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Epidemiology and burden of morbidity and mortality in dyslipidemias and atherosclerosis

Epidemiología y carga de morbilidad y mortalidad en dislipidemias y aterosclerosis

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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,

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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.

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