Netherlands
The Journal of Medicine

EDITORIAL

The rise and fall of postprandial lipids

M.B. Katan

Wageningen Centre for Food Sciences and Division of Human Nutrition, Wageningen University, Bomenweg 2, 6703 HD Wageningen, the Netherlands, fax: +31 (0) 317-485369, e-mail: wcfs1@wur.nl

ABSTRACT

The remnants of absorbed fat particles which circulate after a meal might cause atherosclerosis, but such a causal role is still unproven. High levels of such lipoprotein remnants are often found in patients with the metabolic syndrome. Increased activity and weight loss will diminish the cardiovascular risk factors caused by this syndrome including elevations of postprandial remnants.

It is now 25 years since Donald Zilversmit published his hypothesis that atherogenesis is a postprandial phenomenon.[1] At that time the proposal met with a warm reception because it appeared to solve two dilemmas. The first dilemma was the vexing question why low-density lipoproteins (LDL) cause atherosclerosis. Although the evidence for a causal role of high LDL levels was less complete than it is now, it was already impressive: the epidemiology was highly consistent, mutations that caused high LDL levels caused premature coronary heart disease, and diets that lowered (LDL) cholesterol lowered the incidence of coronary heart disease in randomised clinical trials.[2] The one piece of the puzzle that refused to fit was the mechanism. Cholesterol was probably deposited in atherosclerotic plaques by macrophages that had accumulated cholesterol-rich lipoproteins, but LDL does not accumulate in macrophages:[3] when the concentration of LDL outside the cell becomes too high, macrophages simply shut down their LDL receptors and so avoid being overloaded with cholesterol. The lipoproteins that do accumulate in macrophages are remnants of triglyceride-rich lipoproteins.[3] These arise during digestion of such lipoproteins in the capillaries of fat tissue and of muscles that can use fatty acids as fuel. Digestion of the triglyceride core leaves remnants that are relatively rich in cholesterol, and such remnants are avidly taken up by macrophages. What Zilversmit now proposed was that people who eat a lot of triglycerides (i.e. fat) and who do not efficiently clear triglyceride-rich particles will have remnants in their circulation which cause atherosclerosis. Although this hypothesis did not explain how LDL causes atherosclerosis, it seemed a promising explanation for the occurrence of atherosclerosis in coronary patients with normal LDL values.

The Zilversmit hypothesis had a second attraction. At the time that it was proposed, the most effective way to lower cholesterol was through diets high in polyunsaturated fatty acids, i.e. high in vegetable oils such as soybean or sunflower oil which are rich in linoleic acid. However, there was increasing concern that such high-fat or high-oil diets caused obesity or cancer. The evidence supporting such adverse effects of high-oil diets was soft, and has subsequently eroded,[4,5] but at the time there was a groundswell in favour of diets low in fat and high in carbohydrates. The Zilversmit hypothesis nicely fitted with that mood, because low-fat high-carbohydrate diets were thought to produce fewer chylomicrons and therefore fewer remnants of triglyceride-rich lipoproteins circulating after a meal.

The paper by Van Oostrom and co-workers[6] in this issue illustrates that things have turned out to be less simple. Van Oostrom *et al.* tried to explain why at a given (LDL) cholesterol level, Northern Europeans have higher rates of coronary heart disease than Southern Europeans. The

authors hypothesised that the Mediterranean diet high in unsaturated fatty acids – mainly monounsaturates from olive oil – might produce lower levels of chylomicron remnants throughout the day than the Dutch diet, and that this might explain the lower rates of coronary heart disease seen in Mediterranean countries. The results of the study were negative: young men and women from Barcelona in Spain and from Utrecht in the Netherlands had similar levels of triglycerides in their blood throughout the day when eating their habitual diets. The only difference was that the Spanish had their highest blood triglyceride levels after lunch and the Dutch after dinner, which fits with the Spanish habit of eating the main meal of the day at noon.

The present study of postprandial lipoproteins was not the only one to yield a negative result in spite of much effort. Over the past 25 years a vast research effort has gone into studies of postprandial lipoproteins but many questions have remained open, including the seemingly simple question of which types of fat cause the greatest increase in postprandial remnant levels. Why has it been so hard to verify the hypothesis put up 25 years ago? One reason is technical. Measuring post-meal lipoprotein levels is cumbersome, and it is hard to tell which component of which particle should be quantified at which point in time. Van Oostrom *et al.*[6] took an innovative approach here in that they had subjects measure their own blood triglyceride levels six times throughout the day with a hand-held self-monitoring device. This allowed measurement over three days in each group, which reduced variability, and it obviated the need to admit subjects to the clinic for frequent blood letting. However, it is uncertain how well blood triglyceride levels after a meal reflect the presence of the hypothetical harmful particles that cause atherosclerosis. Another issue is how baseline triglyceride levels, i.e. the fasting or pre-meal levels, should be factored in. Low-fat high-carbohydrate diets cause less of a postprandial rise in triglycerides than high-fat diets, but high-carbohydrate diets cause higher baseline levels so that the absolute level reached after a meal may be the same. Which is worse?

A more fundamental question is that of causality. Postprandial lipaemia is associated with coronary heart disease,[7] but does the one cause the other? Poor lipid clearance after a fat meal is typically seen in patients with central obesity and low physical activity, and such patients usually have a host of abnormalities which are all associated with coronary heart disease, such as low HDL, high fasting triglycerides, insulin resistance, high blood pressure, high levels of C-reactive protein and the other paraphernalia of the metabolic syndrome. The only way to prove that post-meal remnants are causal would be to apply a treatment that changes only the level of remnants while leaving all other lipoproteins undisturbed. Such a treatment does not exist, for clearance of one type of lipoprotein affects that of other types.

Thus proof of a causal role of postprandial lipoproteins may be a long way off. Does that matter to the clinician? From a scientific point of view it would be highly satisfactory if the role of remnants in atherogenesis could be cleared up, but from a clinical point of view the advice to patients with postprandial hyperlipaemia would probably remain the same: eat less, exercise more, and lose weight.

REFERENCES

1. Zilversmit DB. Atherogenesis: a postprandial phenomenon. Circulation 1979;60:473-85.
2. Truswell AS. Review of dietary intervention studies: effect on coronary events and on total mortality. Aust N Z J Med 1994;24:98-106.
3. Goldstein JL, Ho YK, Brown MS, Innerarity TL, Mahley RW. Cholesteryl ester accumulation in macrophages resulting from receptor-mediated uptake and degradation of hypercholesterolaemic canine beta-very low density lipoproteins. J Biol Chem 1980;255:1839-48.
4. Katan MB, Willett WC, Grundy SM. Beyond low fat diets. New Engl J Med 1997;337:563-6.
5. Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer—a pooled analysis. New Engl J Med 1996;334:356-61.
6. Van Oostrom AJ, Real JT, Carmena R, Ascaso J F, Castro Cabezas M. Daylong triglyceridaemia in healthy Mediterranean and Northern European subjects. Neth J Med 2004;8:279-85.
7. Weintraub MS, Grosskopf I, Rassin T, et al. Clearance of chylomicron remnants in normolipidaemic patients with coronary artery disease: case control study over three years. BMJ 1996;312:936-9.