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Approach to hypertriglyceridemia syndromes: the importance of distinguishing between primary and secondary etiologies

Acercamiento a los síndromes de hipertrigliceridemia: la importancia de distinguir entre etiologías primaria y secundaria

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INTRODUCTION

Hypertriglyceridemia (HTG) is a common clinical problem. Current medical guidelines define normal fasting plasma triglycerides (TG) concentrations as less than 150 mg/dL. According to the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), mild-to-moderate common HTG (CHTG) is defined by TG concentrations between 150-880 mg/dL, and severe HTG refers to ranks higher than 880 mg/dL.[1,2] The prevalence of HTG varies among ethnic groups; it is hugely prevalent in Hispanics. In Mexico, the pervasiveness of mild-to-moderate hypertriglyceridemia is around 31%, with ~5% of the Mexican population showing critical HTG.[3] Standards recommend advising all subjects suffering from HTG on lifestyle modifications. For patients having CHTG, the main goal is to decrease cardiovascular risk by reducing low-density lipoprotein cholesterol (LDL-c) and non-high-density lipoprotein cholesterol (non-HDL-c) as well as apolipoprotein B levels (apo B). If the patient has dangerous HTG, the chief goal is to reduce the danger of pancreatitis.[4] Recent epidemiologic and genetic studies establish TG-rich lipoproteins (TRL) and their leftovers rich in cholesterol (RCL) as essential contributors to atherosclerotic cardiovascular disease (ASCVD).[5,6] So novel therapies that target TRL and inflammation are in development to reduce residual ASCVD risk.[7] Various methods for measuring residues exist; however, because cholesterol remnants lipoproteins (RLP-c) are heterogeneous populations of different sizes and lipid composition, a direct assay has not yet been developed.[8]

Metabolism of triglycerides and triglyceride-rich remnant lipoproteins

Enzymes such as diacylglycerol acyltransferase are responsible for TG synthesis. They originate in the intestine built from dietary fatty acids or free fatty acids (FFA) extracted from the circulation or are newly synthesized in the liver. Microsomal triglyceride transfer protein (MTTP) unites lipids apolipoprotein B-48 (apo B-48) or apo B 100 in the intestine or liver, respectively, forming chylomicrons (CHY) which enter plasma indirectly through lymphatics, or very-low-density lipoprotein (VLDL) that transport TG, respectively. Hydrolysis of circulating CHY or VLDL particles type one or two by lipoprotein lipase (LPL) releases FFA and produce chylomicron remnant, whose clearance requires apolipoprotein E (apo E), as apo B-48 does not have the low-density lipoprotein receptor-binding domain and VLDL-remnant lipoproteins (intermediate density lipoprotein, IDL), that can bind to low-density lipoprotein receptor-related protein 1

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(LRP-1) in the liver. In contrast, another part, under the action of hepatic lipase (HL), is transformed into LDL.

Atherobiology of RLP-c lipoproteins

RPL-c elements are partially TG-depleted post lipolytic particles whose cholesterol content is more likely to cause atherosclerosis. Just like LDL, RCL can invade the arterial intima.[6] Once there, fragments could even be trapped preferentially to LDL simply because of affinity to extracellular proteoglycans. In contrast to LDL, apo C3 and apo E-enriched remnants can be directly taken up by macrophages in their native condition, without enzymatic modification or specific receptors, leading to foam cells' formation.[9] Beyond LDL, the RLP-c proteins transport up to 30% of the cholesterol load in postprandial conditions, meaning more cholesterol per particle than LDL does. Increased production and delayed catabolism of TGRL lead to its increase and greater concentrations of RLP-c. APOC3 reduces VLDL and CHY lipolysis by inhibiting LPL and blocking TRL and RLP uptake by hepatic receptors. Thus, HTG results from increased production or decreased catabolism of CHY and VLDL or VLDL alone; has a direct effect on the composition of LDL and high-density lipoprotein (HDL), caused by elevated activity of cholesteryl ester transfer protein that shifts TG from CHT and VLDL to LDL and HDL, in exchange for cholesteryl esters.[10] In a recent study, it is shown that apoB48-containing particles in subjects with HTG are released across the entire chylomicron-VLDL size range. This process persists for many hours, elevating their concentrations and adding to the circulating population of particle remainders.[11]

The five steps for differential diagnosis in clinical practice

1. Syndromic diagnosis. In 1994, the European Consensus[12] established the initial approach to the patient affected by dyslipidemia. The division in lipid phenotypes *(Table 1)* allows elucidating the most frequent primary and secondary causes. However, syndromic judgment has no impact on cardiovascular prevention and may overestimate or underestimate treatment.
2. Family history. Screening closest relatives of patients with primary dyslipidemias (those showing cholesterol or triglycerides levels higher than 300mg/dL, premature coronary heart disease, frequent pancreatitis events, xanthomas, xanthelasmas, etcetera).[13]
3. Search for secondary causes. Environmental origins should be excluded. A variety of lifestyle factors and medical conditions can cause hypertriglyceridemia *(Figure 1)*. Common secondary roots include obesity, uncontrolled diabetes, hypothyroidism,

Table 1: Syndromic diagnosis.

Type	TC	TG	HDL-C
Mixed hyperlipidemia	> 200	> 150	
Hypertriglyceridemia			
Isolated	< 200	> 150	
Severe		> 500	
Hypoalphalipoporteinemia			< 40
Hyperalphalipoproteinemia			> 60
Hypercholesterolemia			
Isolated	> 200	< 150	
Severe	> 300		

TC = total cholesterol, TG = triglycerides, HDL-c = high-density lipoprotein-cholesterol.

smoking, alcohol abuse, endocrinopathies, and various commonly used drugs *(Table 2)*.[14]

4. Etiological diagnosis. Most patients enduring HTG do not have a recognizable genetic cause. Primary severe HTG has both monogenic and polygenic determinants. For example, Familial chylomicronemia syndrome (FCS, type 1), a rare form of monogenic HTG with an estimated one in a million prevalence. Also consider the

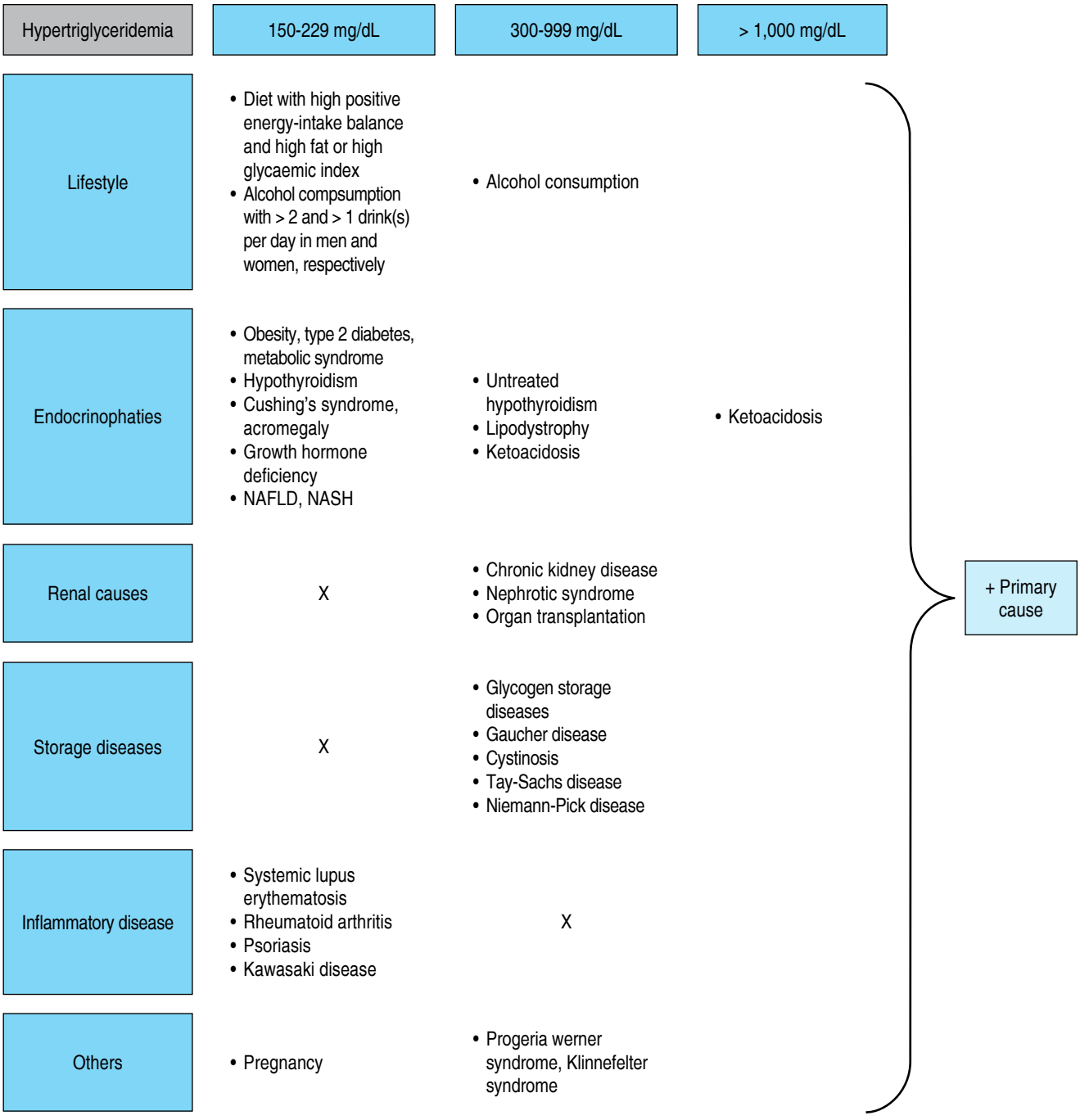

Figure 1: Secondary causes of hypertriglyceridemia.

Table 2: Drugs associated with high triglycerides levels.

Hormonal	• Oral oestrogens (40%) • Selective estrogen receptor modulators (20%) • Steroids • Tamoxifen (20%) • Raloxifen (20%) • Clomiphene (40%) • Growth hormone therapy • Androgen deprivation therapy (15%)
Cardiometabolics	• Non cardioselective beta blockers (20%) • Thiazides (15%) • Diuretics (10%) • Bile acid sequestrants
Immunosuppressants	• Cyclosporine (20%) • Sirolimus (30%) • Tacrolimus (30%) • Interferon alpha (20%)
Anti-cancer therapeutics	• L-asparaginase • Cyclophosphamide • Tyrosin-kinase inhibitors (20-70%)
Others	• Retinoids (40%) • Protease inhibitors (100%), ITRN (50%), ITRNN (40%), INH, INTEG (0%) • Antidepressants y atypical antipsychotics (30%) • Propofol (20%)

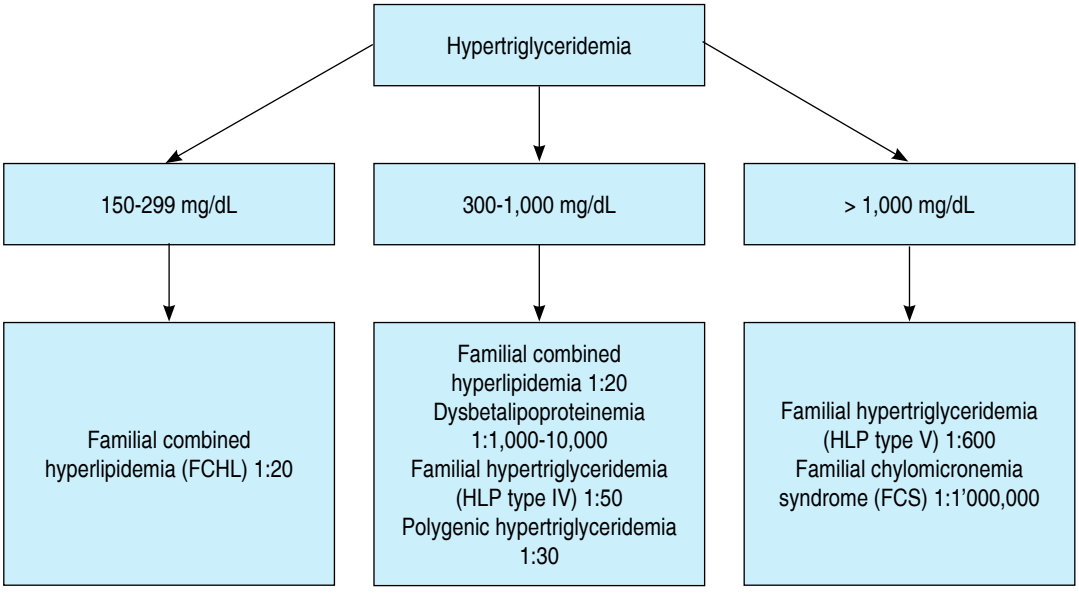

Figure 2: Primary causes of hypertriglyceridemia.

detection of rare, biallelic (homozygous or compound heterozygous) variants in one of six genes: LPL (accounting for 90% of cases), APOC2, APOA5, LMF1, GPIHBP1, ANGPTL3.[13] Familial HTG (gype V) highly oligogenic, could be a cause of critical HTG frequently confused with other primary dyslipidemias.[15] A significant number of conditions *(Figure 2)* that cause mild-to-moderate HTG ought to be excluded.

5. Assessment of cardiovascular risk. All current recommendations on the prevention of ASCVD in clinical practice endorse evaluating the total CVD threat. The Globorisk score[16] in people over 40 is a good tool for assessing cardiovascular hazards in Mexican people. The 2019 ESC/EAS guidelines establish that persons having documented ASCVD, diabetes type one or two, extreme levels of individual danger factors, or chronic kidney disease (CKD) generally have very prominent or high total CV peril. No risk estimation models are needed for such persons.[2]

RECOMMENDATIONS AND CONCLUSIONS

The objective of the differential analysis is to identify dyslipidemias exhibiting atherogenic potential from those without it. One must always search for secondary causes in all scenarios.

1. High-risk primary hyperlipidemias ought to be treated with intensity regardless of the existence of other hazard factors (i.e., familial hypercholesterolemia and familial HTG).
2. Etiological diagnosis is essential to categorize the patient. It must systematize the scrutiny of dyslipidemias and promote inquiry studies in first-degree relatives.
3. Subclinical atherosclerosis should be sought in asymptomatic individuals revealing the most atherogenic primary dyslipidemias.

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