

Fasting versus Nonfasting Triglycerides and the Prediction of Cardiovascular Risk: Do We Need to Revisit the Oral Triglyceride Tolerance Test?

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Historically, triglycerides have been measured in the fasting state for 2 reasons. First, because of the marked increase in triglycerides after fat ingestion, the variability in triglyceride measurements is much smaller in the fasting state. Second, before the availability of direct assays for LDL cholesterol (LDL-C),¹ estimation of LDL-C was performed in clinical practice almost exclusively by use of the Friedewald equation, which requires that both the HDL-C concentration and the fasting triglyceride concentration divided by 5 be subtracted from the total cholesterol concentration.

The recommendations to measure triglycerides in the fasting state did not, however, derive from a consistent set of prospective cohort studies showing that fasting concentrations were superior to nonfasting concentrations for the detection of cardiovascular risk. Instead, following screening guidelines, most epidemiologic investigations simply relied on fasting triglycerides. Taken as a whole, such studies indicate that fasting triglycerides are a univariate predictor of vascular disease. Controversy exists, however, regarding the clinical usefulness of fasting triglycerides as an independent predictor of risk, because adjustment for other covariates—in particular HDL-C—markedly decreases both the magnitude and significance of observed epidemiologic effects (1). The extent to which investigators have sought to avoid nonfasting triglycerides as a method for risk detection is evident in a recent metaanalysis that limited evaluation only to those epidemiologic studies that measured fasting triglycerides, specifically “to exclude the possibility of postprandial effects” (2).

Is it possible, then, that recommendations to measure triglycerides in the fasting state have systematically underestimated the impact of hypertriglyceridemia in

clinical practice? Atherosclerosis has long been hypothesized to be a disorder influenced by postprandial effects. As early as 1950, J. R. Moreton, writing in the *Journal of Laboratory and Clinical Medicine*, suggested a linkage between chylomicronemia, fat tolerance, and atherosclerosis (3). A major source of circulating triglycerides is dietary fat, which, after hydrolysis into free fatty acids and glycerides, is transported through the intestinal villi and absorbed by enterocytes, where these particles are synthesized into chylomicron-associated triglycerides for entry into the blood compartment and ultimately storage in adipose tissue. Postprandial lipids and their associated partially hydrolyzed chylomicron remnants appear to promote early atherogenesis, adversely affect endothelial function, associate with atherogenic small LDL particles, and correlate with both prothrombotic and proinflammatory biomarkers, including factor VII, plasminogen activator inhibitor-1, and C-reactive protein (4). Thus, measurement of postprandial triglycerides—particularly because they peak 3–4 h after ingestion of a fat-rich meal—might well provide more relevant information on vascular risk than measurements based on fasting concentrations.

Two manuscripts recently published in the *Journal of the American Medical Association* directly address these issues by comparing fasting with nonfasting triglycerides with respect to the prediction of future cardiovascular events. The first report derived from the Women’s Health Study cohort, in which 26 509 initially healthy American women were followed over an 11-year period for myocardial infarction, stroke, coronary revascularization procedures, and cardiovascular death (5). In that analysis, both fasting and nonfasting triglycerides were associated with future cardiovascular risk after adjustments were made for age, blood pressure, smoking status, and hormone-replacement therapy. Among the fasting participants, further adjustment for total cholesterol and HDL-C markedly weakened this association. These data were consistent with prior work; however, nonfasting triglycerides maintained a strong independent relationship with future cardiovascular events in fully adjusted analyses:

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¹ Nonstandard abbreviations: LDL-C, LDL cholesterol; and OTTT, oral triglyceride tolerance test.

The hazard ratios [95% confidence interval (CI)] for increasing tertiles of nonfasting triglycerides were 1.0 (referent), 1.44 (0.90–2.29), and 1.98 (1.21–3.25) (P for trend = 0.006). Moreover, in analyses stratified by time since the last meal, triglyceride concentrations measured 4 h postprandially had the strongest association with cardiovascular events, with a fully adjusted hazard ratio (95% CI) for the highest to the lowest tertile of 4.48 (1.98–10.15) (P for trend <0.001).

The second report derived from a prospective cohort of 7 587 women and 6 394 men in Copenhagen with 26 years of follow-up (6). In this study, nonfasting triglycerides were also found to significantly predict future vascular events in both sexes after multivariate analysis. In subgroup analyses, these effects were somewhat greater for women than for men and were consistent for the endpoints of myocardial infarction, ischemic heart disease, and total mortality. Moreover, peak triglyceride and remnant lipoprotein cholesterol concentrations were observed 4 h after the last meal, the same time frame for which the maximal predictive value was observed in the Women's Health Study data. In the Copenhagen data, the highest risks were observed among the individuals with the very highest postprandial triglyceride concentrations (≥ 5 mmol/L).

Although the large sample sizes and prospective natures of these 2 recent studies make these results compelling, the observations should not be surprising. Prior cross-sectional surveys often suggested that postprandial triglycerides were more strongly associated with atherothrombosis than fasting concentrations in both the cerebral and coronary circulations (2, 4, 7). Furthermore, the Women's Health Study and Copenhagen data are consistent with several prior prospective reports that linked postprandial triglycerides to vascular events. These data not only derive from typical Western populations in the US and Europe (8–11) but also extend to otherwise low-risk populations in which overt hyperlipidemia is less prevalent. In this regard, nonfasting triglycerides have been prospectively associated with increased vascular risk in Japanese men and women, even after adjustment for both total cholesterol and HDL-C (12). Similarly, in an Asia Pacific Cohort Studies Collaboration study that included data from 26 cohorts, nonfasting triglyceride concentrations were a more potent predictor of incident vascular events than were fasting triglycerides (13).

How might these data have an impact on clinical practice? One approach would be to drop recommendations for fasting and accept triglyceride concentrations measured at any time convenient for the patient. After all, because most individuals consume 3 or more meals daily and because triglycerides may take 8–12 h to return to fasting concentrations after eating, most of the day is spent in the postprandial state.

An alternative approach would be to reconsider the use of a formal oral triglyceride tolerance test (OTTT), which, like its cousin the glucose tolerance test, provides a mechanism to standardize the metabolic response to fat loading. The several OTTT protocols that have been investigated include those that vary fat intake according to body weight (1 g dairy cream/kg body weight) as well as those that use a fixed combined challenge (50 g fat plus 50 g carbohydrate) (14). In controlled studies of healthy individuals, as well as those with metabolic syndrome or diabetes, methods that measure blood concentrations 2–4 h after the administration of calibrated fat loads have proved to be reproducible and palatable approaches for assessing postchallenge triglyceride concentrations (14, 15).

Prior studies have shown that postprandial triglyceride measurements obtained after a formal fat challenge predict the presence of coronary heart disease (16). As is true for fasting triglycerides, postprandial lipemia can be affected by ethnicity, alcohol consumption, and menopausal status, and thus these factors should be considered in clinical practice. It is important to recognize that outpatient use of a formal OTTT rather than measuring a simple nonfasting triglyceride concentration would substantially increase patient time and effort and require that direct LDL testing be used in nearly all cases. Given these limitations, a third alternative choice might be to rely on non-HDL-C, as is currently suggested by the Adult Treatment Panel III (17). Effectively the sum of all atherogenic lipoproteins, non-HDL-C is an accurate and reliable marker in the nonfasting state and has proved to be more effective for risk prediction than LDL-C, even when triglyceride concentrations are increased (18). Because total cholesterol and HDL-C are easily measured in the nonfasting state, this approach also has practical advantages for daily practice.

Although measuring postprandial triglycerides or formal use of an OTTT may have pathophysiologic appeal, no randomized trial to date has demonstrated that triglyceride reduction lowers cardiovascular risk in the absence of other lipid effects. Nonetheless, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group reported a benefit of gemfibrozil on coronary heart disease without a significant change in LDL-C (19), and the Helsinki Heart Study showed a benefit of gemfibrozil in the subgroup with a high LDL-C/HDL-C ratio and a high triglyceride concentration (20). More recently, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial failed to significantly reduce the primary cardiovascular endpoint despite a 29% difference in triglyceride concentrations between fenofibrate and placebo, as well as a 12% difference in LDL-C concentration and a 5% difference in HDL-C concentration (21). On the

other hand, several trials of ω -3 fatty acid supplementation have shown a benefit for reduction of cardiovascular risk, particularly for sudden death.

The inclusion criteria for all of these trials targeting triglycerides relied on fasting concentrations; however, if concentrations measured in the fasting state are not the best indicator of atherogenicity associated with hypertriglyceridemia, then it is possible that these trials may not have defined the best possible population for study. Although the correlation between fasting and nonfasting triglyceride concentrations is high, the fact that postprandial triglycerides may be a more potent predictor of risk suggests that the concordance for individuals is only modest and that the variability in post-

prandial concentrations captures relevant information about an individual's metabolism (5). Thus, future endpoint trials of triglyceride-lowering agents may need to consider participant inclusion based on the measurement of nonfasting triglycerides rather than fasting triglycerides. In fact, perhaps such trials should be designed around the results of a formal OTTT.

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