CONTROVERSY

Triglyceride Levels Should be Lowered to Reduce Cardiovascular Risk

Se debe disminuir el nivel de triglicéridos para reducir el riesgo cardiovascular

AGONIST

PABLO CORRAL[MTSAC,]

INTRODUCTION

Hypertriglyceridemia is defined as fasting and postprandial triglyceride (TG) levels greater than 150 and 175 mg/dL, respectively. This elevation results from either increased TG production, decreased catabolism of TG-rich lipoproteins (TRL) or impaired clearance. The estimated prevalence of hypertriglyceridemia is 25% worldwide. (1)

The role of TG as a risk factor for cardiovascular disease (CVD) has been the subject of debate within the medical and scientific communities for many years. (2) The residual atherosclerotic risk, as previously defined, is attributable to the persistence of atherogenic particles with apolipoprotein B (ApoB). These particles are not exclusively present in low-density lipoprotein cholesterol (LDL-C); they are also found in other very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and cholesterol remnants. These particles are characteristically present in patients with type 2 diabetes, metabolic syndrome and insulin resistance.

The following discussion will present the arguments in favor of considering TG, expressed as absolute value, non-high-density lipoprotein cholesterol [total cholesterol (TC) minus high-density lipoprotein cholesterol (HDL-C)] or cholesterol remnants, as a significant risk factor for CVD. It will be demonstrated that lowering TG values contributes to lowering CVD risk. This argument is supported by recent evidence from epidemiological, genetic, and interventional studies. (Figure 1). (3,4)

ARGUMENTS IN FAVOR OF THE ROLE OF TRIGLYCERIDES AS CVD RISK FACTOR

1. Epidemiological evidence:

Population-based studies: Several observational studies, including the PREDIMED study and the Copenhagen General Population Study, have consistently demonstrated a correlation between elevated TG levels and an increased risk of cardiovascular events (CVE) such as myocardial infarction and coronary artery disease. (5-7)

Follow-up data: Longitudinal studies have observed that individuals with hypertriglyceridemia have a higher incidence of CVE, independently of other risk factors such as LDL-C levels. (8)

2. Biochemical mechanisms:

Atherosclerotic plaque formation: TG contribute to atherosclerotic plaque formation from their remnants, which are cholesterol-rich particles that infiltrate the arterial wall, contributing to the development of atherosclerotic plaques. When these particles become trapped in the vascular subendothelium, they trigger a retention process, leading to the generation of atherosclerotic plaque and subsequent complications, such as rupture. This is the classic pathophysiological process of atherosclerosis. (9)

Endothelial dysfunction and inflammation: Elevated TG levels are associated with endothelial dysfunction and with the production of inflammatory mediators and cytokines within the vascular subendothelium. These mediators can contribute to the progression of atherosclerosis. This raises the double effect or impact in terms of vascular damage derived from these lipoproteins, not only capable of internalizing in the subendothelium but also of generating local inflammation that enhances the deleterious mechanism. (9)

3. Genetic and intervention studies:

Mendelian randomization: Studies using the Mendelian randomization technique have found a causal relationship between genetic variants that elevate TG levels and an increased risk of CVD. (10)

INTERVENTION CLINICAL TRIALS:

Therapeutic agents for the treatment of elevated TG levels include statins, fibrates, peroxisome prolifera-

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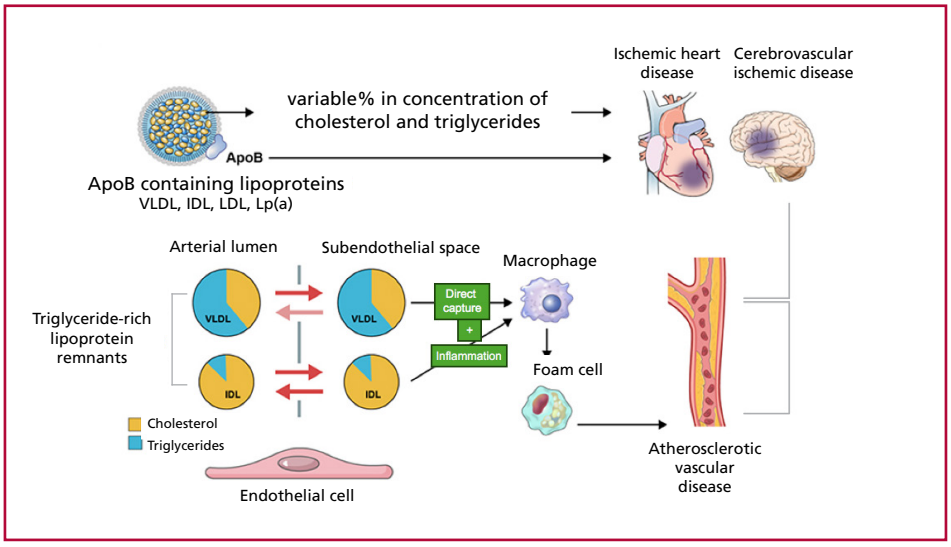

Fig. 1. Triglycerides, remnants and cardiovascular disease

IDL: intermediate-density lipoproteins; LDL: low density lipoproteins; Lp(a): lipoprotein(a); VLDL: very low density lipoproteins

tor-activated receptor alpha (PPAR-α), and omega-3 polyunsaturated fatty acids. Fibrates have the greatest power to reduce TG (a reduction between 30-50%, depending on baseline plasma concentrations) and non-HDL cholesterol (between 6-16%). In patients with severe hypertriglyceridemia, the use of fibrates can lead to an increase in LDL levels. Eicosapentaenoic acid (EPA) is less effective than fibrates at reducing TG levels, but it has several other notable benefits, such as improving vascular endothelial function, inhibiting platelet aggregation, and having anti-inflammatory properties.

Subgroup analysis of pharmacological interventions to lower TG, such as fibrates, has been shown to reduce the risk of CVEs in patients with elevated TG levels. Additionally, the legacy effect, evidenced in the long-term follow-up of patients who received fenofibrate, shows a clear benefit with these drugs. (11,12) High-dose omega-3 fatty acids (specifically EPA), demonstrated a clear benefit on CVD risk in the REDUCE-IT trial in those patients with high TG levels. The impact on TG levels is proposed to be one of the mechanisms that explains this benefit. (13)

CONCLUSIONS

While TG have historically been overshadowed by the focus on LDL-C, the cumulative evidence suggests that they should not be ignored as a risk factor for CVD and should clearly be taken into account when assessing atherosclerotic residual risk. TG and their remnants have direct implications in the pathogenesis of atherosclerotic CVD and their management could represent an additional therapeutic strategy in the global effort to combat the epidemic of CVD. However, further research is needed to optimize treatment strategies and to establish clear guidelines on the appropriate timing and manner for intervention in cases of hypertriglyceridemia.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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ANTAGONIST

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"To be or not to be—that is the question" is perhaps one of the most famous quotes in world literature. It is also the opening line of Hamlet's soliloquy in William Shakespeare's eponymous play. With all the respect that the play and its author deserve, I will borrow it to argue my position on this interesting controversy.

The association between lipids, particularly cholesterol, and the risk of developing CVD began to be robustly established in 1953 with the publication by Ancel Keys. (1) Since then, the role of cholesterol in the development of atherosclerotic CVD and the impact of lowering cholesterol levels, particularly LDL-C, on reducing cardiovascular risk have been clearly demonstrated. (2)

There is also evidence of the association between TG levels and increased risk of atherosclerotic CVD. (3,4) However, in my role as an antagonist in this controversy, it is necessary to analyze why I should not focus on reducing TG levels to reduce CV risk. I bring up a phrase that I have heard repeatedly from Dr. Corral, who acts as an agonist in this debate: "Correlation does not imply causation". Returning to the opening quote of the text, the key question is: are TGs a causal factor or simply a marker of cardiovascular risk? This distinction is fundamental and extends beyond a mere semantic difference. While a marker allows for identifying those individuals or populations at greater risk of developing an event (in this case, a CVE), treatment cannot modify this risk. In contrast, a risk factor is a condition that, when modified, reduces the chance of an event occurring, thereby becoming a therapeutic target.

From a physiological point of view, lipids circulate in the bloodstream bound to proteins, forming particles called lipoproteins, whose content varies from one particle to another. TG are primarily transported in particles that originate in the liver (VLDL and IDL) and in chylomicrons, which originate in the intestine. Although these particles are rich in TG, it is estimated that they carry approximately one third of circulating cholesterol (remnant cholesterol), (5) and their constitutive protein is ApoB, as in LDL-C. (6) Consequently, the question arises as to whether the increased CV risk observed in patients with elevated TG levels is directly associated with this elevation (causation) or with the concomitantly transported cholesterol (correlation). Although this analysis focuses on lipid particles, the common factor in atherogenic risk associated with both lipid fractions seems to be more related to the number of ApoB particles than to the mass of cholesterol within ApoB particles. (7)

It is also relevant to consider what happens in patients with extremely high TG values due to genetic alterations in their metabolism. Although this brief pathophysiological review might suggest that TGs are not the main cause of the problem, different research groups have evaluated strategies to reduce cardiovascular risk by lowering TG levels.

In this context, I will focus on the two most widely used pharmacological groups for the treatment of mild and moderate hypertriglyceridemia: fibrates and omega-3 fatty acids.

The most prominent studies on fibrates are the BIP (Bezafibrate Infarction Prevention) study, (8) the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study (9) and the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study. (10) In these studies the use of bezafibrate (BIP) and fenofibrate (FIELD and ACCORD) did not result in a significant reduction in CVE, despite achieving reductions in TG levels of 21%, 29% and 25.6%, respectively. However, a meta-analysis that included 45 048 patients with hypertriglyceridemia and low HDL-C levels showed significant reductions of 10% in major CVEs and 13% in coronary events. (11) This suggests that the impact of TG may have clinical relevance in patients with low HDL-C. It also raises questions about the adequacy of the populations evaluated in the aforementioned studies to confirm causation of hypertriglyceridemia in atherosclerotic disease.

The PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study was conducted to answer this question. (12) This trial included patients with diabetes, plasma TG levels between 200 and 499 mg/dL and HDL-C levels ≤ 40 mg/dL who were randomly assigned to receive pemafibrate or placebo. Despite a 26.2% reduction in TG levels in the treated group, the incidence of the primary CV endpoints was not significantly lower. This finding could be attributed to

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the increase in ApoB levels observed in the pemafibrate-treated group, which reopens the debate: "TG or ApoB, that seems to be the question".

With regard to omega-3 fatty acids, I will voluntarily omit the GISSI-Prevenzione study. The omission is not due to any personal convenience in my role as antagonist; rather, the decision is based on the fact that the baseline treatment used in the study does not align with the current concept of cardiovascular risk management. (13) The JELIS (Japan EPA Lipid Intervention Study) deserves to be mentioned in first place. This study evaluated the use of EPA in subjects with hypercholesterolemia who were receiving statins and who had mean TG levels of 154 mg/dL (111 mg/dL - 224 mg/dL). (14) Patients treated with EPA 1800 mg daily experienced a 19% reduction ($p = 0.048$) in the incidence of major coronary events compared with those receiving statins alone. However, the difference in TG reduction between the two groups was only 4% (9% vs. 5%), suggesting that this modest decrease alone would not fully explain the observed benefit. More recently, the REDUCE-IT study evaluated the use of icosapent ethyl in patients with CVD or diabetes associated with other risk factors treated with statins, with TG levels between 135 and 499 mg/dL. (15) Patients treated with 4 g/day of icosapent ethyl had a 25% reduction (HR 0.75, $p < 0.001$) in the risk of presenting the composite ischemic events (nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) and CV death, and the risk of the secondary end point was also lower. Contrary to the findings of the JELIS study, a greater reduction in TG levels was observed in this case, reaching 18.3%. Is this 18.3% reduction sufficient to justify the CV benefit? I believe not, and I support my position with two arguments. First, the STRENGTH (Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial, which evaluated a combination of EPA with docosahexaenoic acid (DHA) in a similar population, found no reduction in CVD despite a reduction in TG levels that was virtually identical to that reported in the REDUCE-IT trial. (16) Second, in the REDUCE-IT trial subgroup analysis, the benefit was similar in patients with baseline TG levels < 150 mg/dL versus those with levels ≥ 150 mg/dL, or < 200 mg/dL versus ≥ 200 mg/dL. Additionally, TG levels at one year after randomization were not predictive of CV benefit. The study was favorable even in the subgroup of patients with TG levels < 150 mg/dL, (17) suggesting that other mechanisms may be responsible for the CV benefit observed in the REDUCE-IT study. (18)

Considering the aforementioned points, it can be concluded that lowering TG levels should not be considered a primary strategy for reducing CV risk. In this context, hypertriglyceridemia should be regarded as a risk marker rather than a therapeutic target, given its association with elevated levels of remnant cholesterol and ApoB-rich particles, which appear to be the primary contributors to the observed increase in CV risk. Therefore, the therapeutic approach should focus on reducing ApoB-rich particles.

Furthermore, certain treatments, such as icosapent ethyl, could offer an alternative approach due to their pleiotropic effects that extend beyond the mere reduction of TG levels.

To conclude, I would like to reiterate and adapt to the context the famous phrase from Hamlet with which I began this post of this controversy: "To be or not to be a lipid fraction causative of atherosclerosis, that is the question.".

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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AGONIST REPLY

First, I would like to express my gratitude to my friend, Dr. Augusto Lavalle Cobo, for facilitating this exchange and for his clear exposition and review of the available evidence, primarily from pharmacological intervention studies.

However, I must point out that if it is suggested that TG levels should not be measured and treated, neither non-HDL-C nor ApoB (which is recommended in all national and international guidelines) should be used as a therapeutic target. This is because the representation of blood TG levels is provided by the remnant TG-rich particles containing ApoB, and these particles have the dual capacity to cause damage, infiltrate the subendothelium, and create an inflammatory phenomenon that speeds up and enhances the development of atherosclerosis.

Despite what has been previously mentioned, we must understand and re-examine the physiology and pathophysiology of lipids, wherein LDL particles emerge as a consequence of the catabolism and degradation of VLDLs secreted by the liver. This continuous metabolic process (from VLDL, traversing IDL, culminating in LDL) is distinctive and linear, and the presence of elevated TG levels clearly evidences increased cardiovascular risk.

In my daily practice, I ask myself: why would I order determination of ApoB or estimation of non-HDL-C in a patient? The answer to this question is simple: because that patient has elevated TG levels, residual risk attributable to TRL and cholesterol remnants, and it has been demonstrated that, in that context, measuring LDL-C alone is not sufficient for risk assessment (in my patient with TG levels of 70 mg/dL, measuring ApoB or calculating non-HDL-C does not provide more information for management).

In conclusion and referring to the initial point of the controversy (lowering TG to reduce cardiovascular risk), it is crucial to acknowledge that TGs are not merely a "marker" of CV risk (as are, for example, troponin T or NT-proBNP). The futility observed in various pharmacological studies conducted to date should not make us ignore the fact that my patient, with TG levels of 300 mg/dL, should be "treated", which is not the same as "medicated", because they have an evident risk with interventions (diet, exercise, future ApoC3 inhibitors?) that can modify this biomarker and improve cardiovascular prognosis.

Pablo Corral

ANTAGONIST REPLY

It is a pleasure to share this controversy with Dr. Pablo Corral, with whom, in addition to a great interest in lipids, I have a deep friendship. I congratulate Dr. Corral for the clear and precise explanation offered during his intervention as a proponent of the agonist position in this controversy. In his presentation, he highlights the evidence from various types of studies demonstrating the relationship between elevated TG levels and increased risk of atherosclerotic cardiovascular events.

As the saying goes: "Tell me who you hang out with and I will tell you who you are". In this regard, it is noteworthy to mention that TG, as previously indicated, circulate in the bloodstream in particles that contain ApoB as a constituent protein. In most of these particles, TG are associated with other lipid fractions, such as cholesterol, which justifies measuring ApoB or estimating non-HDL-C to assess an individual's residual lipid risk.

Personally, when I see a patient with moderate hypertriglyceridemia, I ask myself the following question: should I focus on lowering TG or be more aggressive in lowering ApoB? After all that has been said, you can probably imagine my approach.

I would like to conclude with a reflection that may seem obvious, but which is always important to emphasize when we talk about cardiovascular risk: the necessity of a comprehensive approach. This is even more relevant when we refer to hypertriglyceridemia, since, in many cases, this condition reflects a poor "cardiometabolic" state. In such cases, lifestyle interventions (e.g., weight control, improved diet, and increased physical activity) have been shown to not only positively impact cardiovascular risk but also reduce plasma TG levels.

Augusto Lavalle Cobo