Postprandial lipoprotein metabolism—pivot or puzzle?1,2

Peter L. Zock

The hypothesis that postprandial increases in blood lipids and lipoproteins play a causal role in the etiology of cardiovascular disease (CVD) is now 28 y old (1). It states that atherosclerosis is produced largely by triacylglycerol-rich lipoprotein particles that circulate the first few hours after a meal but are not seen in the fasting state in healthy persons. The hypothesis has generated much research but as yet no definitive conclusions. A large number of studies show that clearance of postprandial lipoproteins is slower in patients with diabetes or CVD and that it is associated with several changes in the blood lipoprotein profile, such as low HDL-cholesterol concentrations, high fasting triacylglycerol concentrations, elevated apolipoprotein C-III, and the presence of small, dense LDL particles (2). However, large prospective studies are needed to establish the independent predictive value of postprandial lipids for CVD endpoints. Ideally, such studies should quantify the triacylglycerol response over a fixed number of hours after a standardized meal in thousands of people and monitor the incidence of CVD during many years of follow-up. This is nearly unfeasible because of the huge amounts of labor and cost needed to perform standardized meal tests on a very large scale. Alternatives are to measure the characteristics of lipoproteins that are pronounced in the postprandial state or that reflect a slowed triacylglycerol metabolism. However, lipoprotein metabolism is very complex and not completely understood, and there is no consensus on which changes in lipid composition, size, and density or in apolipoproteins are most relevant. Many studies have focused on small, dense LDL particles, but most prospective studies have not shown their additive predictive value over and above those of standard lipid risk factors, ie, LDL cholesterol, HDL cholesterol, fasting triacylglycerols, and apolipoprotein B (3). Another approach is to focus on the apolipoprotein constituents of triacylglycerol-rich lipoprotein particles that affect their metabolism, such as apolipoproteins C and E. One prospective, nested, case-control study in diabetic patients with previous myocardial infarction showed that fasting apolipoprotein CIII was a strong independent predictor of coronary events during 5 y of follow-up (4). Postprandial lipoprotein clearance is also closely linked to fasting triacylglycerol concentrations. As their independent predictive value for CVD endpoints is established (5), fasting triacylglycerols may be seen as the currently most relevant indicator of postprandial lipemia.

If we assume that the postprandial lipid response is an important indicator of CVD risk, then what is the role of diet? Most studies have focused on dietary fatty acids. In this issue of the Journal, Hilpert et al (6) report the postprandial effects of test meals with 50 g of fat differing in monounsaturated fatty acids (MUFA), the n–3 fatty acid α-linolenic acid (ALA), and the n–3 very-long-chain polyunsaturated fatty acids (VLCPs) on apolipoprotein-defined lipoprotein subclasses in 15 diabetic patients. They found that a meal containing 4 g VLCPs significantly attenuated the postprandial increase in the apolipoprotein B and C–containing lipoprotein fraction compared with a meal containing MUFA only. The treatments did not significantly affect 3 other postprandial apolipoprotein B–containing lipoprotein subfractions or total apolipoprotein B, although the meal with 2.8 g ALA rather than the VLCP meal tended to attenuate the apolipoprotein B, C, and E–containing lipoprotein fraction. Postprandial triacylglycerol concentrations, which were tested in the same subjects and reported in an earlier article by the same study group (7), were not significantly lower after the VLCP meal. Thus, results on markers of triacylglycerol-rich lipoproteins were not consistent, but they suggest that different unsaturated fatty acids may have differential effects on postprandial lipoprotein metabolism. Caution is needed, because testing multiple outcomes in a small study can easily produce chance findings. Further studies should have a larger sample size and also determine the effects of longer-term VLCP intakes on fasting apolipoprotein C concentrations, because these may have predictive potential (4).

Hilpert et al extend their findings by relating the postprandial apolipoprotein changes to the acute effects of the test meals on vascular reactivity, which were reported earlier (7). The postprandial change in apolipoprotein B and C–containing lipoproteins after the VLCP-rich test meal were, to some extent, inversely associated with the postprandial change in flow-mediated dilatation (FMD) of the brachial artery. The authors suggest that their findings provide a potential mechanism for the atherogenic effects of apolipoprotein B and C–containing lipoproteins. This inference needs some comments. First, the value of post hoc cross-sectional analyses in a study with only 15 subjects can be questioned. Second, it could be that postprandial lipid and endothelial responses are both linked to a common underlying factor or to some phenotypical characteristic of the subjects—perhaps the degree of insulin resistance of the subjects or low-grade inflammatory processes triggered by postprandial metabolism. Third, the acute effects of fatty acid intakes on

1 From Unilever Food & Health Research Institute, Vlaardingen, Netherlands.
2 Address reprint requests to PL Zock, Unilever Food & Health Research Institute, Olivier van Noortlaan 120, 3133 AT Vlaardingen, Netherlands. E-mail: peter.zock@unilever.com.
endothelial function may well be different from those of long-term intakes (8). But, even if we assume that the relation between apolipoprotein B and C-containing lipoproteins and FMD responses is causal, the relevance to CVD risk is not clear. Although endothelial dysfunction is considered an early marker of atherosclerosis, the evidence on its independent predictive value for CVD endpoints is as yet limited and inconsistent (9–11). In a prospective study of 631 subjects, von Willebrand factor and soluble vascular adhesion molecule-1 showed prognostic value in diabetic patients as markers of endothelial function but less so in nondiabetic subjects (9). A recent prospective study conducted in 842 asymptomatic subjects from the general population showed no independent predictive effect of FMD on CVD endpoints during 3 y of follow-up (11).

How do the findings of Hilpert et al relate to other studies on VLCP and postprandial lipid response? It is well established that longer-term high intakes of VLCP affect both fasting and postprandial triacylglycerols (12). However, the acute effects of meal fatty acid composition on postprandial triacylglycerols are less clear (13). A study of similar size and design as that of Hilpert et al found no effects of modulating VLCP, ALA, and MUFA composition in a test meal on postprandial triacylglycerol concentrations (14). The results from the large Quantification of the Optimal n–6/n–3 Ratio in the UK Diet (OPTILIP) Study (15) deserve special attention. Two hundred fifty-eight subjects were supplied with diets with different contents of n–6 and n–3 polyunsaturated fatty acids. After 6 mo, the diet containing 1.3 g VCLPs lowered the fasting triacylglycerol concentration by 11% and the 3-h postprandial triacylglycerol concentration by 7% compared with diets that were high in ALA or linoleic acid (15). This supports the notion by Hilpert et al that VLCPs provide beneficial effects on triacylglycerol concentrations over and above other unsaturated fatty acids. Notably, the subjects in the OPTILIP Study had normal triacylglycerols and were only slightly overweight. It is conceivable that absolute effects on triacylglycerol metabolism would have been larger in diabetic patients or in persons with more visceral fat. The OPTILIP Study provides important evidence that not only high doses, but also moderate amounts, of VCLPs achievable without fish-oil supplements can have significant effects on blood triacylglycerol concentrations. The observed 11% reduction in fasting triacylglycerols can be predicted to reduce CVD risk by ~3–8% (16). This decrease explains only part of the inverse relation between VLCP or fish consumption and CVD risk (17), but it is relevant at the population level.

Most people in affluent societies spend most of their time in the postprandial state, and it is plausible that this may play a pivotal role in atherosclerosis. However, the postprandial lipid response has many features and is difficult to measure, and its value as an independent predictor of CVD is unclear. Mechanistic studies are needed to further unravel and understand postprandial lipoprotein metabolism and its relations with insulin, inflammatory processes, and early atherosclerosis. Such research is important, because growing insights may, in the long term, yield new targets for dietary and drug interventions. The whole range of disciplines and tools will be needed: molecular biology and genomics to find missing pieces of the puzzle, classic biochemistry and physiologic studies to put the pieces together, and human interventional and observational studies to determine what the puzzle means for CVD risk. This will take many decades. In the mean time, the health effects of diet through lipoprotein metabolism should be evaluated by the established, independent risk factors for CVD, including fasting triacylglycerols.

PLZ is an employee of Unilever. Unilever markets food products, some of which are high in unsaturated fatty acids.

REFERENCES