The Forgotten Risk Factor

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The relation of serum TG concentrations and risk for CHD has been an issue of great interest and controversy. Unlike analyses with LDL-C and HDL-C, for which very strong and consistent relations with CHD risk have been demonstrated in observational and interventional studies, those with TG are ambiguous. Thus, TG represents a clinical conundrum: should it be measured, what does it mean, and should it be treated if elevated? In the past, the lack of an independent effect led one authority to advise against measuring TG or taking the serum TG concentration into account when assessing CHD risk. Also, TG measurement was fraught with problems, such as the confounding effect of free glycerol. In recent years, both analytic methods and biostatistical analysis have improved, and this forgotten risk factor has arisen again.

A number of factors have contributed to the conflicting views concerning TG concentration and CHD risk, including a weakening of the effect in multivariate analyses that control for HDL-C compared with univariate analyses. The inverse metabolic relation between HDL and the TG-rich lipoproteins may contribute to this weakening.

An important confounder of TG and CHD risk is the heterogeneity of the TG-rich lipoproteins. TG-rich particles derived from dietary lipid intake are not thought to be associated with increased risk for CHD, although extreme elevations of TG (TG >11.29 mmol/L) carry the risk of pancreatitis. Chylomicron remnant particles, on the other hand, are thought to be atherogenic. Through the action of lipoprotein lipase, VLDLs, the TG-rich lipoproteins secreted by the liver from endogenously produced lipids, are converted to IDLs, which are also believed to be atherogenic. The relation between the concentration of the larger VLDL particles and atherogenicity is unclear at this time. Protocols for measuring remnant lipoproteins have been developed only recently. If these become generally available, they should be of assistance to the physician in refining lipid profile assessment.

Some studies have reported that the degree of postprandial lipemia is a better indicator of atherogenicity than fasting serum TG levels. In some studies, the degree of postprandial lipemia was associated with risk for CHD or with the extent of coronary blockade. Furthermore, postprandial lipemia is associated with insulin resistance and hyperinsulinemia and may be an important marker for CHD independent of elevations of LDL-C.

Whether isolated hypertriglyceridemia in the absence of either an increased LDL-C or a decreased HDL-C is atherogenic has been a matter of dispute. Existing evidence suggests that TG is an important risk factor in subgroups of the population. In a 14-year follow-up of the Framingham Heart Study, TG was an independent risk factor in women between the ages of 50 and 69 years. Also, data from the Paris Prospective Study support the significance of hypertriglyceridemia as a risk factor in patients with non-insulin-dependent diabetes mellitus. In this issue of Circulation, the 8-year follow-up to the Copenhagen Male Study by Jeppesen et al adds support by showing increased CHD risk in middle-aged and elderly men in the middle and highest thirds of TG levels and a gradient of risk for TG levels even when stratified for HDL-C. In fact, TG levels increased within each level of HDL-C. In this report, fasting hypertriglyceridemia was a strong predictor of CHD independent of other risk factors, including HDL-C. This finding represents an important addition to our understanding of the complex association between CHD risk and TG.

In a recent meta-analysis of 17 population-based prospective studies, Hokanson and Austin present a strong case for TG as an independent risk factor for CHD. On the basis of data from a total of 46,413 men and 10,864 women, elevated TG was associated with an 30% increase in cardiovascular risk in men and a 75% increase in cardiovascular risk in women. Adjustment for HDL-C and other risk factors attenuated these risks but did not render them nonsignificant. Although the status of TG as an independent risk factor is controversial, elevated TG is increasingly recognized as a marker among metabolic and clinical conditions that are associated with increased risk for atherosclerosis. These include postprandial lipemia; insulin resistance; hyperinsulinemia; low HDL-C; small, dense LDL particles; increased oxidizability of LDL; poorly controlled diabetes; and central obesity.

Furthermore, TG as a synergistic risk factor with other lipid risk factors is becoming accepted. In the Helsinki Heart Study, the group of patients who benefited the most from treatment with gemfibrozil were those who had what is described as the lipid triad: a combination of high LDL-C, relatively low HDL-C, and high TG. This subgroup accounted for 70% of the event reduction in the Helsinki Heart Study. Similarly, in the observational PROCAM study, the combination of an increased ratio of LDL-C to HDL-C in combination with an elevated TG carried the highest risk for CHD. Of >4000 subjects with an LDL-C:HDL-C ratio of >5 and a TG level...
>2.26 mmol/L, ~5% accounted for ~25% of the cardiovascular disease in this population. 13

More recent trials that used the HMG-CoA reductase inhibitors, or statins, have provided interesting insights into the atherogenicity of TG-rich lipoproteins. In the Monitored Atherosclerosis Regression Study (MARS) of lovastatin, the progression of mild to moderate coronary lesions correlated best with lipoprotein remnant particles and was correlated with a high ratio of apolipoprotein C3 in VLDL and LDL as contrasted with HDL, suggesting impaired metabolism of lipoprotein remnant particles. 14,15 Baseline TG levels were predictors of CHD risk in the West of Scotland Coronary Prevention Study (WOSCOPS) (personal communication, James Shepherd, MD, 1997). Also, as reported at the European Society of Cardiology meeting (Stockholm, Sweden, August 24–28, 1997), the increased risk in the Scandinavian Simvastatin Survival Study (4S) associated with increased TG levels appeared to be abolished by lipid-lowering treatment with simvastatin. Interestingly, a subgroup analysis from the Cholesterol and Recurrent Events (CARE) trial suggested that patients whose baseline TG concentration was <1.62 mmol/L experienced significant benefit (32% risk reduction, $P<.001$), whereas those whose baseline TG was ≥1.62 mmol/L did not.16

Whether lowering isolated hypertriglyceridemia can reduce coronary morbidity and mortality rates cannot be examined until a trial that manipulates only TG concentration can be designed, if such a design is even possible, given that available drugs that reduce TG also alter the concentrations of other lipoprotein families. However, the current evidence makes a compelling argument for including TG in the lipoprotein profile in the evaluation of patient risk for coronary disease. For the present, a measurement of a fasting TG and its association in conjunction with LDL-C and HDL-C concentrations and other risk factors would seem to be the most practical way of assessing any additional risk posed by hypertriglyceridemia.

HDL-C and LDL-C are well established as strong, independent CHD risk factors. However, it seems that TG continues to struggle to prove its credentials. The growing attention to hypertriglyceridemia and increased CHD risk is encouraging to veterans of the “triglyceride wars” and congruent with another trend in CHD risk management, namely, the concept of global risk assessment, in which TG and other risk factors are considered in the context of patients’ global risk for developing CHD.

**References**


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