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everal epidemiological studies have reported that elevated serum triglyceride (TG) levels are associated with the risk of coronary artery disease (CAD).\(^1\)\(^,\)\(^2\) Additionally, elevated serum TG levels appear to be associated with a residual risk of atherosclerotic cardiovascular disease (ASCVD), despite the use of low-density lipoprotein cholesterol (LDL-C)-lowering statin therapy.\(^3\)\(^,\)\(^4\) However, an independent association between serum TG levels and the risk of future CAD events remains controversial, because this association is attenuated after adjusting for other lipid profile parameters, such as LDL-C and high-density lipoprotein cholesterol (HDL-C).\(^1\)\(^,\)\(^2\) Recent genetic evidence and Mendelian randomization studies provide robust evidence of the role of serum TGs in the causal pathway for ASCVD, indicating a possible pathogenetic role of these lipids in atherosclerosis rather than merely serving as biomarkers of disease risk.\(^5\)\(^,\)\(^6\)

Kajikawa et al have previously demonstrated endothelial dysfunction even in individuals with serum TG levels of 106–131 mg/dL.\(^7\) However, whether patients with high-normal serum TG levels (100–149 mg/dL) are at an increased risk of cardiovascular events remains unclear. Those authors evaluated the association between serum TG levels and future cardiovascular events in patients with CAD in a post-hoc analysis of the FMD-J (Flow-Mediated Vasodilatation-Japan) study A.\(^8\) Their present study\(^9\) in this issue of the Journal demonstrates that elevated serum TG levels are significantly associated with an increased risk of first major cardiovascular events (MACE). After adjusting for various confounders, serum TG levels >100 mg/dL were significantly associated with an increased risk of cardiovascular events compared with levels <100 mg/dL. They conclude that serum TG levels >100 mg/dL (even in those with high-normal serum TG levels) are independently associated with the incidence of MACE in patients with CAD treated with optimal medical therapy.

However, serum TGs per se do not accumulate in atherosclerotic plaques and are unlikely to directly cause atherosclerosis. TGs are major components of TG-rich lipoproteins (TRLs), such as chylomicrons (CMs), very low-density lipoproteins (VLDLs), and intermediate-density lipoproteins (IDLs). The core TGs comprising CMs and VLDLs are catabolized rapidly in the circulating blood by lipoprotein lipase (LPL) on the blood vessel walls, producing CM remnants and VLDL remnants, which are rich in cholesterol relative to TGs. Thus, elevated serum TG levels reflect increased levels of TRLs and may serve as biomarkers of elevated levels of cholesterol in remnants and as causal factors for atherosclerosis and ASCVD. VLDL and VLDL remnants can penetrate the arterial

Figure.  Suggested role of raised plasma triglycerides and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis. Triglycerides and remnant cholesterol could act through triglyceride hydrolysis and cholesterol accumulation in arterial wall foam cells, leading to development of atherosclerosis. FFA, free fatty acids; LDL, low-density lipoprotein; LPL, lipoprotein lipase. (Reproduced with permission from reference 5.)

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Triglycerides as Residual Risk for Atherosclerotic Cardiovascular Disease

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intima and be taken up by macrophages directly without undergoing oxidative modification unlike that observed with LDL particles. Moreover, LPL on the endothelial surface or within the arterial intima degrades TGs in VLDL and VLDL remnants with liberation of free fatty acids and monoacylglycerols, both of which cause tissue toxicity and precipitate local inflammation. It is therefore presumed that elevated serum TGs, including TRLs and remnants, are associated with low-grade inflammation and accelerated foam cell formation via macrophage uptake directly at the arterial wall followed by the development of atherosclerosis (Figure). Elevated VLDL TG levels furthermore activate cholesteryl ester transfer protein, which causes TG enrichment of LDL and HDL. The TG content of these particles is hydrolyzed by hepatic triglyceride lipase, resulting in the formation of small-dense LDL and HDL particles. To summarize, elevated serum TG levels are being increasingly investigated as a residual risk factor for ASCVD even in those receiving optimal statin therapies.

Unfortunately, most previous clinical trials could not provide strong evidence regarding the role of TG-lowering therapy in reducing the risk of ASCVD. A meta-analysis of fibrate trials demonstrated that TG-lowering measures significantly reduced the risk of MACE, even when fibrate was used as an add-on to statin therapy. However, there is lack of evidence to establish target serum TG levels for optimal management. The Japan Atherosclerotic Society guidelines for the prevention of ASCVD have established target serum TG levels <150 mg/dL in patients with or without CAD. A previous observational study in Japan demonstrated significant differences in linear trends for cardiac mortality based on quintiles of serum TG levels in patients with CAD even after adjusting for non-HDL-C and HDL-C, with serum TG levels of the lowest quintiles being <98 mg/dL. The present study also demonstrated that serum TG levels >100 mg/dL were significantly associated with an increased risk of cardiovascular events compared with levels <100 mg/dL. These data suggest that in clinical practice, attention should be focused on strict lowering of both serum TG and LDL-C levels to prevent ASCVD in patients with CAD.

The present study highlights that serum TG levels serve as a residual risk factor for ASCVD even in patients with optimal medical therapy and that it is important to strictly maintain target serum TG levels for optimal management of patients with CAD. A large-scale clinical trial has been performed using a selective peroxisome proliferator-activated receptor alpha modulator. Future clinical trials are warranted to determine whether serum TG-lowering therapy reduces the risk of ASCVD in patients with elevated serum TG levels.

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