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

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

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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]

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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

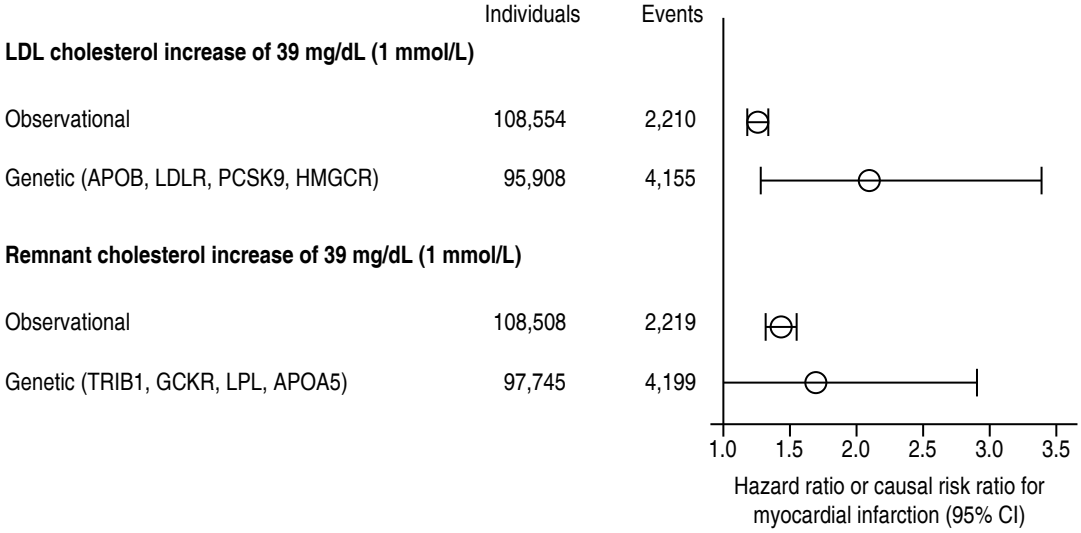

Figure 1: Comparison of risk of myocardial infarction by 1 mmol/L (39 mg/dL) higher levels of low-density lipoprotein (LDL) cholesterol AND remnant-cholesterol from observational and genetic studies, data from individuals in the Copenhagen General Population Study. Adapted from: Handelsman Y et al.[17]

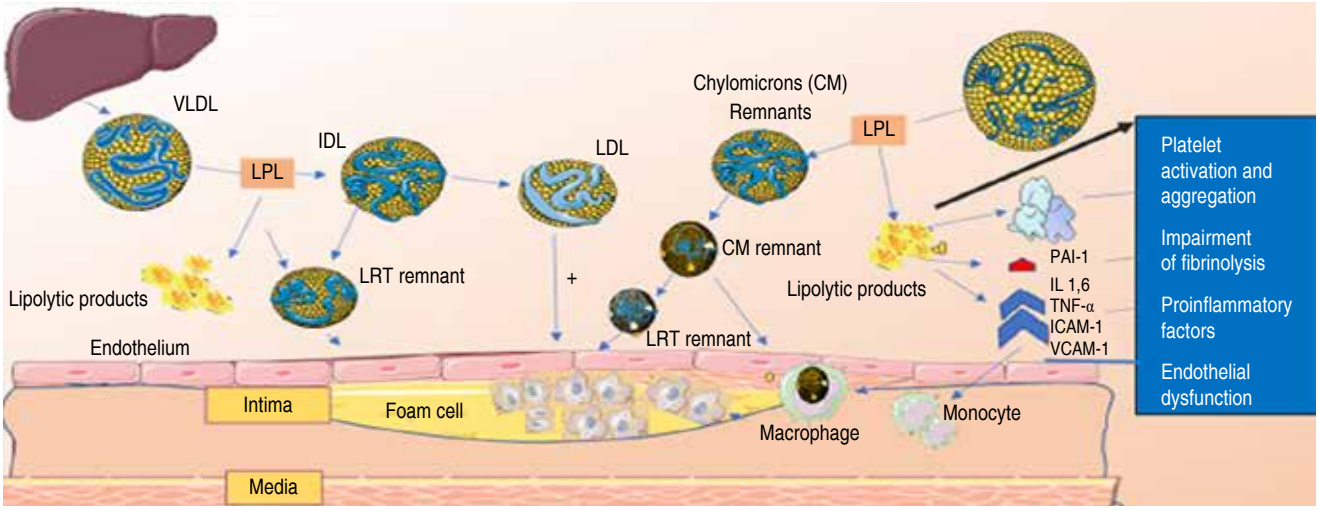

Figure 2: Possible mechanisms of atherogenesis by TRL. These particles also contain cholesterol esters, can penetrate the arterial intima, and are taken up by macrophages, transforming them into foam cells. TRL also promotes endothelial dysfunction through oxidized fatty acids (lipolytic products), by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

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