

Is Hypertriglyceridemia a Key Detrimental Factor or Associative Triggering Factor for Cardiovascular Abnormalities?

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ABSTRACT

Elevation of fasting plasma triglycerides above the normal level (150 mg/dL) is an indication of hypertriglyceridemia (borderline high, 150–199 mg/dL; high, 200–499 mg/dL; very high, above 500 mg/dL). A plethora of experimental and clinical studies evidenced a perceptible association between hypertriglyceridemia and cardiovascular disease. Hypertriglyceridemia could lead to endothelial dysfunction, atherosclerosis, hypertension, and ischemic heart disease. In addition, studies have demonstrated the myocardial susceptibility to ischemia-reperfusion injury in the hypertriglyceridemic condition. Importantly, hypertriglyceridemia alone may cause cardiovascular abnormalities like atherosclerosis even in absence of hypercholesterolemia. It is worth-mentioning that a pharmacological reduction in triglyceride levels diminishes the cardiovascular disease pathogenesis. It is a subject of contemporary interest to detail whether hypertriglyceridemia a key detrimental factor or an associative triggering factor for cardiovascular abnormalities. This review will discuss the potential role of hypertriglyceridemia in the pathogenesis of cardiovascular disorders.

Introduction

Hypertriglyceridemia (HTG) refers to an elevation of fasting triglyceride (TG) levels above normal (> 150 mg/dL). As per the suggestion of the 'Third Report of the National Cholesterol Education Program (NCEP), HTG may be categorized as borderline high (150–199 mg/dL of TGs), high (200–499 mg/dL of TGs), and very high (above 500 mg/dL of TGs).^[1] The US National Health and Nutrition Examination Survey conducted between 2001 and 2006 reported that the prevalence of severe HTG among US adults was approximately 1.7% equating to roughly 3.4 million peoples,^[2] indicating the incidence of HTG in US adult population. The

common causes for HTG are familial lipoprotein lipase deficiency, chylomicronemia, elevated levels of very low-density lipoproteins (VLDL), reduced levels of high-density lipoproteins (HDL), and the presence of type 1 and 2 diabetes mellitus.^[3]

Accumulating evidence suggests a strong link between HTG and cardiovascular disease.^[4] Elevated levels of nonfasting/postprandial TGs could directly correlate with elevated remnant cholesterol.^[5] Nordestgaard and Freiberg suggested that, as all cells have ability to degrade TGs, it is biologically unlikely that it is the TG molecules that cause cardiovascular disease. Nevertheless, the elevated remnant cholesterol due to HTG might lead to cholesterol entrapment in the arterial intima, resulting in accelerated atherosclerosis and cardiovascular disease.^[5] Epidemiological studies with reference to relating HTG and cardiovascular disease support the vision that TG-rich lipoproteins are an independently associated risk factor.^[6] Experimental and clinical studies evidenced an association of HTG with endothelial dysfunction.^[7,8] HTG is independently associated with endothelial dysfunction in coronary heart disease patients.^[8] Further, it has been documented that HTG is a risk factor for the pathogenesis of atherosclerosis^[9,10] and hypertension.^[11] Worthy of note is that the condition of HTG could aggravate myocardial ischemia/reperfusion (I/R) injury and coronary artery disease.^[12–14] This review is focused on the plausible role of HTG in the induction and progression of cardiovascular disorders, including endothelial dysfunction, atherosclerosis, hypertension, coronary artery disease, and ischemic myocardial injury.

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Hypertriglyceridemia-associated endothelial dysfunction and atherosclerosis

Endothelium is an innermost lining of the blood vessel. Endothelial dysfunction refers to an impairment of endothelium-dependent vasodilatation caused by decreased nitric oxide (NO) generation and bioavailability in the inner vessel wall.^[15–18] Considerable number of studies demonstrated the role of HTG in the pathogenesis of endothelial dysfunction and atherosclerosis.^[7–10] HTG was reported to induce endothelial dysfunction in the rat by impairing NO-dependent vasodilation in the rat aorta.^[19] Kusterer *et al.*^[20] demonstrated with evidence that the chronically selective HTG induced endothelial dysfunction in rats that is associated with an increased vascular superoxide production and a subsequent decrease in NO bioavailability. The authors suggested that HTG could be an independent risk factor for the development and progression of atherosclerosis associated with endothelial dysfunction.^[20] A clinical study in healthy young men afflicted to mild to moderate HTG supported the association of elevated TG levels with endothelial dysfunction.^[21] The authors noted an elevation in plasma concentration of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), in healthy young men with mild to moderate HTG.^[21] Thus, it is suggested that HTG might have an ability to increase ADMA levels, which might account for the pathogenesis of endothelial dysfunction. It is worth-mentioning that triglyceride-rich lipoprotein (TGRL) lipolysis products endow with a pro-inflammatory stimulus, resulting in the alteration of endothelial barrier function.^[22] The authors reported that TGRL lipolysis releases neutral and oxidized free fatty acids (FFAs) that induce endothelial cell inflammation.^[22] Norata *et al.*^[23] further confirmed the potential involvement of hypertriglyceridemic TGRLs in endothelial dysfunction via induction of a pro-inflammatory and pro-thrombotic state.^[23] In addition, Norata *et al.*^[24] demonstrated a severe impairment in endothelial function (assessed by determining flow-mediated dilation of the brachial artery) during the postprandial phase in hypertriglyceridemic subjects. The authors noted that postprandial-TGRLs upregulated the expression of several pro-inflammatory genes, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), P-selectin, interleukin-6 (IL-6), and ADAM metallopeptidase with thrombospondin type 1 (ADAMTS1).^[24] Moreover, Benitez *et al.*^[25] suggested that increase in leukocyte cell adhesion molecules in primary hypertriglyceridemic subjects would highlight the inflammatory process in the pathogenesis of atherogenesis. Taken in-concert, it is suggested that HTG might be an independent risk factor for endothelial dysfunction and atherosclerosis by virtue of its ability to induce oxidative stress, vascular inflammation, and prothrombotic events in the vessels.

HTG and hypertension

The National Health and Nutrition Examination Survey have indicated that 50 million or more Americans have high blood pressure. Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension.^[26] Endothelial dysfunction augments loss of normal vasorelaxation and the inability of arteries to dilate, which consequently leads to an induction of hypertension.^[27] Recently a study performed among Chinese nonagenarians/centenarian demonstrated the

association of HTG with systolic blood pressure (SBP). The authors stated a significant relationship of abnormal serum TG levels with higher SBP.^[11]

Hypertriglyceridemia and ischemic heart disease

Myocardial ischemia is associated with a reduction in coronary flow, followed by diminution in oxygen and nutrient supply to the heart. Reperfusion to an ischemic myocardium could further augment the ischemic damage, known as I/R injury.^[28–30] Hyperlipidemic myocardium is rather sensitive and more vulnerable to I/R-induced myocardial injury.^[31] HTG is an independent risk factor for coronary heart disease.^[13] Hypertriglyceridemic condition enhances myocardial susceptibility to I/R injury.^[12,14,32] Carvajal *et al.*^[12] demonstrated implication of free radicals and calcium overload in enhanced I/R injury in hypertriglyceridemic and hypertensive rats. A study by Monti *et al.*^[33] demonstrated impaired systolic and diastolic recovery from low flow ischemia due to increased TGs. The authors concluded that high TG levels impaired myocardial recovery after low-flow ischemia in association with a release of endothelin-1, a potent vasoconstrictor.^[33] Subsequently, HTG male rats were shown to be more prone to cardiac damage as a result of I/R as HTG males had a higher incidence of arrhythmias than females, but only HTG males suffered lethal ventricular fibrillation.^[34] In summary, HTG exaggerates myocardial I/R injury, and indirectly elicits cardiac damage and promotes impairment in cardiac functioning.

Conclusion

Patients with HTG are at significant risk for cardiovascular disorders even if LDL cholesterol levels are at control. HTG could provoke and augment cardiovascular disorders by inducing cardiovascular inflammation and oxidative stress. HTG might be marked as a key triggering factor that initiates the development of cardiovascular disease. Further studies are needed to explore the precise signaling mechanism involved in the pathogenesis of HTG-associated cardiovascular complications. A pharmacological reduction in elevated TG levels could reduce the risk of cardiovascular events.

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