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EDITORIAL

Atherogenic dyslipidaemia: the other pandemic, associated with diabesity☆

Dislipemia aterogénica: la otra pandemia, asociada a la diabesidad

Jesús Millán Núñez-Cortés[a,b,*], **Juan Pedro-Botet**[b,c]

[a] *Lipids Unit, General University Hospital Gregorio Marañón, Madrid, Spain*
[b] *Atherogenic Dyslipidaemia Work Group, Spanish Artherosclerosis Society, Spain*
[c] *Lipis and Vascular Risk Unit, Hospital del Mar, Barcelona, Spain*

When medicine successfully combats the current COVID-19 pandemic caused by coronavirus SARS-CoV-2, we will still face the challenge of another pandemic, that has already been around for many years and which, rather than disappearing, has been increasing its impact year after year. In this sense, a great deal of cardiovascular morbimortality is associated with high cardiovascular risk which is characteristic of certain cardiometabolic disorders. Diabetes mellitus type 2 and obesity are paradigmatic elements of this and at the same time are frequently found encompassed in what is recognised from a clinical and physiopathological viewpoint as metabolic syndrome.[1]

In the study by Ruiz-García and cols. published in this edition of *Clin Invest Arterioscl*,[2] the SIMETAP study group presents the prevalence of characteristic changes of artherogenic dyslipidaemia in population analysis in primary care. The results leave no room for doubt. In this study the factors most significantly associated with atherogenic dyslipidaemia, or one of its constitutive elements such as low HDLc, are obesity and/or diabetes, together with a tobacco habit. Furthermore, it highlights the association of hypertriglyceridaemia in this population with low rates of HDLc. This study is therefore a wake-up call for the critical need for a diagnostic and therapeutic proposal to detect and treat, respectively, atherogenic dyslipidaemia and especially in patients with disorders known as cardiometabolic.

The Atherogenic dyslipidaemia workgroup of the Spanish Arthrosclerosis Society has recently made public the prevalence of this specific dyslipidaemia in diabetics (PREDISAT study). Up to 41% of diabetic patients have atherogenic dyslipidaemia[3] with mean aglyceridemia close to 500 mg/dL and HDLc of 33 mg/dL. Therapeutic intervention appears to be largely inadequate because, in the majority of case statins are the most widely used treatment whilst more appropriate hypotriglyceridemiants are not used. Following pharmacological treatment 35% of the diabetic population still continue having atherogenic dyslipidaemia. Moreover, a lower proportion of older patients receive treatment and the problem is therefore clearly undertreated and undercontrolled.[4] However, in diabetic patients in secondary prevention, the prevalence is greater still (51%), regardless of the fact this is a coronary cardiac, cerebrovascular or peripheral arterial disease.[5]

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* Corresponding author.
E-mail address: jesus.millan.nunezcortes@madrid.org (J.M. Núñez-Cortés).

It is precisely the high prevalence of atherogenic dyslipidaemia in patients with high or very high risk treated with statins, that has led to the consideration of risk attributable to this disorder, even considering a conventional treatment with hypocholesterolemiants, regardless of having target LDLc levels. This is the origin of the concept of residual risk of lipid origin: the persistence of an elevated cardiovascular risk despite standard and acceptable control of LDLc. Residual risk is again endorsed by the Ruiz-García and cols. Study.[2] This is a concept which, despite everything, is found to be evolving because the building blocks of a residual risk fraction are increasingly described and they do not only focus on lipoproteins rich in triglycerides, as in the case of lipoprotein (a) [Lp(a)]; or they are not strictly lipid, as in the case of the inflammatory phenomena or the prothrombotic agents that accompany metabolic syndrome, diabetes mellitus or visceral obesity.[6] It is precisely in diabetic patients where inflammation may be a major contributing factor to residual cardiovascular risk, particularly in those with nephropathy; although they are also very directly related with obesity or the elevation of the c-no-HDL.[7]

The concentration of triglycerides and HDLc allows us to identify people with atherogenic dyslipidaemia and with high cardiovascular risk. In fact, the number of triglycerides is a surrogate marker of lipoproteins rich in triglycerides and their remnants.[8] And, as is known, the remaining lipoproteins contribute unequivocally to increasing the risk of lipid origin. In recent results from the cohort of the Copenhagen study it was confirmed that the risk of severe coronary accident recurrence in patients with myocardial infarction or previous stroke is directly related to the rate of cholesterol linked to remaining lipoproteins: +23% with figures of 19—38 mg/dL, +48% with 39—57 mg/dL, and +79% with figures higher than 58 mg/dL.[9] Moreover, in people who are overweight or obese with high cardiovascular risk, the levels of triglycerides and remnant cholesterol but not LDLc, are associated with the cardiovascular objectives regardless of other risk factors.[10]

Remnant lipoproteins are derive d by lipolysis from VLDL (which contain apoB) and from chyomicrons (which contain apoB48), and their composition and size varies when they are enriched with cholesterol and apoE esters.[11] The quantitative determination of remnant lipoproteins lacks standardisation in its measuring technique, but may be essential for explaining the causes of residual risk of lipid origin. This is especially the case if it is related to another component of atherogenic dyslipidaemia, such as the already quoted drop in HDLc. Recently in a population of approximately 1,500 individuals, with a 25-year follow-up it was reported that the triglyceride/HDLc index is a good predictor regardless of the appearance of diabetes mellitus,[11] and this elevates this parameter to the category of a general population predictor.

The need for suitable control of these patients must be insisted upon. In the NHANES study, approximately 25% of the patients treated with statins presented with a concentration of triglycerides above 150 mg/dL.[12] Therefore, despite the fact that in the guidelines it is generally recommended that a statin be the first line treatment, this may be insufficient for a considerable percentage of cases, which require a complementary therapeutic strategy due to the need to reduce the residual risk from hyperglyceridaemia. First in ranking of options are the fibrates. In the ACCORDION study, the patients with the highest triglyceride levels and lowest HDLc levels had better long-term outcomes when they were treated with a combination of statins with fenofibrate rather than only statins. There was a lower incidence of cardiovascular mortality, of non fatal myocardial infarction, heart failure or severe coronary episodes; and together with this there was a significant reduction in mortality from all causes (-35%) after almost 5 years of follow-up.[13] These data present an opportunity for more selective PPAR-α modulators, such as the pemafibrate[14] or dual drugs which combine an apoCII mimetic with a apoCIII antagonist.[15]

The treatment of elevate rates of LDLc is a ''first line'' treatment objective and cornerstone of cardiovascular prevention. However, this lipid fraction does not faithfully reflect the underlying lipid disorder in a high percentage of patients with elevation of lipoproteins rich in triglycerides (intermediate density VLDL, remnants). This is pointing us in the correct and complementary direction of good LDLc control: (a) a better knowledge of current management in the diagnosis of this lipoprotein alteration intended to introduces the necessary changes to clinical practice, and (b) greater knowledge which may lead to clarifying therapeutic aspects such as the non-HDLc as therapeutic target, more effective and safer intervention strategies against overall dyslipidaemia (for example, drug combinations), or clinical outcomes which include those that lead to the evaluation of atheromatous plaque evolution.

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