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SPECIAL ARTICLE

How to mitigate residual risk? Risk factor management, a holistic approach to cardiovascular risk and treatment goals other than LDL (non-HDL-C, Lp(a), TG, apoB)

¿Cómo mitigar el riesgo residual?: manejo de factores de riesgo, estrategia holística de abordaje del riesgo cardiovascular y objetivos de tratamiento diferentes a LDL (c-no-HDL, Lp(a), TG, apoB)

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Abstract

Triglycerides are associated with cardiovascular risk largely mediated by their final product of catabolism, the cholesterol-rich remnant, which may come from the liver or the intestine. There is a direct association between fasting and postprandial triglycerides and cardiovascular risk. ApoB is associated with the number of particles and the amount of RC, which explains its determining role in CVD. Non-HDL cholesterol represents atherogenic lipoproteins, with correlation and concordance with apoB; both are cardiovascular risk markers. Lipoprotein (a) is a cardiovascular risk factor not only because of the cholesterol and apoB it contributes, but also because of its proinflammatory and prothrombotic activity. Viewing these factors holistically, it is important to note that it is primarily a reduction in apoB, remnant cholesterol and non-HDL cholesterol that reduces cardiovascular events. A 10% weight loss improves TG levels without reducing apoB or cardiovascular risk. Of the classic lipid-lowering agents, high-dose statins and ethyl eicosapentanoate reduce cardiovascular risk through apoB, RC, and non-HDL reduction. To date, we do not have lipid-lowering agents aimed at reducing Lp(a), which is only slightly reduced by PCSK9 inhibitors and markedly reduced by LDL apheresis. These residual risk markers serve not only to stratify cardiovascular risk but also to establish follow-up goals.

Keywords: *Residual risk. Lipid-lowering therapy. ApoB. Non-HDL cholesterol. LpA. Cholesterol remnants.*

Resumen

Los triglicéridos se asocian a mayor riesgo cardiovascular, en gran parte mediado por su producto final de catabolismo, el remanente rico en colesterol; este último puede ser de origen hepático o intestinal. Hay una asociación directa entre triglicéridos en ayunas y posprandial con el riesgo cardiovascular. La apoB se asocia con el número de partículas y el número de RC, lo que explica el rol determinante en la enfermedad cardiovascular. El colesterol no-HDL representa las lipoproteínas aterogénicas y tiene correlación y concordancia con la apoB; ambos representan dos marcadores de riesgo c ardiovascular. La lipoproteína a constituye un factor de riesgo cardiovascular no solo por el aporte de colesterol y de apoB que representa su composición, sino también por su acción proinflamatoria y protrombótica. En la mirada holística de estos factores es importante destacar que principalmente la disminución de apoB, remanentes de colesterol y colesterol no-HDL

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reduce los eventos cardiovasculares. El descenso del peso en un 10% mejora los niveles de TG sin reducir la apoB ni el riesgo cardiovascular. De los hipolipemiantes clásicos, las estatinas y el icosapento de etilo a dosis altas, reducen el riesgo cardiovascular a través de la disminución de apoB, remanentes de colesterol y colesterol no-HDL. Al día de hoy no se tienen hipolipemiantes dirigidos a reducir la LpA; solo la disminuyen ligeramente los inhibidores de la PCSK9 y, de forma marcada, la técnica de LDL aféresis.

Estos marcadores de riesgo residual sirven no solo para estratificar el riesgo cardiovascular sino también para establecer metas de seguimiento.

Palabras clave: *Riesgo residual. Terapia hipolipemiante. ApoB. Colesterol-no-HDL. LpA. Remanentes de colesterol.*

Introduction

The pathophysiology of triglycerides and apoB in cardiovascular disease

According to epidemiological studies, fasting and postprandial triglyceride (TG) levels are associated with cardiovascular disease (CVD)[1]. The relationship between elevated TG levels and decreased high-density lipoprotein (HDL) has historically explained the increased risk of CVD. However, studies of genetic variants determined that the association between TG levels and CVD was independent of low HDL cholesterol levels[2].

Hyperinsulinism associated with insulin resistance, a characteristic of metabolic syndrome and type 2 diabetes mellitus, is characterized by hyperproduction of apoprotein (apo)B 100 and apoB4 8, which is related to decreased catabolism of triglyceride-rich lipoproteins (TRLs), expressed through decreased lipoprotein lipase (LPL) activity[3]. In this context of more production and less catabolism, remnant cholesterol (RC) is formed in the liver and intestine. Remnant cholesterol is characterized by being smaller and containing a greater amount of free and esterified cholesterol and less apoC. Thirty-two percent of daily cholesterol is known to be derived from RC[4]. A recent study on primary prevention, taking a cut-off point of LDL > 130 mg/dl and RC > 24 mg/dl, showed that elevations in these two parameters almost doubled CVR, similar to what occurred in patients who only had RC > 24 mg/dl, with LDL levels < 130 mg/dl. Thus, the conclusion is that the greatest determinant of CVR is RC[5].

Apoprotein B (apoB) differs from other apolipoproteins in that it cannot be exchanged for other lipoproteins, and therefore remains bound to the particle to which it is secreted. Since each lipoprotein contains a copy of apoB, its concentration is a substitute marker for the number of RC, LDL and Lp(a) particles6. The concentration of apoB particles in the arterial lumen is the main determinant of the number of apoB particles which will be trapped within the arterial wall. The proportion of apoB particles trapped within the arterial wall is also influenced by the size of the apoB particles and the glycosaminoglycan structure in the subendothelial space[7]. The uptake of apoB particles deposits atherogenic cholesterol within the arterial wall. The concentration of apoB represents the atherogenic risk of the TRL remnants and low-density lipoproteins (LDL).

Materials and method

Informal consensus methods were employed based on the scientific evidence and the clinical judgement and experience of a group of experts from different medical specialties. A literature search was performed to find observational studies, clinical trials and systematic reviews or meta-analyses evaluating therapy with TGs, apoB non-HDL cholesterol and Lp(a), published through December 8, 2022, in the PubMed/Medline, EMBASE, SciELO, Google Scholar and Cochrane Clinical Trials electronic databases.

Content

A holistic approach to cardiovascular risk

Hepatic steatosis is defined as having more than 5% fat in the hepatocytes according to histological analysis and imaging, together with dyslipidemia, obesity and type 2 diabetes mellitus[8]. Imaging studies have shown a correlation between the intrahepatic TG content and very low-density lipoprotein (VLDL) synthesis. Very low-density lipoprotein secretion is biphasic in relation to the progression from steatosis to steatohepatitis and fibrosis; as inflammation and fibrosis advance, there is less VLDL secretion[9]. A weight loss of just 10% has been proven to lower the intrahepatic TG content; likewise, nutrition interventions restricting carbohydrates have shown a reduction in TG levels and liver fat after six months[10]. Several clinical trials have shown that both aerobic and resistance exercise reduce liver fat. Optimized peripheral insulin resistance reduces the excessive release of free fatty acids and glucose for TG synthesis in the liver. Physical activity increases the oxidation of fatty acids in the liver and decreases their synthesis, preventing mitochondrial and hepatocellular damage

through a reduction in the release of damage-associated molecular patterns. Thus, physical exercise is a proven therapeutic strategy for improving fatty liver disease and plasma TG levels[11]. Bariatric surgery improves atherogenic dyslipidemia by 70%, characterized by lowered TGs and increased HDL-C. One of the factors found to affect the lipid profile is apoC-III reduction and its redistribution between the TRL fraction and the HDL fraction, remembering that one of the main functions of apoC-III is to inhibit lipoprotein lipase (LPL), the enzyme responsible for TRL catabolism. This change in direction of apoC-III toward HDL is likely related to decreased insulin resistance[12].

Regarding the family of antidiabetic medications, according to kinetic studies, pioglitazone has lowered apoC-III levels, thus favoring TRL catabolism[13]; in the IRIS study on secondary prevention, pioglitazone reduced cardiovascular events by 24%[14]. Furthermore, liraglutide reduced cardiovascular events by 22% in the LEADER study[15]. In kinetic studies, after six months of treatment, liraglutide has proven to lower apoB48 production and increase chylomicron catabolism[16]; in the liver, it decreased production and increased catabolism of apoB 100 through increased expression of the LDL receptor, secondary to a reduction in its regulating protein, known as PCSK9[17].

As for the lipid-lowering drugs, within the family of fibrates, a recent study like PROMINENT, with pemafibrate, has shown a 60% TG reduction, with moderate apoC-III and non-HDL cholesterol reduction and no changes in apoB. This lack of apoB reduction would explain why this study was stopped for futility[18]. In the REDUCE-IT study on secondary prevention, the patients have received 4 g/day of a concentrated form of omega-3, icosapent ethyl, which has proven to reduce cardiovascular events by 25%, partly due to a reduction in RC and apoB of 32% and 5 to 6%, respectively[19].

Treatment goals

The goals for fasting and postprandial TG should be less than 150 mg/dl and 175 mg/dl, respectively. For RC, targets of less than 30 mg/dl are recommended. On the other hand, apoB levels depend on the cardiovascular risk; thus, for patients with very high cardiovascular risk, the apoB targets are less than 70 mg/dl[20].

Is LDL-C the only treatment goal?

As has been mentioned, apoB is the constitutive lipoprotein of lipid particles and is strongly associated with atherosclerotic disease. Therefore, measuring the total apoB amount is a very close estimate of a specific person's atherogenic burden. The lipid profile classically includes total-C, LDL-C, HDL-C, triglycerides and some calculated fractions of these values, like non-HDL-C and RC. Non-HDL-C results from subtracting HDL-C from total-C (non-HDL-C = total-C – HDL-C). ApoB – known as apoB 100 – is part of LDL-C and the non-HDL-C fractions, like very low-density lipoprotein cholesterol (VLDL-C) and intermediate-density cholesterol (IDL-c), while apoB 48 is a constitutive part of chylomicrons (Fig. 1). From a conceptual perspective, if the lipoproteins composed of apoB can be estimated, theoretically and concomitantly, the risk of atherosclerotic cardiovascular disease would be more precisely estimated. Consequently, non-HDL-C could be a substitute marker in cardiovascular risk. Some data support this, in which the attributable risk burden is higher with non-HDL-C and apoB levels, but not with LDL-C levels[21]; furthermore, non-HDL-C was a better predictor of the severity of coronary arteriosclerosis[22].

The epidemiological relationship between LDL-C and atherosclerotic disease has been convincingly proven. This relationship is so direct that the treatment guidelines, without exception, state it as the main therapeutic goal in the treatment of lipid disorders[23,24]. However, there are clinical circumstances in which it is possible that LDL-C may not reflect the true cardiovascular risk of a particular patient. Thus, it has been reported that, although patients have reached the LDL-C goals, cardiovascular events persist in those who have already experienced a clinical event. These events are encompassed within what is known as residual risk (RR). Lipid and non-lipid factors affect RR. The non-LDL-C particle-dependent RR is the one with a lipid source of RR[25].

Therefore, cardiovascular risk apart from LDL-C must be identified individually for each patient. Thus, the quantification of lipid fractions, like the measurement of total-C, HDL-C, non-HDL-C, triglycerides, direct measurement of apoB 100 and Lp(a) is especially useful for revealing the persistence of lipid RR.

There is, therefore, reason to consider that the therapeutic goal in some patients with lipid disorders is not just LDL-C, as lipid RR orients the clinician to seek other therapeutic goals like non-HDL-C and RC, which aim at quantifying non-LDL-C linked atherogenic apoB and are also involved in recurrent cardiovascular events.

The LDL-C and non-HDL-C levels are correlated, but are discordant in some individuals, which indicates that some have high LDL-C and low non-HDL-C and others, on the contrary, have low LDL-c and high non-HDL-C. Under these conditions, non-HDL-c levels have proven to be better predictors of cardiovascular clinical events than LDL-C. Thus, the current guidelines consider non-HDL-C to be a secondary treatment goal, but if the patient has reached the target LDL-C, non-HDL-C becomes a primary goal together with LDL-C. To remember the non-HDL-c tar-

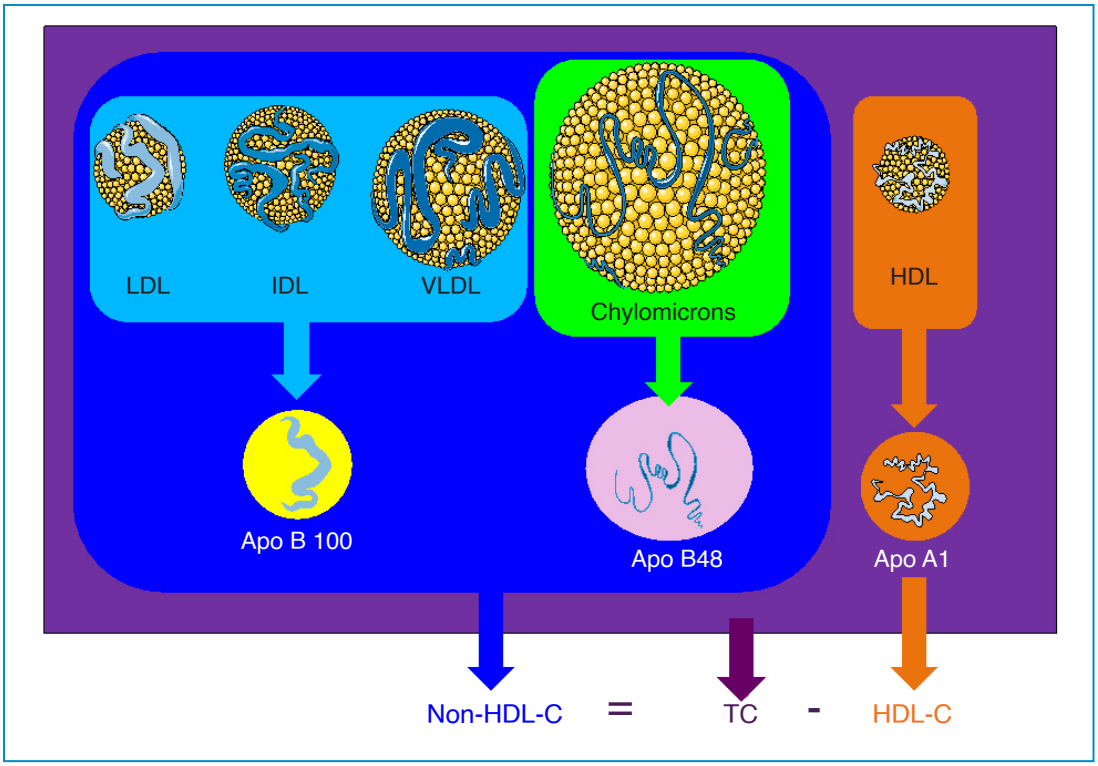

Figure 1. Method for calculating non-HDL-C. The apoB 100 lipoprotein is part of LDL-C, IDL-c and VLDL-C, and apoB 48 lipoprotein is part of the chylomicrons. Non-HDL-C reflects the total burden of atherogenic apoB.

gets practically and generally, we must keep in mind that their value is 30 mg/dl higher than the LDL-C targets; therefore, for example, in a patient with high cardiovascular risk, the LDL-C target is 70 mg/dl and the non-HDL-C target is 100 mg/dl, while for a patient with moderate risk, the LDL-C target is 100 mg/dl and the non-HDL-C target is 130 mg/dl[26] (Table 1).

The holistic way of approaching lipid cardiovascular risk consists of estimating all the lipoproteins and calculating non-HDL-C and RC which, apart from LDL-C, provides information on the total apoB burden which must be addressed, and which is responsible for RR. Normally, patients have more than one abnormality in their lipid or lipoprotein levels, but the disorders can be encompassed within increased LDL-C, non-HDL-C, TGs and Lp(a), and reduced HDL-C.

The role of Lp(a) in residual risk

Lipoprotein (a) is composed of a particle similar to low-density lipoproteins, in which apoB 100 is covalently bound by a single disulfide bond to apo(a), which is the distinctive component of Lp(a). There is an inverse correlation between the size of the isoform and the plasma concentration of Lp(a); smaller isoforms contribute to a greater production and concentration of apo(a) than larger isoforms. This relationship occurs because small apo(a) leads to a greater rate of production and secretion by the liver and, therefore, to a greater concentration of Lp(a)[27].

Lipoprotein (a) can be measured both in serum as well as plasma, and there is no difference between fasting or non-fasting samples. Lipoprotein (a) has a similar size and density to LDL, and therefore constitutes an "interference" in LDL-C measurement by any method, such as estimation by calculation, analytic measurement and even the reference method: beta quantification using ultracentrifugation. This causes a significant LDL-C overestimation error when Lp(a) is high, as Lp(a) contributes cholesterol to the LDL-C measurement. The correction which is usually used to subtract the Lp(a)-c contribution from LDL-C and estimate the true LDL-C value is not recommended because the 30% proportion of Lp(a) mass used as an estimator of Lp(a)-c varies widely, and the calculation also involves converting from nmol/l to mg/dl, which is imprecise[28]. Recently, a promising and validated test has been designed to measure Lp(a)-c, in which the contribution of Lp(a)-C to LDL-C is, on average, 17 mg/dl in individuals with elevated Lp(a), a figure

Table 1. Ten-year cardiovascular risk catetories with the lipoprotein goals and targets to be reached according to the AACE/ACE CPG.

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-c (mg/dl)	Non-HDL-c (mg/dl)	Apo B (mg/dl)
Extreme risk	- Progressive ACVD which includes unstable angina in individuals after reaching an LDL-c of < 70 mg/dl - Established clinical cardiovascular disease in individuals with Stage 3 or 4 DM, CKD or HeFH - History of premature ACVD (< 55 men, < 65 women)	< 55	< 80	< 70
Very high risk	- Current or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; 10-year risk > 20% - DM or Stage 3 or 4 CKD with one or more risk factors - HeFH	< 70	< 100	< 80
High risk	- ≥ 2 risk factors and a 10-year risk of 10% -20% - DM or CKD in Stage 3 or 4 with no other risk factors	< 100	< 130	< 90
Moderate risk	< 2 risk factors and less than 10% 10-year risk	< 100	< 130	< 90
Low risk	0 risk factors	< 130	< 160	NR

which is clinically relevant[29]. An immunochemistry test minimizing the effect of size isoforms, calibrated using WHO/IFCCLM reference material and reported as nmol/l, is recommended for measuring Lp(a).

Elevated Lp(a) is recognized as a potentiator of cardiovascular risk[24], and its measurement is useful for optimizing risk classification. Knowing the Lp(a) level in individuals with very high Lp(a) allowed risk reclassification to a higher category in approximately one third of those in primary prevention and in more than half the patients in secondary prevention. Since Lp(a) levels are generally genetically determined, they are usually stable throughout life. Measuring Lp(a) once in a lifetime should be enough for most individuals, unless a secondary cause arises to modify its level or if some therapeutic measure to decrease it is being monitored. Likewise, we suggest measuring Lp(a) in patients with aortic valve stenosis, as Lp(a) has proven to exacerbate the pathogenesis of this valve disease. It should also be measured in patients with severe hypercholesterolemia (LDL-C > 190 mg/dl) with suspected or confirmed familial hypercholesterolemia, since the coexistence of these conditions and elevated Lp(a) dims the prognosis and severity of CVD[30]. In the same vein, Lp(a) measurement should also focus on subjects with other dyslipidemias, like combined familial hyperlipidemia or dysbetalipoproteinemia. In addition, Lp(a) measurement should be considered in patients being treated with statins who maintain an “apparent” elevated LDL-C, that is, they do not respond to treatment, as this can be attributed to elevated Lp(a), which contributes cholesterol to the LDL-c measurement. The Lp(a) concentration should be used as a tool to help make the clinical decision of ordering statin treatment in patients 40 to 75 years old with intermediate risk[24].

The various scientific societies have suggested different Lp(a) values which are associated with higher cardiovascular risk. The European Atherosclerosis Society (EAS) and Heart UK suggest that the Lp(a) risk is significant at levels of 50 mg/dl (100-125 nmol/l), which correspond to the 80th percentile of the European population, both in patients with CVD as well as those with diabetes mellitus or the general population[31]. However, this threshold level overlooks the risk seen in populations in primary prevention with levels between 25 and 50 mg/dl. The Canadian Cardiovascular Society suggests a cut-off point of more than 30 mg/dl, while the 2018 American Heart Association/American College of Cardiology guidelines define an Lp(a) level of 50 mg/dl as a risk potentiating factor[32].

The proposed mechanism through which Lp(a) participates in the genesis of atherosclerosis varies and includes the cholesterol content (similar to the LDL particle) and mediation in inflammatory responses mediated by their oxidized phospholipid content. Based on the structural similarity between apo(a) and plasminogen, prothrombotic phenomena could also be involved[32].

In summary, data from genetic and clinical observation studies show an association between elevated Lp(a) levels and the risk of developing atherosclerotic CVD.

Conclusions

Moderate hypertriglyceridemia is associated with more CVR, which is largely explained by increased remnant cholesterol and apoB. Nutritional and lifestyle interventions associated with moderate weight loss, together with decreased insulin resistance, are associated with lowered RC and apoB. Antidiabetic drugs which act on insulin sensitivity, like pioglitazone and liraglutide, lower CVR because they reduce remnant cholesterol and apoB. As far as the new lipid-lowering drugs, high-dose icosapent ethyl is highlighted, as it decreases CVR by reducing RC and apoB.

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Conflicts of interest

None.

Ethical responsibilities

Human and animal protection. The authors declare that no experiments were conducted on animals or humans for this study.

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Use of artificial intelligence to generate text. The authors delcare that they have not used any type of artificial intelligence generator to draft this manuscript or create the figures, graphs, tables or their respective captions or titles.

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