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Editorial

Nonfasting Lipid Profiles: The Way of the Future

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An increase in the plasma concentration of triglycerides is an established risk factor for cardiovascular disease *(1)*, most likely because the cholesterol content of the triglyceride-rich lipoproteins or remnant cholesterol seems to be causally associated with ischemic heart disease *(2)*. At the beginning of the last decade, however, there were discussions about whether increased triglycerides could be used as a predictor of cardiovascular disease at all, partly because when results were adjusted for other cardiovascular risk factors, and in particular for HDL cholesterol, the relationship between triglycerides and cardiovascular disease was attenuated. Such thinking no longer appears to be prevalent, as recent evidence has demonstrated that the causal association between triglyceride-rich lipoproteins and cardiovascular disease cannot be explained by low HDL cholesterol *(1, 2)*. Also, there has been an assumption that triglycerides should be measured in the fasting state because the concentrations of fasting triglycerides are lower and possibly less variable from measurement to measurement compared with triglycerides measured in the nonfasting state.

The current practice of using fasting lipid profiles was challenged in 2007 by 2 large studies that in combination showed that nonfasting triglycerides could be superior to fasting triglycerides in predicting risk of cardiovascular disease *(3, 4)*. One study from the Women's Health Study including 26509 women found that increased concentrations of both fasting and nonfasting triglycerides were associated with increased risk of cardiovascular disease *(3)*. However, when the results were adjusted for other cardiovascular disease risk factors such as total and HDL cholesterol concentrations, the risk estimates for fasting triglycerides were attenuated. No similar attenuation was observed for nonfasting triglycerides, which remained a strong independent risk factor for cardiovascular disease after adjustment for other cardiovascular disease risk factors, with a hazard ratio of 1.98 for the highest vs the lowest tertile. Furthermore, in that study, after stratifying for time since the last meal, the strongest predictive power for cardiovascular disease when using the highest vs the lowest tertile of nonfasting triglycerides occurred when the women had eaten 2–4 h before blood sampling, resulting in a hazard ratio of 4.48.

In the other study based on 7587 women and 6394 men from the Copenhagen City Heart Study, we found that progressively higher concentrations of nonfasting triglycerides were associated with increasingly higher risk of ischemic heart disease, myocardial infarction, and all-cause mortality *(4)*. In that study, participants were divided into 6 groups with progressively higher concentrations of nonfasting triglycerides. The multivariable adjusted hazard ratios for myocardial infarction for women were 1.7 for triglycerides of 89–176 mg/dL (1–1.99 mmol/L), 2.5 for 177–265 mg/dL (2–2.99 mmol/L), 2.1 for 266–353 mg/dL (3–3.99 mmol/L), 2.4 for 354–442 mg/dL (4–4.99 mmol/L), and 5.4 for ≥443 mg/dL (≥5 mmol/L) compared with women with triglyceride concentrations <89 mg/dL (<1 mmol/L). The corresponding results were similar for men, although somewhat attenuated and likely explained by much higher alcohol intake in men compared with women. Finally, in a further study from the Copenhagen City Heart Study published in 2008, progressively higher concentrations of nonfasting triglycerides were also associated with increasingly higher risk of ischemic stroke *(5)*.

Until recently, it has been common clinical practice in most countries to measure not only triglycerides but also total, LDL, and HDL cholesterol concentrations in the fasting state *(1)*. This has been standard practice primarily because of the known increases in concentrations of triglycerides that occur after large oral fat loads during fat tolerance tests, and importantly, the practice is not supported by any evidence that fasting lipid profiles are superior to nonfasting lipid profiles. It often has been assumed that the calculation of LDL cholesterol using the Friedewald equation requires a fasting lipid profile; however, there is now evidence suggesting that this is not necessarily the case *(1)*. Indeed, several studies have established that lipids and lipoproteins, including calculated LDL cholesterol, exhibit only minimal and clinically insignificant changes in response to food intake *(6, 7)*, even among those with diabetes *(8)*.

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In 33 391 individuals aged 20–95 years from the Copenhagen General Population Study, we previously demonstrated maximum mean changes from fasting concentrations of −8 mg/dL (−0.2 mmol/L) for total cholesterol at 0–2 h after the last meal, −8 mg/dL (−0.2 mmol/L) for LDL cholesterol at 0–2 h, −4 mg/dL (−0.1 mmol/L) for HDL cholesterol at 0–5 h, and 26 mg/dL (0.3 mmol/L) for triglycerides at 1–4 h after the last meal *(6)*. Similar results were obtained in a parallel study by Mora et al. based on the Women's Health Study *(7)*. Another study based on data from the laboratory information system at Calgary Laboratory Services in Canada, which included 209 180 individuals with complete lipid profiles (HDL, LDL, and total cholesterol and triglycerides), 99% being community-based and 1% being hospital-based, showed an average change from fasting concentrations of 26 mg/dL (0.3 mmol/L) for triglycerides and −4 mg/dL (−0.1 mmol/L) for LDL cholesterol after food intake, with no major changes in concentrations of total and HDL cholesterol *(9)*. A study of 12 744 children aged 3–17 years in the US National Health and Nutrition Examination Survey found an average change from fasting concentrations of 9 mg/dL (0.1 mmol/L) for triglycerides and −4 mg/dL (−0.1 mmol/L) for total and LDL cholesterol after food intake, again with no major changes in concentrations of HDL cholesterol *(10)*. Finally, nonfasting lipid profiles are excellent at predicting increased cardiovascular risk *(4, 6, 7)*.

Despite this evidence, many world guidelines still recommend measuring lipid profiles in the fasting state, including the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *(11)*. In contrast, in Denmark since 2009, it has been recommended by the National Society of Clinical Biochemistry to measure lipid profiles in the nonfasting state, with the possibility of repeating measurement of triglycerides in the fasting state if nonfasting concentrations are >350 mg/dL (4 mmol/L) *(1)*. Because other societies and countries likewise may introduce nonfasting lipid profiling as the standard in the future, it is important to establish an optimal cutpoint for nonfasting triglycerides to be used for the reporting of abnormal lipid profiles.

In this issue of *Clinical Chemistry*, White et al. provide an elegant approach for estimating the optimal cutpoint for reporting increased nonfasting triglycerides *(12)*. For this purpose, they used participants from the Women's Health Study who had blood drawn and who reported the time of last meal before blood sampling. In the study, 20 118 participants were fasting and 6391 were nonfasting, and the combined end point examined included myocardial infarction, ischemic stroke, coronary revascularization, and death by any cardiovascular cause. The follow-up was 97% complete for morbidity and 99% for mortality. The study found that among the 6391 nonfasting participants, the optimal cutpoint for assessing increased risk of cardiovascular disease was above vs below 175 mg/dL (2 mmol/L). This was done by using logistic regression to evaluate the area under the ROC curve, with cardiovascular disease events as the dependent variable and nonfasting triglycerides as the independent variable. The authors divided the nonfasting triglycerides in the range of 100–300 mg/dL (1.13–3.39 mmol/L) into groups of 25 mg/dL (0.28 mmol/L) and used these groups to determine the concentration with the highest *c*-statistics and the highest Youden indices, finding that 175 mg/dL (2 mmol/L) was the optimal cutpoint for high vs low risk of cardiovascular disease. Furthermore, using Cox proportional hazard models, they compared this cutpoint to other recommended cutpoints—175 mg/dL (2 mmol/L) by the European Society of Cardiology and the European Atherosclerosis Society *(13)*, 180 mg/dL (2 mmol/L) by the Athens Expert Panel *(14)*, and 200 mg/dL (2.3 mmol/L) by the American Heart Association (AHA) *(15)*—and found that the cutpoint of 175 mg/dL (2 mmol/L) advised by the 2 first groups of experts was superior to that recommended by the AHA in predicting increased cardiovascular disease risk.

One apparent limitation of the study by White et al. *(12)*, as the authors also mention, is that their study was conducted only in women. Previous studies showed that there is some difference in the predictive value of nonfasting triglycerides between men and women *(1, 4, 5)*, as the results for men are somewhat less predictive than those for women *(4)*. In addition, it would be interesting to see the results obtained by combining the data from both the fasting and the nonfasting participants, since it would be helpful to have a cutpoint that could be used in either the fasting or nonfasting state.

It is quite reasonable to suggest that lipid profile testing performed on samples collected in the nonfasting state at a random time convenient for the patient and the laboratory represents the way of the future. Arguments in support of this approach include the following: 1) most people are in the nonfasting state for most of the day, 2) this state may be a better reflection of the true metabolic state of a person, 3) nonfasting triglycerides possibly are better at predicting cardiovascular disease risk than fasting triglycerides, and 4) nonfasting lipid profiles simplify blood sampling for patients, laboratories, general practitioners, and hospital doctors alike. The study of White et al. *(12)* is timely, as the current trend toward the use of nonfasting lipid profile testing has created an urgent need for evidence-based cutpoint values for the reporting and flagging of abnormal nonfasting triglycerides in laboratory reports.

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