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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

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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;

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[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.

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