the degree of distal flow or perfusion, as well as the presence of collateral circulation. For each of these variables there are numerous classifications that extend beyond the scope of this review. Finally, it is important to establish the location and extension of the disease and the identified lesions, for which it is not only useful the correct knowledge of the anatomy but the use of the international nomenclature and definition of the different segments of the coronary tree.[4] With the information of morphology, complexity and extension, the risk for every case may be established using different risk scores for decision-making. One of the most used risk calculators is the SYNTAX score; that has been thoroughly validated, is easy to do at the website (www.syntaxscore.com), and it may estimate the risk of clinical events and the prognosis with the different revascularization treatment alternatives.[5]

CORONARY INTRAVASCULAR ULTRASOUND (IVUS)

As mentioned, the main limitation of coronary angiography is that the images only depict the vascular lumen, creating a «luminogram». The IVUS permits the direct visualization from the

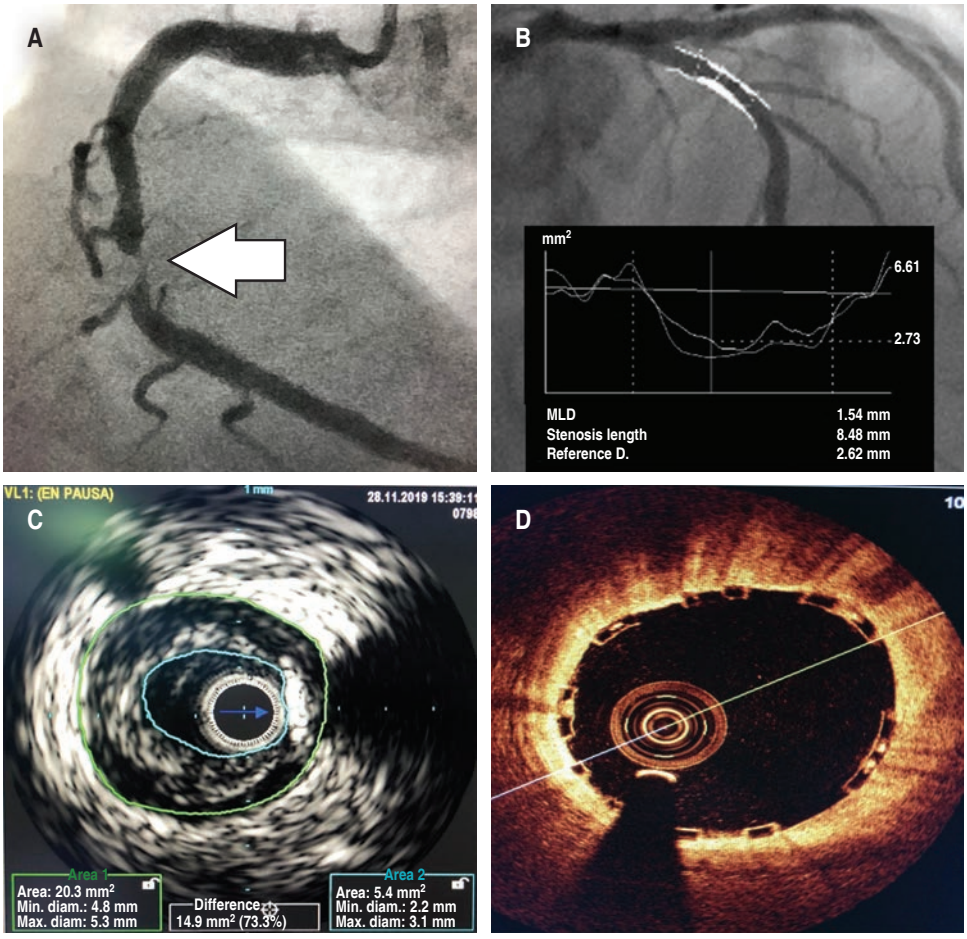


Figure 1:

Images of atherosclerotic plaques through invasive procedures: **A)** Angiography of a critical lesion of the right coronary artery (arrow). **B)** Quantitative coronary angiography of a borderline lesion in the proximal left anterior descending coronary artery with measurements. **C)** Intravascular ultrasound showing a significant obstructive stable plaque. **D)** Optic coherence tomography after placement of a coronary stent.

interior of the vessel, enabling a circumferential analysis of the vascular wall. The procedure is done using a guiding catheter for coronary angioplasty and a 0.014" coronary guide wire. A special catheter containing the miniaturized ultrasound transducer of < 1 mm is then advanced to the distal segment of the coronary artery and a slow pullback is done, usually by a mechanical retraction system at a rate of 0.5 mm/s. The images obtained with transducers of 40 to 60 MHz, allow a full vision of the vascular wall at high resolution *(Figure 1C)*. The procedure lasts an additional 10 to 15 minutes, and it may be performed as many times as necessary in a single intervention. The complications are quite uncommon with experienced hands, being coronary vasospasm the most frequent (1%). The information gathered represents a considerable segment of the entire length of the coronary vessel and it reveals the extension, magnitude, and characteristics of the disease with great detail, being important in the decision-making process. The measurement at the reference segments, and at the level of stenosis called «minimal luminal area» shows the severity of the lesion, being less than 4.0 mm^2 a significant obstruction in non-left-main lesions. The length, volume, plaque characteristics, areas of dissection, vulnerable plaques or calcifications can be seen with great detail and may prove to be important in the decision-making process. In case of a percutaneous coronary intervention with a stent, it enables a better selection of the material and a better outcome through the optimal placement, attachment and post-dilation that decreases the complications of thrombosis and restenosis in the medium or long-term follow up. Undoubtedly, it is a great advance in the assessment of ischemic

heart disease, and it let to make better therapeutic decisions.[6]

OPTICAL COHERENCE TOMOGRAPHY (OCT)

This novel imaging technique generates tomographic images from almost-infrared light produced by a rotational optic fiber. The images have a significantly higher resolution (10-20 µm) but less penetration. The technique to perform the procedure is similar to the one described for the intravascular ultrasound. The difference is that in order to avoid the interference of the red blood cells, it becomes necessary the administration of a contrast agent, synchronized with a rapid automated retraction system that obtains and reconstructs the images in seconds. It is ideal for visualizing the intimal layer, dissection areas and vulnerable plaques. The adequate placement and attachment of stents may be clearly seen even in longitudinal and even tridimensional reconstruction *(Figure 1D)*. Although it is less used than IVUS, both techniques are useful and complementary.[6]

INDICATIONS OF CORONARY ANGIOGRAPHY

The indication for invasive coronary angiography will essentially depend on the patient's clinical status. In all cases the goal is to establish the diagnosis, prognosis, and the type of treatment with or without coronary revascularization. We may distinguish three types of indications: acute coronary syndromes, chronic coronary syndromes or as a routine procedure for direct diagnosis *(Table 1)*.

ACUTE CORONARY SYNDROMES

This may be the clearest indication for an invasive coronary angiography. The proven benefit of arterial reperfusion therapy in this clinical condition and the importance of timing have been deemed essential in the treatment of coronary syndromes. In case of a ST-segment elevation myocardial infarction the early coronary angiography, whether in the context of primary angioplasty or following fibrinolysis, have a clear recommendation in international guidelines (class I, level A). The procedure should also be done between 12 to 24 hours if the patient remains symptomatic, clinically unstable or with signs of important residual ischemia (class I, level C).[7] In patients with very high-risk non-ST-segment elevation myocardial infarction, immediate (within 2 hours) coronary angiography with an invasive strategy is suggested, or within 24 h in patients with high risk, including ST-segment depression or dynamic EKG changes, cardiac biomarkers, signs of ischemia or with any other high-risk clinical variables (GRACE score > 140).[8] After this period of time, the decision will depend on the clinical condition, evolution and the level of induced ischemia.

Table 1: Indications for invasive coronary angiography.

ACS-STEMI	Angiography and primary angioplasty are recommended over fibrinolysis in patients with < 12 hours of onset of symptoms or in > 12 hours, after fibrinolysis, if symptoms persist, or there are hemodynamic instability or severe arrhythmias
ACS-NSTEMI	Urgent angiography (< 2 h) is indicated in very high-risk patients. Within 24 hours at high risk: persistent angina, ECG changes or enzyme elevation. In 12-48 h if symptoms persist, or there are severe ischemia or LV dysfunction
CCS	Persistence of symptoms after optimal medical treatment. Severe ischemia unveiled with non-invasive studies, or inconclusive results with a high probability of the disease. Significant high-risk lesions on coronary CT angiography
Direct	Before high-risk heart surgery, or organ transplantation. Prior to surgery for aneurysm or aortic dissection. Hypertrophic cardiomyopathy with angina or Kawasaki disease with documented coronary aneurysms

Indications for invasive coronary angiography: ACS-STEMI = ST segment elevation acute coronary syndrome; ACS-NSTEMI = non-ST segment elevation acute coronary syndrome; CCS = chronic coronary syndrome; EKG = electrocardiogram; LV = left ventricular.[7-9]

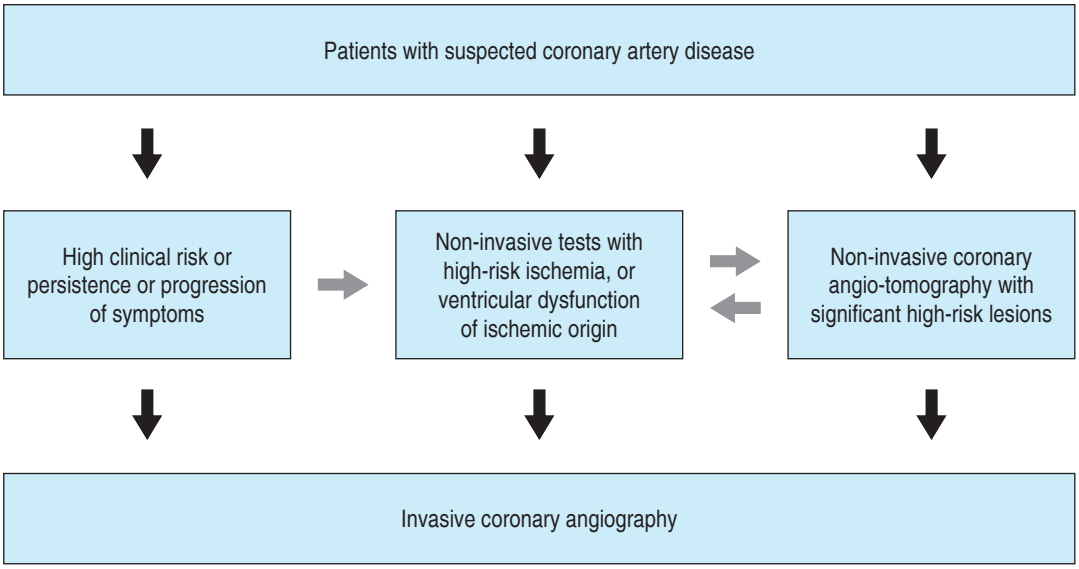


Figure 2: Diagnostic pathways in patients with suspected coronary artery disease. Solid black arrows show the preferred decision algorithm, and alterative personalized options in gray arrows.

CHRONIC ISCHEMIC HEART DISEASE (CHRONIC CORONARY SYNDROME)

It is this condition the one with greater difficulty for clinical decision-making within the diagnostic algorithm of ischemic heart disease *(Figure 2)*.

In high or very high-risk patients, whether because of symptom persistence (severe, progressive, or refractory angina) or severe ischemia with high-risk markers put in evidence through non-invasive tests, it becomes clear that an invasive coronary angiography with eventual subsequent revascularization is the step to follow. With low-risk or low probability of coronary atherosclerosis patients, the recommended diagnostic study is a non-invasive CT coronary angiogram. However, if extensive or critical proximal high-risk disease is documented with this diagnostic study, the patient must be referred for an invasive coronary angiography. The same applies to patients with documented ventricular dysfunction and a history or suspicion of chronic ischemic heart disease where invasive coronary angiography is indicated because of the probability of high-risk lesions, and the benefit of revascularization in most of these cases.[9] The more difficult decision lies in the intermediate-risk group, in which it is necessary to consider not just the risk profile but the co-morbidities, characteristics of the symptoms, the grade and extension of ischemia in each case, and of course the patient's preference. The ischemia trial compared conservative treatment with optimal medical management versus an initial invasive strategy in 5,179 patients with chronic ischemic heart disease, without finding significant differences in the occurrence of major clinical events in both study groups after three years of follow-up.[10] This demonstrates the efficacy of an adequate medical treatment and it shows that an invasive strategy, either with angioplasty or surgery, must be reserved for those patients that remain symptomatic or that exhibit severe ischemia or high-risk coronary stenosis with a poor prognosis. Finally, it may become necessary to perform and invasive coronary angiography if the symptoms or the non-invasive studies are inconclusive and if the clinical conditions of the patient suggest the likelihood of coronary artery disease or possible benefit of revascularization. Certainly, in the absence of symptoms, without significant documented ischemia or the absence of obstructive lesions by non-invasive angio-tomography, there is no indication to perform an invasive coronary angiography.

DIRECT DIAGNOSTIC STUDY

Some critical clinical conditions may indicate a direct coronary angiography as a routine procedure. Some of them are the preoperative evaluation before cardiac surgery in heart valve disease, before cardiac or organ transplantation, patients with proximal aortic disease with dissection or aneurysm subject to surgery, hypertrophic cardiomyopathy with persistent angina or asymptomatic Kawasaki disease with documentation of coronary aneurysms. In some countries, certain labor regulatory conditions in high-risk jobs, may indicate an invasive procedure but in this instance CT non-invasive coronary angiography has become the first line diagnostic study.

PERSPECTIVE AND CONCLUSIONS

Under the Hippocratic precept *primum-non-nocere* or first, do no harm, any clinical study, especially if it is invasive, must have a clear indication and a prognostic and therapeutic objective. The technological advances are surprising; they have resulted in the ability to see the coronary anatomy rapidly, and directly, with great accuracy and precision. The great progress with non-invasive studies, especially CT angiogram, has also yielded impressive results, is necessary to consider the best alternative for each case. It should be emphasized that cardiac catheterization and invasive angiography entail high costs, potential complications and may lead to specific therapeutic decisions. Therefore, the indication must be substantiated by risk determinants that put the need for subsequent revascularization in the therapeutic scenario, counting with the empowerment of the patient to participate in this decision. For interventional cardiologists, few moments are as intense and as satisfying as being in the cardiac catheterization laboratory. They will give what they were to be in the catheterization room every day, but at the same time will do everything possible to ensure that patients who do not require an invasive study were in the same room. If the catheter was «the key in the lock», let us use it wisely.

REFERENCES

1. Escudero X. Historia de la hemodinamia y la cardiología intervencionista en México. México: Ed. PyDESA; 2017.
2. Al-Hijji MA, Lennon RJ, Gulati R, El Sabbagh A, Park JY, Crusan D et al. Safety and risk of major complications with diagnostic cardiac catheterization. Circ Cardiovasc Interv. 2019; 12 (7): e007791.
3. Brener MI, Bush A, Miller JM, Hasan RK. Influence of radial versus femoral access site on coronary angiography and intervention outcomes: a systematic review and meta-analysis. Catheter Cardiovasc Interv. 2017; 90 (7): 1093-1104.
4. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. J Am Coll Cardiol. 1999; 33 (6): 1756-1824.
5. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005; 1 (2): 219-227.
6. Mintz GS, Guagliumi G. Intravascular imaging in coronary artery disease. Lancet. 2017; 390: 793-809.
7. Ibáñez B, James S. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology. Eur Heart J. 2018; 39: 119-177.
8. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021; 42 (14): 1289-1367. doi: 10.1093/eurheartj/ehaa575.
9. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41 (3): 407-477.
10. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020; 382: 1395-1407.

Correspondence:
Xavier Escudero MD, FACC, FSCAI
E-mail: xescuderodr@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100810

The continuous assistance, referral and discharge criteria, implementation barriers

La asistencia continua, los criterios de derivación y de alta, los obstáculos de implementación

Guillermo Saturno-Chiu, MD*

INTRODUCTION

Cardiovascular (CV) disease is one of the greatest health problems of our century. These diseases appear in a good proportion of patients with clearly defined risk factors. Adequate control of one of them: dyslipidemias, has a considerable impact on the possibility of a major cardiovascular event occurring. For this, within health systems, both patients and physicians face a series of obstacles to achieve adequate care on an ongoing basis.

THE IMPORTANCE OF A STRICT CONTROL OF LIPID CONCENTRATIONS

For a strict control of lipid concentrations, both physicians and patients need to become aware of what is being prevented. On one hand, physician must have the clinical sensitivity to do so, overcoming daily problems in care in public and private health services. It has been observed that both physicians and patients pay little attention to attain a perfect lipid control. The causes are diverse, and within them, some are attributable to practitioners, and other to patients themselves or to the health care system. Sometimes a physician does not intensify the treatment or does not pay attention to a perfect lipid control due to ignorance or to the lack of updated knowledge, that justify the relevance of a perfect lipid control, or because the professional underestimates the problem.[1] The saturated consultation of many physicians and the lack of knowledge about what to prevent, tend to create an ambience of conformism about the patient´s health. Additionally, some physicians do not believe in the long-term positive impact of lipid control, and they pay little attention in caring, «trusting» that no major CV event will occur. On the other hand, many patients may abandon or reduce the vigilance in this matter, either due to the cost of treatment or because of the misconception that establishes that medications must be taken only when there are symptoms. On many occasions, after the physician prescribes a treatment, the patient decides not to take it, or to halve the dose, breaking up treatment compliance. When for some reason the treatment is not intensified or monitored, the phenomenon has been called *clinical inertia*.[1] The causes for which clinical inertia occurs are summarized in *Figure 1*. Several studies have shown that close monitoring of patients provides favorable long-term results. An example is the MIRVAS study, which encompassed 247 patients that were randomized into two groups, one with programmed visits at 2, 5, 12, 24 and 36 months. These visits were aimed to monitor the strict control of risk factors, including lipid serum concentrations and to advise about a healthy lifestyle. In the other group of 126 patients, these ones have a single appointment a year, delegating in themselves the responsibility of their own treatment. This situation occurs usually in many health systems. The intervention

* Director of UMAE (Medical Unit of High Specialization). Hospital de Cardiología CMN Siglo XXI, IMSS. Mexico.

Received:
02/07/2021
Accepted:
11/07/2021

How to cite: Saturno-Chiu G. The continuous assistance, referral and discharge criteria, implementation barriers. Cardiovasc Metab Sci. 2021; 32 (s3): s269-s272. https://dx.doi.org/10.35366/100810

group had a higher survival rate compared to the other group (3-year survival rate 97.4 vs 85.5%, p = 0.003). The intervention group results demonstrate that the comprehensive and intensive control of CV risk factors reduces the absolute risk of CV morbidity by 28.5% and total mortality by 11.9%.[2] This simple study shows the importance of forming a group of health professionals who have the necessary preparation to detect severe pathological scenarios in dyslipidemia, with defined study protocols and precise therapeutic surveillance. Hence the need to have a continuous patients care system, going from hospital attention of severe clinical conditions to primary care.[3]

BARRIERS IN THE IMPLEMENTATION OF A CONTINUOUS CARE SYSTEM

There are certain barriers that prevent patients from receiving continuous and effective treatment, not only at the time of diagnosis but also throughout surveillance for the rest of their life, which in certain conditions, includes their family study. The following factors that affect continuity of care are described:

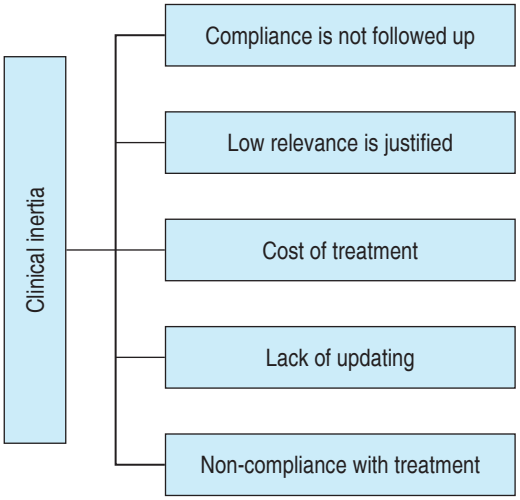


Figure 1: Causes of clinical inertia in treatment.

Table 1: Barriers to implementing a continuous assistance system.

Fragmented health care system
Lack of communication on therapeutic objectives between the two systems
Different therapeutic criteria between the two systems
Difficulty in the use of high-cost drugs

1. **A fragmented health system:** on many occasions, hospital care, where specialists are present to attend acute complications of CV diseases, do not have communication with primary care physicians. The hospital specialists can adopt two behaviors. On one hand, when faced with an interesting case, they may stay close to the patient to carry out studies considered pertinent They establish a treatment, and perhaps publish the case. Finally, the patient is discharged and sent to primary care, with indications to continue the treatment, but without a monitoring protocol, counseling, or contra-referral to evaluate progress or adherence to treatment. In another scenario, the specialists treat the CV event, discharges the patient, and send him to primary care, giving instructions be studied from other clinical entities that may affect the CV risk. On the other hand, the primary care physician may not establish close surveillance for the case, either due to ignoring the objectives pursued, or due to saturation of the care system, worsening the risk that the patient may have in the mid-term future.[4] Likewise, on several occasions and especially in family dyslipidemias, the study does not cover other members of the family, which also affect prognosis of such patients. In this situation, a link between the two care systems is a priority, to define criteria for referral, evaluations and monitoring of patients.
2. **Therapeutic goals are not shared:** often the therapeutic goal in both care systems is not shared due to lack of effective communication. On one hand, hospital care acts independently without considering the primary care system that will give continuity and surveillance to the case. On the other hand, primary care physicians have several limitations to control the case and does not share therapeutic objectives or diagnostic and surveillance strategies with hospital care. Nor does it share the disrupt of other diseases that may generate a transcendent impact in

Table 2: Objectives of a Cardiovascular Risk Unit.

Unified and multidisciplinary consultation
Decisions in clinical sessions
Constant and updated communication on clinical practice guidelines with the primary care system
Virtual consultations and tutorials with PC in the management of patients with elevated CVR
Serves as a link between the two systems
Promotes reasoned prescribing of high-cost medicines
Criteria for referral to hospital care and discharge to primary care

PC = primary care, CVR = cardiovascular risk.

Table 3: Dyslipidemias warranting referral to a Cardiovascular Risk Unit with High Specialty Hospital Counseling.

Referral criteria	
Dyslipidemia	Values (mg/dL)
Hypercholesterolemia	CT > 300
	cLDL > 200
	Lp(a) > 117
Hypertriglyceridemia	TG on an empty stomach > 1,000
	TG > 500 mg/dL with Tx
	TG and CT > 350
cHDL	cHDL < 20
	cHDL > 100

the clinical and lipid evolution of the patient.

3. **The commons criteria of treatment are lost:** the need to reduce and control CV risk factors, requires adequate diagnosis and treatment for different conditions in dyslipidemias. Treatment criteria become complicated when involves the use of high-cost drugs. The justification for its use, the risk of not being able to sustain the treatment or its abandonment, make the situation more difficult. In these cases, the treatment tends to be «replaced» by others with less efficacy in each case, losing the therapeutic objective and the goal in controlling the CV risk factor. *Table 1* lists the factors or barriers that prevent continued care in patients with dyslipidemia.

THE CONTINUOUS ASSISTANCE

To establish continuity in patient care, a clear definition of the functions of both systems must be ensured: hospital and primary care. This implies that the diagnostic and treatment strategies are shared by the two care levels in such a way that both pursue the same study and management objectives. A confronted care system, poorly communicated and without shared objectives, advances or evolutions; leaves patients in a therapeutic vacuum that puts them in risk. For this, it would be useful to set up a Cardiovascular Risk Unit to serve as a link between Primary Care and specialized Hospital Care. In some countries, these units are made up of cardiologists, endocrinologists, and specialists in internal medicine, conforming a multidisciplinary health group that study, modify, adjust and establish a link with both systems of care. The proposal of such units has the following advantages:

1. Control and monitor the evolution of patients, establishing frequent appointments, whose objective is to achieve therapeutic goals. The attainment of that these goals have a beneficial impact on the patient's prognosis, then awakening and reinforcing the interest of patients to achieve these goals. Above all, the physician-patient bond is strengthened.
2. Serving as a link between primary and hospital care, in such way that both systems are informed about the evolution, prognosis, and the reach of therapeutic

Table 4: Criteria for discharge from a Cardiovascular Risk Unit to Primary Care.

Hypercholesterolemia	Secondary hypercholesterolemia Polygenic hypercholesterolemia
Hipertriglyceridemia	Mixed hyperlipidemias after strict cardiovascular evaluation Secondary hypertriglyceridemias
cHDL	After controlled cardiovascular evaluation
Primary prevention	Controlled non-genetic forms
Secondary prevention	Controlled non-genetic forms with stable cardiovascular evaluation

goals. In that form, both systems are aware of the patient.

3. Controlling the indication of high-cost drugs, becomes reasonable the economic burden on the system. Their prescription is done following precise established guides and goals. The justification of the use of these costly treatments and their temporality should be promoted within the system in order to get physicianto prescribe them reasonably.
4. Establishing criteria for specialized hospital admission and control criteria in primary care. This relieves pressure on saturated healthcare systems.

Table 2 establishes the objectives of a Cardiovascular Risk Unit.

CRITERIA FOR REFERRAL AND DISCHARGE OF A CARDIOVASCULAR RISK UNIT

Although the criteria can be defined in the dynamics of each particular health system, it is important to mention that those severe and complex dyslipidemias commonly associated to adverse outcomes, merit closer monitoring and a well-defined study protocol. In general, in familial dyslipidemias, characterized by having very high total cholesterol, LDL or triglyceride concentrations, as well as patients with a family history of severe dyslipidemias or cardiovascular death at early ages, would be candidates for study and referral to these units. In these clinical presentations, the possibility of genetic and family studies, or the use of high-cost drugs, justify an adequate study and a precise therapeutic definition.

Table 3 shows the dyslipidemias that would warrant referral to a cardiovascular risk unit with highly specialized hospital counseling.[5]

The criteria for discharge from a CV risk unit are patients with secondary dyslipidemias and in those whose clinical-pathological condition allows periodic surveillance with an acceptable risk of control in primary care. It should be noted that the proposal includes the notion that the patients is not finally discharged, but sent to primary care, to continue the accompaniment and surveillance their clinical conditions.

Table 4 shows the criteria for discharge from a Cardiovascular Risk Unit in the lipid scenario.

CONCLUSIONS

Strategies must be focused on improving the prognosis and survival of the patient. Medical and health management strategies must be designed for this purpose. Updating and overcoming administrative barriers are part of main objectives in patient care. The creation of CV risk units is one of the proposals to achieve these goals and improve the patient's life prognosis.

REFERENCES

1. Pillips LS, Branch J, Cook CB et al. Clinical inertia. Ann Intern Med. 2001; 135: 825-834.
2. Moreno-Palanco MA, Ibáñez-Sanz P, Ciria-de Pablo C et al. Impacto de un tratamiento integral e intensivo de factores de riesgo sobre la mortalidad cardiovascular en prevención secundaria: estudio MIRVAS. Rev Esp Cardiol. 2011; 64: 179-185.
3. Jennings C, Astin F. A multidisciplinary approach to prevention. Eur J Prev Cardiol. 2017; 24: 77S-87S.
4. San Vicente BR, Pérez II, Ibarra AJ et al. Guía de Práctica Clínica sobre el manejo de los Lípidos como factor de riesgo cardiovascular. Vitoria-Gasteiz; Osakidetza, 2008.
5. Sanchez-Chaparro MA, Pérez-Martínez P, Ibarretxe D et al. Criterios de derivación para pacientes a las unidades de lípidos de la Sociedad Española de Arteriosclerosis. Clin Invest Arteriscler. 2019; 31: 26-30.

Correspondence:
Guillermo Saturno-Chiu, MD
E-mail: jasl97@yahoo.com.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100811

Hypertension and dyslipidemia

Hipertensión y dislipidemia

Arturo Guerra-López, MD*

Cardiovascular diseases (CVD) are the leading cause of death, both in Mexico and in the rest of the world. Cardiovascular (CV) risk factors are not only etiopathogenic agents of CVD, but also, their presence worsens their outcomes, including mortality. High blood pressure (HBP) is one of the main leading cardiovascular (CV) risk factors next to dyslipidemia, diabetes mellitus, obesity, smoking, and physical inactivity.

The main objectives of this text are to discuss the relationship between HBP and dyslipidemia, and their pathogenic mechanisms, which increase the underlying vascular damage in the development of CVD. Also, some epidemiologic aspects of CVD in Mexico will be discussed, to better understand the proper way to get control of the disease and how the combination of both pathologies, HBP and dyslipidemia, increment their potential damage due to the addition of multiple pathophysiologic mechanisms.

HBP is one of the leading CV risk factors in Mexico, as the national surveys on health and nutrition, organized by the Mexican Federal Secretary of Health and the National Institute of Public Health have revealed.[1,2] After HBP, diabetes, tobacco smoking, and dyslipidemias are the most relevant risk factors.[3] The rate increases as the population ages.

In Mexico the underreporting, undertreatment and poor cipher control of HBP are of great concern, explaining in part the steady increase of atherosclerotic cardiovascular diseases (ASCVD) in our country. Ischemic heart disease was the leading cause of general mortality and stroke, the sixth, in 2019.[4] The so called «rule of the halves»[5] establishes that of the entire universe of patients with HBP, only half of them is aware that are hypertensive, only half of these informed patients receive antihypertensive treatment, while among those treated, only half are controlled.[6] This rule is a measure of the health authority's efficacy, the medical community's attitude and knowledge, and the general society information level. In time, in the most advanced countries this rule had been changed, increasing the number of awareness, treatment and control rates. This has not happened in Mexico. Different governmental and independent studies have shown dissimilar total control rates (the proportion of all hypertensive universe that are controlled, not only the control rate of treated patients), varying from 5% to 20%.[7-9]

HBP is a condition that has serious health repercussions, damaging the arterial vessels and the parenchyma of organs of vital importance as the brain, eye, heart, and kidney. In patients aged 40-89 years, starting from blood pressure figures of 115/70, every 20 mmHg increase of systolic pressure or 10 mmHg of diastolic pressure doubles the mortality risk due to ischemic heart disease or stroke.[10,11]

National Health and Nutrition Survey in the last four lustra have shown that in Mexico, HBP ranks high among the nine most common causes of death, to the point that in 2015 was responsible of 18.1% of the preventable deaths.[12] A form of estimating the burden of a particular disease in a nation or subnational region is the calculation of DALYs (disability-adjusted life years), an indicator which unites premature mortality with disability. HBP in our country ranks fifth place among the risk factors responsible for the national disease burden.[13]

* Hospital Excel. Tijuana, Baja California, México.

Received:
11/06/2021
Accepted:
28/06/2021

How to cite: Guerra-López A. Hypertension and dyslipidemia. Cardiovasc Metab Sci. 2021; 32 (s3): s273-s276. https://dx.doi.org/10.35366/100811

Different sources (national surveys carried out in 2000, 2006 and 2012 and academic independent studies)[1,7-9,14] confirm that depending on the characteristics of the sample and the blood pressure measure technique, prevalence of hypertension varies from 25 to 32%.[1-3,7-9,12] Although from 2000 to 2006, there was a slight increase in HBP prevalence, from the latter year to now, HBP prevalence has remained stable. We do not consider the findings of the so-called Half-way National Health and Nutrition Survey,[2] because the technique to measure blood pressure was changed. According to various studies, HBP rises with age, until more than half of people over 70 years of age are hypertensive. Most Mexican hypertension investigators agree that men are more affected than women in younger ages. But upon reaching the menopause, prevalence tends to be similar in both genders, and in older age groups, there are more hypertensive women, probably because more men have already died.

Moreover, dyslipidemia is another risk factor of great importance in Mexican population. The 2006 National Health and Nutrition Survey (ENSANUT 2006) showed that in the Mexican population aged 20 to 69 years, the prevalence of several types of lipid abnormalities was as follows. Total cholesterol (TC) ≥ 200 mg/dL, was 43.6%. Hypertriglyceridemia (triglycerides [TG] ≥ 150 mg/dL) was found in 31.5% of participants, while prevalence of hypoalphalipoproteinemia (HDL-c < 40 mg/dL) was 60%, and that of combined dyslipidemia (TC ≥ 200 mg/dL plus TG ≥ 150 mg/dL) was 18.2%.[15] Hypertriglyceridemia was found more elevated in the RENATHA study:[16] which showed a prevalence between 25-65% in diverse states of the republic, with a national mean value about 50%, while the Lindavista study[9] found 62% of hypoalphalipoproteinemia in the cohort, and hypertriglyceridemia in half the women and nearly two-thirds of the male respondents. This lipid combination is probably the consequence of abnormal Amerindian genes plus a recent drastic change in eating habits, and lack of physical exercise. For those reasons, our population is prone to abdominal obesity, the so-called «metabolic syndrome» (dysmetabolic obesity), dysglycemia, diabetes, and atherogenic dyslipidemia.

The combination of HBP and dyslipidemia increases four times the risk of CVD, as was demonstrated by Yusuf's INTERHEART study.[17] This combination of risk factors is frequently found in Mexican population, concerningly associated to obesity and diabetes mellitus. In the FRIMEX study[8] of 140,017 persons, it was demonstrated that to a higher total cholesterol value, corresponded a greater prevalence of HBP (19.9% when TC was < 200 mg/dL, 27,8% with TC between 200-239 mg/dL, and up to 33% when TC was ≥ 240 mg/dL).

The relationship between HBP and dyslipidemia is signaled by several pathophysiological mechanisms including, but not limited to endothelial dysfunction, oxidation, inflammation, and the role of the renin-angiotensin-aldosterone system (RAAS), among other processes, all of them having a paramount participation in the genesis of both risk factors and their vascular and organ consequences.

A healthy endothelium should respond to increased pressure, to shear, and to perpendicular stress, producing vasodilating substances. A healthy endothelium must maintain the equilibrium between the vasodilating substances nitric oxide, prostacyclin, bradykinin, and acetylcholine, among others; and the vasoconstrictor substances, like angiotensin II, endothelin, thromboxane A2, and others. Risk factors such as HBP and dyslipidemia potentiate each other, altering the normal endothelium function.

In this context, the RAAS plays a primary role in this homeostatic equilibrium when it is overexpressed. Angiotensin II has been named the proinflammatory «honorary cytokine» causing through various mechanisms endothelial dysfunction, decreasing nitric oxide availability, increasing PAI-1 production, promoting platelet aggregation, causing vasoconstriction, and producing overactivity of the membrane NADPH oxidase, one of the main producers of reactive oxygen species (ROS). Among the consequences of the increase of ROS are the start-up of the nitroxidation cascade, the increment of low-density lipoprotein (LDL-c) peroxidation and damage to all biomolecules These processes disrupt vascular permeability, generate more infiltration of leukocytes, and

activate transcription factors like the nuclear factor-kappa B (NF-κB), which is also activated by angiotensin II. NF-κB[18,19] is a crucial promoter of a variety of cellular responses, including tissue growth, inflammation, autophagy, apoptosis, production of adhesion molecules (as vascular cell adhesion molecule-1, VCAM-1), release of chemokines (as the monocyte chemoattractant protein-1 (MCP-1), and interleukins 1, 6 and 8 (IL1, 6 and 8), among others. All these substances lead to atherogenic mechanisms, as are tissue cholesterol entrapment, inflammation, vascular tissue remodeling, proliferation of smooth muscle cells, activation of metalloproteinases, debilitation of the fibromuscular atheroma cap, etc.

The main target in the treatment of dyslipidemias is the LDL-c. The desirable value of the concentration of total cholesterol, LDL–c and triglycerides to be reached by treatment depends on the risk profile of each patient. But in the patient with both conditions, a primordial therapeutic target is also attaining recommended blood pressure ciphers.

In conclusion, HBP is one of the most important cardiovascular conditions in Mexico. A combination of HBP and dyslipidemia increases the pathogenic power of each on the cardiovascular system. The mechanisms that link both HBP and dyslipidemia, from a pathophysiological point of view are complex, but the RAAS has a primary role, and its inhibition is part of the integral treatment. Inflammation, oxidation, and endothelial dysfunction, as well as coagulation disorders, are some of its deleterious consequences.

As physicians, we must commit our efforts to detect hypertension and dyslipidemias in time and give the appropriate treatment to the patients.

REFERENCES

1. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados nacionales. 2a ed. Cuernavaca, México: Instituto Nacional de Salud Pública; 2013.
2. Shamah-Levy T, Ruiz-Matus C, Rivera-Dommarco J, Kuri-Morales P, Cuevas-Nasu L, Jiménez-Corona ME et al. Encuesta Nacional de Salud y Nutrición de Medio Camino 2016. Resultados Nacionales. Cuernavaca, México: Instituto Nacional de Salud Pública; 2017.
3. Rosas-Peralta M, Palomo-Piñón S, Borrayo-Sánchez, G, Madrid-Miller A, Almeida-Gutiérrez E, Galván-Oseguera H et al. Consenso de hipertensión arterial sistémica en México. Rev Med Inst Mex Seguro Soc. 2016; 54 Supl 1: S6-S51.
4. INEGI General mortality data in both genders, 2019. Available in: https://www.inegi.org.mx/contenidos/saladeprensa/boletines/2019/EstSociodemo/DefuncionesRegistradas2019.pdf
5. Wilber JA, Barrow JG. Hypertension-a community problem. Am J Med. 1972; 52: 653-663.
6. Hadaye R, Kale V, Manapurath RM. Strategic implications of changing rule of halves in hypertension: A cross-sectional observational study. J Family Med Prim Care. 2019; 8: 1049-1053.
7. Velázquez Monroy O, Rosas Peralta M, Lara Esqueda A, Pastelín Hernández G, Attie F, Tapia Conyer R. Hipertensión arterial en México: resultados de la Encuesta Nacional de Salud (ENSA) 2000. Arch Cardiol Mex. 2007; 72: 71-84.
8. Meaney E, Lara-Esqueda A, Ceballos-Reyes GM, Asbun J, Vela A, Martínez-Marroquín Y et al. Cardiovascular risk factors in the urban Mexican population: the FRIMEX study. Public Health. 2007; 121: 378-384.
9. Meaney A, Ceballos-Reyes G, Gutiérrez-Salmeán G, Samaniego-Méndez V, Vela-Huerta A, Alcocer L et al. Cardiovascular risk factors in a Mexican middle-class urban population. The Lindavista Study. Baseline data. Arch Cardiol Mex. 2013; 83: 249-256.
10. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003; 42: 1206-1252.
11. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360 (9349): 1903-1913.
12. Campos-Nonato I, Hernández-Barrera L, Pedroza-Tobías A, Medina C, Barquera S. Hipertensión arterial en adultos mexicanos: prevalencia, diagnóstico y tipo de tratamiento. Ensanut MC 2016. Salud Publica Mex. 2018; 60: 233-243.
13. Anonymous. Global Burden Disease Profile: Mexico. Institute for Health Metrics and Evaluation (IHME) at the University of Washington. Available in: https://www.healthdata.org/sites/default/files/files/country_profiles/GBD/ihme_gbd_country_report_mexico.pdf
14. Olaiz-Fernández G, Rivera-Dommarco J, Shamah-Levy T, Rojas R, Villalpando-Hernández S et al. Encuesta Nacional de Salud y Nutrición 2006. Cuernavaca, México: Instituto Nacional de Salud Pública; 2006.
15. Aguilar-Salinas CA, Gómez-Pérez FJ, Rull J, Villalpando S, Barquera S, Rojas R. Prevalence of dyslipidemias in the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex. 2010; 52 Suppl 1: S44-S53.
16. Rosas Peralta M, Lara Esqueda A, Pastelín Hernández G, Velázquez Monroy O, Martínez Reding J, Méndez Ortiz A et al. Re-encuesta Nacional de Hipertensión Arterial (RENAHTA): Consolidación Mexicana de los Factores de Riesgo Cardiovascular. Cohorte Nacional

de Seguimiento. Arch Cardiol Mex. 2005; 75: 96-111.
17. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364: 937-952.
18. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001; 104: 365-372.
19. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther. 2017; 2: 17023.

Correspondence:
Arturo Guerra-López, MD
E-mail: guerradr@prodigy.net.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100812

Microbiota: a relationship for life

Microbiota: una relación para toda la vida

Nayelli Nájera PhD,* Guillermo Ceballos MD, PhD,*
Cristian González-Ruiz PhD,* Eduardo Meaney MD, PhD*

The microbiota is the group of microorganisms that reside in a particular niche. This article will talk address about the microorganisms that reside in the human body. The microbiota is one of the most densely populated and diverse communities on the planet. The human body harbors a significant diversity of microorganisms in the intestinal tract and genitourinary tracts, the oral cavity, nasopharynx, respiratory tract, and the skin.[1]

In the past, the scientific community believed that microbiota consisted only of commensal microorganisms (residing inside us but providing no benefit at all). However, recently multiple functions related to human physiology in which the microbiota is involved have been described. The intense research efforts to explore its role in normal and pathological processes allow scientists to define and named the microbiota as a «metabolic organ».

Some of the functions associated with the microbiota relate to nutrition, immunity, and inflammation, will be described below.

GUT MICROBIOTA (ERRONEOUSLY CALLED INTESTINAL FLORA IN THE PAST)

The intestinal tract is a reservoir of commensal/symbiotic microorganisms (their numbers can be near 1,013-1,014 trillion) of various species, among which there are more than 500 bacterial species and more than 1,100 archaea species (unicellular prokaryotes that belong to a different phylum than bacteria). They can be Gram-negative (Bacteroidetes and Proteobacteria) or Gram-positive (*Actinobacteria* and *Firmicutes*).[2]

The stablished relationship between microorganisms and intestinal epithelial cells is very complex: some of their interactions allow the formation of a mucosal barrier, it can be the site where immunological mediators are secreted, and, where bacterial antigens interact with the body. Other kind of bacteria help to metabolize the ingested food.

The composition of the human microbiota largely depends on environmental factors, such as diet and drug use. Beyond the already documented effects of diet on human health, nutrients such as carbohydrates, proteins, fats, and other compounds as polyphenols and natural and artificial sweeteners, can act on intestinal microbiota, changing the balance between the microorganisms that compose it. Preclinical studies in animals, as well as clinical studies, have shown that the consumption of a high-fat diet promotes a decrease in the number of Bacteroidetes, and an increase in *Firmicutes* and *Proteobacteria*, which could increase the ability to collect and store energy, and increase the intestinal barrier permeability promoting an inflammation condition.[3]

Something similar occurs with high-sucrose, sucralose, and stevia diets, where the number of *Firmicutes* increases causing a deleterious condition that can be synergistically incremented when high-fat diet and sucralose are combined.[4]

Changes in the normal balance among the microbiota components is known as dysbiosis, state that is responsible for the

* Laboratorio de Investigación Integral Cardiometabólica. Escuela Superior de Medicina. Instituto Politécnico Nacional.

Received:
05/07/2021
Accepted:
22/07/2021

How to cite: Nájera N, Ceballos G, González-Ruiz C, Meaney E. Microbiota: a relationship for life. Cardiovasc Metab Sci. 2021; 32 (s3): s277-s279. https://dx.doi.org/10.35366/100812

metabolic alterations in the body that can lead to obesity, type 2 diabetes mellitus, and cardiovascular diseases.[5]

Some examples of the roles of the gut microbiota in cardiovascular disease and health are:

Short chain fatty acid (SCFA)

The intestinal microbiota participates in the digestion of food through two main catabolic pathways, categorized as saccharolytic or proteolytic. The first one, in which the microbiota breaks down polysaccharides, is responsible for most of the SCFA production. In the second pathway, ingested fiber is fermented, also inducing the formation of SCFA along with other potentially toxic metabolites, such as amines, thiols and phenols.

SCFAs directly modulate human health through different tissue-specific mechanisms related to the function of the intestinal barrier, glucose homeostasis, immunomodulation and regulation of appetite and obesity. The digestion of fermentable dietary fiber to SCFA gives us additional energy, so it would be logical to think that this would increase obesity, however, epidemiological studies indicate that a diet rich in fiber prevents the development of obesity, probably because SCFA work as free fatty acid receptors (FFAR) ligands, that increase the expression of glucagon-like-peptide 1 or Peptide YY, (slowing intestinal transit, increasing nutrient absorption, and increasing concentrations of leptin, an anorectic hormone).[6]

In summary, SCFAs, a product of intestinal microbial action, provide great health benefits.

Trimethylamine-N-oxide

Naturally, foods such as red meat, soy, and eggs contain essential compounds for the normal functioning of human cells. Phosphatidylcholine, also called lecithin, is a molecule that participates in the stability of cell membranes and is the main phospholipid of circulating very low-density and low-density lipoproteins (VLDL/LDL). Lecithin can be oxidized to betaine and this molecule is metabolized by intestinal bacteria producing trimethylamine (TMA).

L-carnitine is another example of compounds associated with the production of TMA. It is obtained from the essential amino acids methionine and lysine, and it is essential for energy metabolism, in particular, the catabolism of fatty acids that must be esterified with carnitine to form acyl-carnitine to be transported into the mitochondria for their oxidation (degradation), and be used in the production of ATP.[7,8] Carnitine is also used in the transport of carbons (-CH3CO) in the form of acetyl-carnitine outside the mitochondrial, through the activity of the enzyme carnitine acyltransferase, promoting glucose oxidation.[9,10]

Both phosphatidyl choline and L-carnitine from food are metabolized by the intestinal microbiota to trimethylamine (TMA) which, upon reaching the liver, is oxidized by the enzyme flavin monooxygenase (FMO), producing trimethylamine-N-oxide (TMAO). This molecule has been proposed as a cause of lipid accumulation in the arterial wall, facilitating the influx of lipids, increasing in situ synthesis, and suppressing their elimination, facilitating the formation of lipid-laden macrophages (known as foam cells) within the arterial wall, which is considered to be a pathological condition associated with the development of atherosclerosis.

Multiple clinical studies have shown a positive correlation between the presence of metabolites associated with the production of TMAO (choline, betaine, and L-carnitine) and cardiovascular diseases such as, acute myocardial infarction and stroke. Patients with high circulating TMAO concentrations have a 2.5 times higher risk of suffering a major cardiovascular event, independent of other risks such as lipid concentration. In addition, it is important to consider that dysbiosis, particularly due to the increase of non-commensal bacteria (usually harmless to our body) such as genus *Shigella*, *Vibrio* or *Aeromonas* can produce high amounts of TMA using different substrates from the diet which increases the risk. Thus, the balance of the intestinal microbiota depends mainly on the ingested diet and the adequate regulation of the concentrations of TMA absorbed in the intestine. Therefore, the concentrations of circulating TMAO can be modulated with correct habits and healthy diet.

MICROBIOTA AND OBESITY

As mentioned, a high-fat diet in and the consequent obesity, generates changes in the balance of the normal microbiota components, mainly increasing the ratio of *Firmicutes*/*Bacteroidetes*. This event can be reversed with changes in diet, from a one high in fat to another low in both, carbohydrates and fat (hypocaloric regimes).

Type 2 diabetes mellitus, strongly associated with obesity, has also been associated with low concentrations of SCFA, in particular, butyrate (produced by bacteria in the intestine). When analyzing the feces of patients with metabolic syndrome and insulin resistance, it was found that their microbiota contained minor amounts of butyrate-producing bacteria.

CONCLUSION

The human intestinal microbiota participates in the metabolism of various compounds contained in the diet, and their metabolites can be absorbed by the intestine and modulate the permeability of the intestinal barrier. The bacterial composition varies throughout life, depending on various environmental factors, mainly the type of diet; If the diet is high in fat, carbohydrates, sweeteners (natural or artificial) or low in fiber, it will create a favorable environment for the growth of *Firmicutes* and other non-commensal bacteria. More and more evidence shows that a state of dysbiosis is related to the development of multiple diseases such as atherosclerosis, arterial hypertension, heart failure, chronic kidney disease, obesity and type 2 diabetes mellitus, among many others. For these reasons, the prevention and treatment of cardiovascular diseases must pay attention to the restoration of the patient's microbiota. After all, microbiota will accompany us throughout life ... until death do us part.

REFERENCES

1. Petrosino JF, Highlander S, Luna RA, Gibbs RA, Versalovic J. Metagenomic pyrosequencing and microbial identification. Clin Chem. 2009; 55: 856-866.
2. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464: 59-65.
3. Murphy EA, Velazquez KT, Herbert KM. Influence of high-fat diet on gut microbiota: a driving force for chronic disease risk. Curr Opin Clin Nutr Metab Care. 2015; 18: 515-520.
4. Wang QP, Browman D, Herzog H, Neely GG. Non-nutritive sweeteners possess a bacteriostatic effect and alter gut microbiota in mice. PLoS One. 2018; 13: e0199080.
5. Swithers SE, Shearer J. Obesity: sweetener associated with increased adiposity in young adults. Nat Rev Endocrinol. 2017; 13: 443-444.
6. Delzene N, Cano PD. Interaction between obesity and the gut microbiota: Relevance in nutrition. Annu Rev Nutr. 2011; 31: 15-31.
7. Ussher JR, Lopaschuk GD. The malonyl CoA axis as a potential target for treating ischaemic heart disease. Cardiovasc Res.2008; 79: 259-268.
8. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012; 489 (7415): 220-230.
9. Muoio DM, Noland RC, Kovalik JP, Seiler SE, Davies MN, DeBalsi KL et al. Muscle-specific deletion of carnitine acetyltransferase compromises glucose tolerance and metabolic flexibility. Cell Metab. 2012; 15: 764-777.
10. Noland RC, Koves TR, Seiler SE, Lum H, Lust RM, Ilkayeva O et al. Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. J Biol Chem. 2009; 284: 22840-22852.

Correspondence:
Nayelli Nájera, PhD
E-mail: nnajerag@ipn.mx

The *Cardiovascular and Metabolic Science* (before *Revista Mexicana de Cardiología)* is the official entity of the National Association of Cardiologists of Mexico, the Society of Interventional Cardiology of Mexico, the National Association of Cardiologists of the Medical Center La Raza AC, the National Association of Cardiologists Serving State Workers AC, the Mexican Association for the prevention of Atherosclerosis and its complications AC, the Mexican Society of Preventive Cardiology, the Alliance for a Healthy Heart, the Mexican Society of Cardiac Pacing and Electrophysiology, Medical Association of the Hospital of Cardiology Medical Center S. XXI, Interamerican Foundation of the Heart México. The Journal is currently indexed in several databases, including Scielo, Free Medical Journals, Latindex, BVS, and Google Scholar, among other. Its scopes include original papers related to disease heart, blood vessels and related health sciences. The Journal publishes original research articles (experimental investigation) both clinical and preclinical; epidemiological papers; review topics (usually by invitation), editorials, letters to the editor and news of various associations. In order to be accepted, all manuscripts are initially evaluated by at least two peer reviewers and finally sanctioned by the Editorial Committee. The Journal accepts, in general terms, the stated guidelines by the International Committee of Medical Journal Editors. Manuscripts should be prepared according to the Requirements of Uniforms for Submission of Manuscripts to Biomedical Journals. The updated version is available at: www.icmje.org.

All submissions should be made on line at the Journal's site. New users must first create an account. Once logged in, submission should be made via the Author Center. If you experience any problem with your submission, please contact the editors at revmexcardiol@gmail.com

Submitted manuscripts should not be under review in any other journal. Moreover, all submissions must include full disclosure of all relationships that could be viewed as presenting a potential conflict of interest. If there are no conflicts of interest, authors should state that there are none.

Accepted papers will be owned by the Journal and may not be published (either whole or partial) elsewhere without written permission of the publisher.

Checklist

Check when each section has been duly completed in accordance with specified. Papers will not be accepted for a review if they do not include any (s) of the points previously mentioned.

General aspects

( ) Articles must be submitted electronically.

( ) Manuscripts should be written in English.

( ) The item must be written with a minimum font size 10 double space (28 x 21 cm), with margins of 2.5 cm on each side. The words in another language must be submitted Italicized.

( ) The text should be presented as follows: 1) page title, 2) abstracts and key words, 3) introduction, 4) materials/patients and methods; 5) results, 6) discussion, 7) conclusions, 8) acknowledgments, 9) references, 10) appendices, 11) text boxes, 12) figure captions. Each section will begin in different sheet. The format can altered in review articles, if considered necessary.

( ) Consecutive numbering of the pages, starting with the title page.

( ) List the name, address, telephone number and e-mail of three suggested reviewers who are not members of your workgroup, so they can be considered as potential peer-evaluation candidates.

Text

Title page

( ) Includes: a) title with a maximum of 15 words, b) name(s) of the authors in the order in which will be published; if the paternal and maternal surnames are recorded, linked them with a hyphen, c) degrees of the authors, d) affiliations and institution(s) where was the work performed, e) complete address, telephone, fax and e-mail address of the corresponding author.

Abstract

( ) Both in English and Spanish; with a maximum of 250 words. Structured according to the order of information in the text: 1) Introduction, 2) objectives, 3) material and methods, 4) results and 5) conclusions.
( ) 3-5 Key words.

Text

( ) Divided into subtitles that facilitate the reading: 1) introduction, 2) objectives, 3) material and methods, 4) discussion, 5) results, 6) conclusions, 7) acknowledgments, 8) references, etc.
( ) The names, initials or numbers of the patients studied record should be omitted.
( ) Abbreviations are accepted, but must be preceded for what they mean the first time that they are cited, according to the international units of measurement.
( ) Medicines, drugs and chemicals should be called by its generic name, dosage and route of administration, indicating the international nomenclature.
( ) The statistical methods used should be described at the end of the material and methods section.

Acknowledgements

( ) The acknowledgments and details on supports, drug (s) and team (s) provided (s) should be cited before the references.

References

( ) Vancouver style citation is required. (https://www.library.uq.edu.au/training/citation/vancouv.pdf).
( ) Identified in the text with Arabic numbers and superindex in progressive order of appearance.
( ) Personal communications and unpublished data will be cited unnumbered in a footnote.

Examples of journal articles:

Ohlsson J, Wranne B. Noninvasive assessment of valve area in aortic stenosis patients with. J Am Coll Cardiol 1986; 7: 501-508.

Six or more authors

San-Luis R, Munayer J, Aldana T, et al. Venous connection total anomalous pulmonary. Five years of experience. Rev Mex Cardiol 1995; 6: 109-16.

Books

Myerowitz PD. Heart transplantation. New York: Futura Publishing; 1987: 20-31.

Book chapters

Hardesty R, Griffi th B. Combined heart-lung trans plantation. In: Myerowitz PD. Heart transplantation. New York: Futura Publishing; 1987: 125-140.

Tables

( ) None.

( ) Yes.

Quantity (with letters): _____

( ) The authors declare that all tables in the manuscript are entirely original and do not require reprint permission.
( ) The information provided is not repeated in the text or in Figures. Maximum allowed is the 50 percent plus one of the text sheet.
( ) They are headed by the title and marked progressively with Arabic numbers according to their appearance in the text.
( ) The title of each table alone explains its contents and allows correlate with limited text.

Figures

( ) None.

( ) Yes.

Quantity (with letters): _____

( ) The authors declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

( ) Are considered as photographs, drawings, graphics and schemes. The drawings must be designed by professionals. Maximum allowed is the 50 percent plus one of the text sheet.
( ) The information provided is not repeated in the text or tables.
( ) Are identified progressively with Arabic numbers according to the order of appearance in the text, remember that the counting includes the fotographs, drawings, graphs and diagrams.
( ) Separately attached in JPEG format.

The titles and explanations are presented separately

( ) Photographs that enables the people´s identification are accompanied by consent letters.
( ) Color illustrations are accepted and thus will appear online, but if authors wanted to be published in color of the printed version, must cover the proportional cost of printing.

Figure captions

Quantity (with letter): _____

( ) They are marked with Arabic numberd according to the overall sequence corresponding to them.

Ethical aspects

( ) The humans procedures must conform with the Ethical Standards of the Declaration of Helsinki of 1975 and the 1989 amendments to the agreement about ; issued by the Ministry of Health, published on January 26 1982 and the Scientific Committee and Ethics institution where they where first performed.
( ) Animal experiments conform to the rules the National Research Council and the institution where it was performed.
( ) Any other situation that may be of interest must be notified in writing to publishers.

Transfer of Copyright

Article title:

Author (s):

The authors certify that the above-mentioned article is original work and has not previously published except in abstract form. Once accepted for publication in the *Cardiovascular and Metabolic Science*, copyright will be transferred to the latter. They also state that it has not been sent simultaneously for publication in another journal. The authors agree that, if necessary, this article would be included in the electronic media that the editors of the *Cardiovascular and Metabolic Science* consider appropriate.

The authors report that the order in which their names are mentioned in the article have been agreed between them and is product of the proportion in which they participated in the elaboration of the work.

Signature of all authors

Location and date: