

## Postprandial lipid metabolism in diabetes

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### Abstract

Postprandial lipemia is an inherent feature of diabetic dyslipidemia and highly prevalent in diabetic patients even with normal fasting triglyceride concentrations. Postprandial lipemia is characterized by long residence time of chylomicron and VLDL remnants in the circulation. Insulin resistance causes increased flux of free fatty acids, and thus enhanced VLDL apolipoprotein B (apo B) synthesis in the liver. Together with chylomicron and VLDL remnant competition for the common removal mechanisms the increased substrate input results in exaggerated and prolonged postprandial lipemia. Studies using both apo B-48 and retinyl esters as a marker for intestinally derived particles have shown that increased postprandial lipemia does not predict the presence or absence of coronary artery disease between non-insulin-dependent diabetes mellitus (NIDDM) subjects. Recent data have shown that postprandial triglyceride-rich remnants are atherogenic, and postprandial hypertriglyceridemia contributes to the metabolic disturbances transforming LDL and HDL subclasses into more atherogenic direction in diabetic subjects. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

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Diabetic dyslipidemia is characterized by raised serum fasting triglycerides (TG), especially very low density lipoprotein (VLDL) TG, and lowered serum fasting high density lipoprotein (HDL) cholesterol. These two features are shown to predict coronary artery disease (CAD) mortality and morbidity in patients with non-insulin-dependent diabetes mellitus (NIDDM) [1,2]. However, these lipid abnormalities and other traditional risk factors do not fully explain the increased prevalence of CAD in NIDDM patients. Recently a cluster of metabolic disturbances have been associated with NIDDM and the insulin resistance syndrome (IRS) including postprandial lipemia, preponderance of small dense low density lipoprotein (LDL), preponderance of small dense HDL and alterations in the coagulation factors [3].

The concept of atherosclerosis being a postprandial phenomenon was introduced by Zilverman more than

15 years ago [4] and later confirmed by others [5,6]. Recent data have provided evidence for postprandial lipemia being an independent risk factor for CAD [6,7]. As fasting TG and HDL concentrations are the major determinants of postprandial lipemia, it is to be expected, that NIDDM patients have increased postprandial TG response. Our group and others have shown that increased postprandial lipemia, i.e. fat intolerance is an inherent feature of diabetic dyslipidemia [8–10]. The mechanisms underlying fat intolerance are not fully clear. Increased VLDL production, competition of chylomicrons and VLDL for the common removal mechanisms; first, hydrolysis by the lipoprotein lipase (LPL) and second, uptake by hepatic receptors, may all contribute to the observed long residence time of TRLs. Malmström et al. have recently shown that suppression of hepatic triglyceride rich VLDL1 production by insulin is impaired in type 2 diabetes, and this results in inappropriate release of VLDL1 particles, envisages as liver's chylomicrons, in the postprandial phase [11]. Also, the normal suppression of fatty-acid release by

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insulin from the adipose tissue is impaired in IRS, and further increases the substrate input to the liver [12]. In the postprandial phase the sudden increase in both chylomicron and VLDL TG saturates the lipolytic capacity for hours leading to long residence of TRL remnants in the circulation. Studies by Syväne et al. have shown a lack of normal inverse correlation between postprandial lipemia and plasma LPL activity in NIDDM patients providing further evidence for lipolytic defect [10,13]. The current picture of removal defects is that chylomicron and VLDL remnant uptake by hepatocytes is rate-limiting in non-diabetic subjects. Impaired interaction of remnant particles with hepatic receptors due to abnormal ligand properties may also contribute to postprandial lipemia [14].

It is still a matter of debate which TRL particles are the atherogenic ones in the postprandial period [15]. Postprandial lipemia comprises of intestinal and hepatic derived particles varying in size and apolipoprotein (apo) content as well as lipid composition. Concentration of retinyl esters (RE) after vitamin A administration measures the intestinal TRL particles, but only simultaneous measurement of apo B-48 and apo B-100 allows to distinguish between TRL subclasses of different origin within the same Svedbergs flotation (Sf) range. The study by Syväne et al. using vitamin A have shown larger RE response in Sf 60–400 particles in NIDDM patients compared to controls with similar BMI and age [10]. Curtin et al. used apo B-48 measurement, and the findings were in line with the study of Syväne et al. suggesting prolonged residence time of chylomicron remnants [16]. An angiographic study in non-diabetic patients with CAD found significant correlation between the levels of postprandial chylomicron remnants and the progression of CAD [17]. In patients with NIDDM the magnitude of lipemia did not predict the presence or absence of CAD [10]. Recently, we have studied another cohort of 43 patients with NIDDM, who underwent quantitative coronary angiogram and soybean oil fat tolerance test. The subjects were divided into three groups with similar fasting TG, LDL and HDL cholesterol according to the severity of the angiographic findings. In postprandial phase responses of TG, apo B-48, apo B-100 and RE in TRL were increased, but closely comparable between the groups. The severity of CAD did not correlate with the magnitude of postprandial lipemia (Mero et al., unpublished data). In conclusion, the exaggerated postprandial lipemia is an inherent feature of diabetic dyslipidemia, and seems not be further aggravated by the presence of CAD.

Besides fasting TG, fasting HDL, glycemic control, obesity and nephropathy, also genetic factors modulate postprandial lipemia in NIDDM. Apo E is essential for clearance process of TRL and apo E phenotype determines the affinity to the hepatic remnant receptor.

Syväne et al. found enrichment of postprandial TRL remnants with apo E in NIDDM patients with CAD, which was suggested to be a strong determinant of atherogenicity [18]. In a study by Reznik et al., apo E polymorphism was found to modulate postprandial lipemia in normotriglyceridemic diabetic patients: Subjects with E2/3- or E3/4-alleles had twofold postprandial lipemia compared with E3/3-carriers [19]. We have studied the effect that the  $\epsilon$ -4 allele had on diabetic dyslipidemia in 16 subjects with apo E3/3 and nine subjects with the  $\epsilon$ -4 allele; the subjects were obese and had mild fasting hypertriglyceridemia. Postprandial responses of TG, apo B-48 and apo B-100 were comparable, and the presence of  $\epsilon$ -4 allele did not predict the presence of angiographically verified CAD (Mero et al., unpublished data).

Improvement in glycemic control and increased insulin sensitivity results in lowering of both fasting and postprandial TG concentrations in IRS [20] and in NIDDM patients [21,22]. Of lipid lowering drugs at least gemfibrozil has been proven to be effective in NIDDM: Syväne et al. studied postprandial lipemia in a randomized, double-blind, placebo-controlled trial, and found significant reduction in TG and RE in Sf > 400, Sf 60–400 and Sf 20–60 fractions [10].

Postprandial TRL metabolism is closely coupled with LDL and HDL metabolism. The long residence time of TRL remnants in circulation results in increased exchange of the core lipid cholesteryl ester for TG between the TRL particles and LDL and HDL cholesterol mediated by cholesteryl ester transfer protein. The process enriches LDL and HDL with TG, and hydrolysis by hepatic lipase results in smaller, denser LDL and HDL particles. This pattern further increases the risk for atherosclerosis and CAD in NIDDM [10].

NIDDM patients have increased mortality and morbidity in CAD, part of which may be caused by excess of atherogenic remnants in the postprandial phase. Fat intolerance in diabetes is associated with multiple abnormalities in LDL and HDL even in the absence of fasting hypertriglyceridemia. The clinical implication is that lipid lowering therapy should be aimed to control not only fasting, but also postprandial TG levels in diabetic patients.

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