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Triglycerides as vascular risk factors: New Epidemiologic Insights For Current Opinion in Cardiology

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Abstract

Purpose of review—Targeting triglycerides as a vascular risk factor is justified because of the role of triglyceride-rich lipoproteins in atherogenesis. This review examines recent evidence connecting triglycerides with cardiovascular disease (CVD) in the context of advances in insights concerning the pathophysiology, population burden, and prognostic impact of fasting versus non-fasting values.

Recent Findings—Cross-sectional surveys indicate that mean triglyceride levels in the United States have increased in recent decades. While elevated fasting triglycerides are consistently associated with increased CVD risk, adjustment for other risk factors (especially HDL-C) substantially attenuates this relationship. A recent meta-analysis of 27 prospective studies of Western populations reported a triglyceride impact on CVD in *both sexes*, for both fasting and non-fasting values. Non-fasting triglycerides maintained an independent graded relationship with CVD in fully adjusted analyses, with elevated 4 hour post-prandial triglyceride imposing a 4.5-fold increment relative to lower levels.

Summary—Evidence supports a potential role for both fasting and non-fasting triglycerides as vascular risk factors, owing in part to the accompanying burden of atherogenic remnant particles, small dense LDL, reduced HDL-C and a high frequency of accompanying insulin resistance. Triglyceride-associated CVD risk occurs even in subjects with low LDL-C, and lowering both lipids provides more benefit than reducing LDL-C alone.

Introduction

The role of triglycerides (TG) in promoting cardiovascular disease (CVD) is still debated more than 60 years after a relationship was first postulated [1]. Recent data focusing on the potential importance of non-fasting TG levels seem to settle this debate by establishing a consistent strong relation of TG with CVD risk. In this review we discuss the changing epidemiology of TG in the community, summarize recent reports that underscore the importance of non-fasting values, and highlight the complexity in making causal inferences based on the associations noted given the interdependence of lipid particles.

New Insights into the role of TG in Atherogenesis

It is necessary to contemplate TG as “TG-rich lipoproteins” (commonly referred to as “TRL”) to emphasize the concept that the metabolism and turnover of TG in the circulation

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may be as much (or more) a function of the composition of the other lipid and protein components of these particles as the fatty acid composition and concentrations of TG per se [2;3**]. Clinically, the two main components of TRL are the very-low density lipoproteins (VLDL) and chylomicrons. Since VLDL result from hepatic synthesis and chylomicrons are post-prandially produced by the gut, high TG are thought of as having an endogenous basis (increased hepatic synthesis) or an exogenous origin (dietary), or both. Regardless of the origin of TRL, the action of lipoprotein lipase in the capillary beds of the adipose tissue and muscles generates intermediate density lipoproteins from VLDL or chylomicron remnants [3**].

Remnant TRL levels can be very high in dyslipidemic conditions characterized by high TG, but are ordinarily also present in the normal post-prandial state. They are normally `cleared' by the liver but in persons with CVD, TRL remain increased in the circulation beyond the usual 4–8 hours [4]. This failure to catabolize TRL efficiently appears to be linked to accelerated atherogenesis since TRL appear to be proinflammatory, cause endothelial dysfunction [5], upregulate expression of endothelial adhesion molecules and promote macrophage chemotaxis. TRL are especially prone to enter the arterial wall where they are ingested by macrophages (analogous to oxidized LDL), to then become foam cells [6–8]. Retention of these TRL in the vascular wall also traps the more atherogenic small LDL-C particles [6;9].

The pathogenic effects of higher TRL are intricately linked to those of higher levels of small dense LDL-C and lower concentrations HDL-C that often coexist [10]. This is because higher TRL are a key determinant of heterogeneity of LDL size; LDL particle size is strongly inversely related to the plasma triglyceride level [11]. This appears to result both from the derivation of small LDL particles from triglyceride-rich VLDL and from LDL-C remodeling involving neutral lipid exchange and lipolysis [12]. Smaller LDL particles appear less amenable to physiologic LDL clearance via the LDL receptor, which enhances their potential for avid binding to proteoglycans in the vascular wall. Furthermore, these small LDL particles appear to be more susceptible to oxidation, a property that further increases their atherogenicity [8]. Thus, plasma TG is an indirect indicator of the relative proportion of circulating small atherogenic LDL-C particles, and thus provides an indication of lipid particle size–related coronary risk. Persons with the same LDL-C can have a substantially different CVD risk depending on their plasma TG; those with elevated TG having a greater cardiovascular risk. The association of higher TG with greater levels of small-dense LDL is reversed when high TG levels are lowered with pharmacological treatment [13**].

TRL are also intimately associated with CETP-mediated exchange of TG with cholesterol esters in HDL-C particles. The TG-enriched HDL particles are removed rapidly by hepatic lipase [14]. Thus, higher TRL seem to accelerate the fractional catabolism of HDL ApoA-1 [15], a phenomenon further enhanced by concomitant higher levels of Apo CIII that typically accompany higher TG levels [16]. Hepatic steatosis that accompanies higher levels of TRL may mediate increased hepatic secretion of both Apo CIII and VLDL components [17;18]. As plasma TRL rise, clearance of apoAI and apoAII high-density lipoproteins is enhanced [19]. Smaller HDL particles are removed from the blood and catabolized more rapidly, limiting their efficiency in reverse cholesterol transport and consequently diminishing their cardioprotective effect [20].

These inter-relationships among the lipids are most evident in the context of the metabolic syndrome, a construct that reflects presence of both obesity and insulin resistance. Persons with high TGs accompanied by reduced HDL-C can be presumed to have an atherogenic small LDL-C problem, particularly when accompanied by features of the metabolic

syndrome. It remains to be precisely estimated to what extent insulin resistance is responsible for the risk factor clustering that often accompanies `atherogenic dyslipidemia' and the high CVD risk it imposes. However, it seems likely that insulin resistance is responsible for a substantial proportion of the clustering and attendant elevated CVD risk observed in persons with increased TG. Furthermore, high TRL occur in a metabolic milieu additionally characterized by greater thrombogenicity, inflammation, and diminished fibrinolysis, all of which can further compound the elevated CVD risk. Additionally, several recent reports [21;22] have highlighted the association of novel genetic loci with TG levels in the community, emphasizing the need for additional studies to better elucidate the biological basis of high TG states.

Burden of High TG in the Community

Two recent reports [23;24] evaluated National Health and Nutrition Examination Surveys (NHANES) conducted in 1999–2002 and 2003–2004, assessing trends in mean lipid levels in the United States (US) across these different cross-sectional surveys. The first report noted that mean TG in adults (20–74 years) increased from 114 mg/dl in 1976–1980 to 122 mg/dl in 1999–2002 [23]. In the second report, mean TG increased further to 129.5 mg/dl in 2003–4 [24]. It was estimated that approximately 13% of the US population (27 million people) have TG exceeding 200 mg/dl; 7% have both high TG and low HDL-**C** [24]. A more recent report from the National Lipid Association presented at the American Heart Association 2008 scientific sessions noted that mean U.S.TG continued to increase up to 2006 [25]. Compared to NHANES 1976–1980, data from surveys between 1999 and 2006 indicated that the proportion of individuals with isolated suboptimal TG (<150 mg/dl) increased 5-fold in people ages 60–74 years. About a third of adults have hypertriglyceridemia using this cutpoint (>150 mg/dl). This recent increase in mean TG in the US most likely reflects the increasing prevalence of obesity [25].

Association with Coronary Heart disease risk: Importance of Non-fasting TG

Many epidemiological investigations have explored the connection between TG and CHD risk, but the association had not been well quantified until recently. Primary data from the Reykjavik Study and European Prospective Investigation of Cancer Norfolk Study were used to provide such information [26**] and were incorporated into an updated meta-analysis of 27 additional prospective studies in Western populations comprised of 7, 262,525 participants including 10,158 CHD cases. One important observation from this report was that, in contrast to prior investigations, year-to-year consistency of individual TG values was no different from those reported for blood pressure or for other lipids. In this meta-analysis, the risk factor-adjusted odds for developing CHD in subjects with upper tertile TG was 1.7 (relative to the lowest tertile), a risk ratio similar to that reported in Asian Pacific populations [27]. Furthermore, the data indicated an impact of TG on CHD risk in men as well as women, and also, distinct from other studies there was not much difference in the strength of the relation to CHD incidence in fasting versus non-fasting levels. Also, the continuous graded influence of TG to CHD incidence, like for other risk factors, extends down into what is regarded as the normal range with no indication of a critical value.

Another major recent study [28] focused on relating fasting TG and changes in fasting TG (over a 5-year period) to the incidence of CHD in 13,953 Israeli soldiers aged 26–45 years who were part of the MELANY [Metabolic, lifestyle, and nutrition assessment in young adults] Study. Over a follow-up of 10.5 years, men in the top TG quintile had a 4-fold adjusted-hazard of developing CHD relative to those in the lowest quintile (P<0.001 for trend across quintiles) in analyses adjusting for multiple confounders including HDL-C. Of

note, men in whom TG levels increased 5 years from baseline experienced an over 3-fold greater risk of CHD relative to those in whom TG levels continued to be low [28].

Most prior population studies that initially noted associations between fasting plasma TG and CVD risk found that after adjustment for other risk factors (particularly HDL-C) TG was no longer an independent predictor [29–31]. Only a few studies found that TG maintained its independent predictive power when potential confounders were taken into account [32]. It is difficult to distinguish the effects of TG on CHD risk from that of low HDL-C, or from that of insulin resistance per se, both of which are strongly related to TG. Also, it is not clear whether it is appropriate to adjust for HDL-C which is strongly inversely correlated with TG and also biologically linked to insulin resistance in multivariable analyses. Austin suggests possible underestimation of the TG association with CHD because of the biological variation in its measurement and a the strong inverse correlation between TG and HDL-C making multivariable assessment of its net effect difficult to interpret [33].

Traditionally, TG have been measured in a fasting state because they are alleged to be too variable depending on when after a meal they are measured. Also, before the availability of direct assays, LDL-C estimation requires *fasting* TG values. It is important to note that the ubiquitous use of fasting TG for CVD risk evaluation was not based on epidemiological evidence indicating that fasting specimens are superior. Quite to the contrary, investigators have postulated that humans are in a postprandial state most of the day, and that atherosclerosis is a post-prandial phenomenon [4;34].

As noted above, most epidemiologic investigations that relied upon fasting TG concluded that they are only univariate predictors of vascular disease, the risk ratios becoming attenuated upon multivariable adjustment for HDL-C. Earlier meta-analyses of TG as a CVD predictor universally limited their evaluation to studies using fasting TG, which may have resulted in underestimation of the TG impact on vascular risk [35;36]. Because postprandial lipids and their partially hydrolyzed chylomicron and VLDL remnants appear to promote accelerated atherogenesis by adversely affecting endothelial function, and increasing numbers of atherogenic small LDL particles, thrombosis and inflammation., postprandial TG could provide more relevant information on vascular risk than fasting levels.

Recent reports directly address the matter by comparing fasting with non-fasting TG for CVD prediction [37**–41]. The Women's Health Study involving 26, 509 healthy American women followed 11-years for CVD development and mortality found that both fasting and non-fasting TG were associated with future CVD after adjustments for age, blood pressure, smoking and hormone-replacement therapy [37**]. Consistent with other studies in *fasting subjects*, further adjustment for total cholesterol and HDL-C markedly weakened the association with CVD. However, *non-fasting TG* maintained a strong independent relationship with future CVD in fully-adjusted analyses. The hazard ratios increased sequentially with increasing tertiles of non-fasting TG ; the upper tertile conferring a significant 2-fold increase in risk. Using TG measured 4 hours after a meal yielded the strongest (4.5-fold) relationship with CVD events [37**]. In a follow-up report [40], Mora et al compared the predictive utilities of fasting versus non-fasting values for other lipids noting that the predictive capability of HDL-C, total/HDL cholesterol ratio, and apolipoprotein A-1 did not differ by fasting versus non-fasting state. TG levels predicted better when non-fasting values were used, whereas total cholesterol, LDL-C, and non-HDL cholesterol, apolipoprotein B-100 and B-100/A-1 ratio proved less helpful for CVD risk evaluation when nonfasting concentrations were used [40].

Another long term prospective cohort study involving 7,587 women and 6,394 men in Copenhagen also found that non-fasting TG predicted vascular events after multivariable analysis [41]. The relationship was found in both sexes, and the highest risks were observed in persons with the highest postprandial TG (5 mmol/L). A subsequent report [38], extended these observations to stroke events. **A** third report [39], also based on the Copenhagen General Population Study, showed that postprandial lipid changes at any time are minimal compared to those in a fasting state and, indeed, found that at all times through the day the maximum increase in TG averaged only 0.3 mmol/L or ~ 27 mg/dL with ordinary eating.

Non-fasting TG has also been shown to be prospectively associated with increased CVD risk in Japanese men and women, after adjustment for both total cholesterol and HDL-C and an Asia Pacific Cohort Studies Collaboration with data from 26 cohorts, reported that non-fasting TG was a stronger predictor of CVD than fasting TG [27].

Studies also attest to the fact that TG measured after a standardized fat challenge predicts the presence of CHD [4]. As in the case of fasting TG, postprandial lipemia can be influenced by ethnicity, alcohol consumption, and menopausal status, which must be considered in triglyceride evaluation. However, an outpatient oral TG tolerance test has the disadvantage of increasing patient waiting time and effort and requires a *direct measurement of* LDL for comprehensive lipid evaluation.

TG as an indicator of insulin resistance

Increased TG and decreased HDL-C are key metabolic abnormalities in insulin resistance states, including the metabolic syndrome and type 2 diabetes. The TG/HDL cholesterol ratio has been advocated as a simple clinical indicator of insulin resistance that can serve as a convenient surrogate for evaluating the impact of insulin resistance on CHD incidence. The efficiency of blood lipids and their ratios (including total/HDL-C) for detection of insulin resistance and predicting its CHD hazard was recently investigated in 3014 Framingham Offspring Cohort participants [42*]. The correlation between the TG and the TG/HDL ratio was 0.93, indicating that for CHD risk assessment or evaluation of insulin resistance, measuring one is tantamount to using the other. The total /HDL-C ratio was also highly correlated with the TG/HDL ratio (0.82). Insulin resistance (HOMA-IR) was similarly correlated with the TG/HDL-C ratio (r=0.48), TG itself (r=0.43), and the total/HDL-C ratio (r=0.43). Comparison of the multivariable-adjusted impact of the lipids and their ratios on CHD incidence indicated that the lipid ratios are somewhat more predictive and discriminative than each of their lipid components [42]. However, TG (HR of 2.25, comparing the top tertile to the lowest) was almost as powerful a predictor of CHD as the TG/HDL lipid ratio (HR 2.54) and discriminated cases equally well. The total/HDL-C ratio fared only slightly better (HR 2.78 vs. 2.54). High TG/HDL-C and total/HDL-C ratios both indicated a degree of insulin resistance that warrant testing for impaired glucose tolerance or undetected diabetes. However, the impact of TG or the TG/HDL-C ratio on CHD incidence was only partially attributable to its association with insulin resistance. Surprisingly, CHD risk from insulin resistance appeared attributable as much to its association with an increased total/HDL-C ratio as to a high TG/HDL ratio [42*].

Efficacy of Treating Elevated TG

The current focus on LDL-C for assessing lipid risk and treatment seemingly needs broadening to accommodate the influence of other lipids. Given that the effect of TG on CVD incidence extends incrementally down into its “normal” range, the intensity of therapy to lower TG, especially when only modestly elevated, should be determined taking into account an individual's global CVD risk status.

Use of non–HDL-C, as suggested by the Adult Treatment Panel III [43], is a reliable non-fasting marker that provides the sum of all apolipoprotein B-containing lipoproteins including TRL. Non-HDL-C may be somewhat more effective for CVD prediction than LDL-C, especially when TG are increased [44**]. Accordingly, the NCEP ATP III recommends non-HDL-C as a secondary target of therapy when TG levels are ≥ 200 mg/dL, although a target level for TG-lowering therapy is not specified [43]. Alternatively, apolipoprotein-B itself might be measured as it reflects the presence of all pro-atherogenic particles [45].

At present, no clear evidence exists from intervention trials with a lipid-active drug that lowering TG, independent of a change in other CVD risk factors, reduces major CVD events. However, recent post-hoc analysis of PROVE IT-TIMI trial data [46] found that individuals treated with a high-dose statin who *achieved* a low TG on therapy had significantly fewer CVD events than those with a higher TG, even after adjusting for a lower LDL-C on therapy and other CVD risk factors. However, this finding does not necessarily imply that the extent of drug-induced TG reduction accounts for reduction in CVD events.

Although use of postprandial TG may have pathophysiologic support and demonstrated value for CVD prediction, no randomized trial data exist to demonstrate that *triglyceride reduction per se* lowers CVD incidence in *the absence of other lipid effects*.

Conclusions

High TG merits consideration as a prominent CVD risk factor because this often identifies candidates for CVD with insulin resistance, highly atherogenic small LDL remnant particles, lower values of HDL-C, and other manifestations of the metabolic syndrome. The CVD risk of elevated LDL-C is enhanced by coexistent hypertriglyceridemia and lowering both lipid fractions appears superior to reducing LDL-C alone. Recent epidemiological studies have underscored the associations of both fasting and non-fasting TG with CVD risk.

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