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Abnormalities of triglyceride rich lipoproteins (TRLs) in type 2 diabetes and insulin resistance

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Introduction

Diabetic dyslipidemia is a cluster of plasma lipid and lipoprotein abnormalities affecting all lipoprotein classes. The culprits of dyslipidemia are an elevated plasma triglyceride concentration and low HDL cholesterol concentration. The discovery of heterogeneity within major lipoprotein classes (VLDL, LDL and HDL) has allowed specifying the features of dyslipidemia in type 2 diabetes. The key elements of dyslipidemia also constitute excessive postprandial lipemia and remnant accumulation, small dense LDL and small dense HDL particles. These metabolic components are not isolated abnormalities but metabolically closely linked to each others. Together these components comprise the atherogenic lipid triad that substantially contributes to the increase of CVD risk. As dyslipidemia associates with insulin resistance, visceral obesity and excess liver fat (non-alcoholic fatty liver disease, NAFLD) it is not unexpected that this abnormal lipid profile is common in subjects with type 2 diabetes but also in those with central obesity and the metabolic syndrome.

Metabolism of triglyceride rich lipoproteins

Triglyceride rich lipoproteins (TRLs) are heterogeneous comprising chylomicrons derived from the intestine and VLDL particles secreted by the liver. TRLs are the major carrier of triglycerides in the circulation; chylomicrons after a meal and VLDL particles in the fasting state[1]. Chylomicrons are produced in the enterocytes carrying apo B 48 whereas the structural apolipoprotein of VLDL particles is apo B-100. In circulation chylomicrons and VLDL are metabolized by the same pathways that involve at first step; lipolysis by lipoprotein lipase (LPL) followed by direct receptor-mediated hepatic uptake of TRL remnant particles. At the second step VLDL particles are further converted into IDL and LDL. Notably small dense LDL particles are the end product from the catabolic pathway of large VLDL1 particles.

The serum concentration of TRLs is the end result of their appearance and removal rates (Fig. 1). Traditionally serum triglycerides have been measured in the fasting state after about 8 to 12 hours of fasting. Recently substantial evidence has emerged indicating that non-fasting triglycerides predict more strongly CVD than fasting triglycerides[2,3].

As postprandial lipemia is a distinct feature of diabetic dyslipidemia the underlying mechanisms are of critical importance[1]. Recent discoveries have evidence of that intestinal overproduction of apo B48 containing chylomicrons contributes to postprandial lipemia and is linked to insulin resistance in enterocytes[4]. Today emerging data suggest

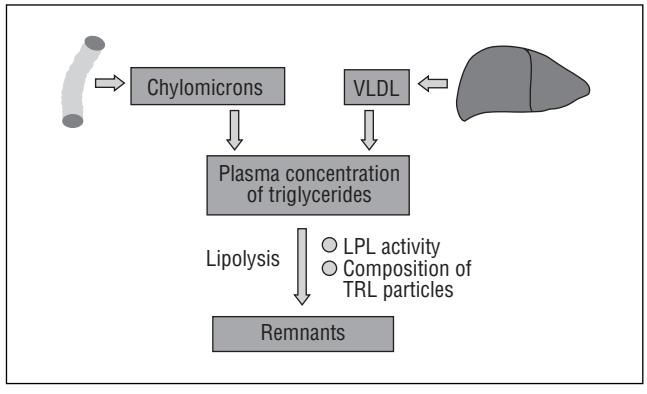

Figure 1 Sources of TRL particles.

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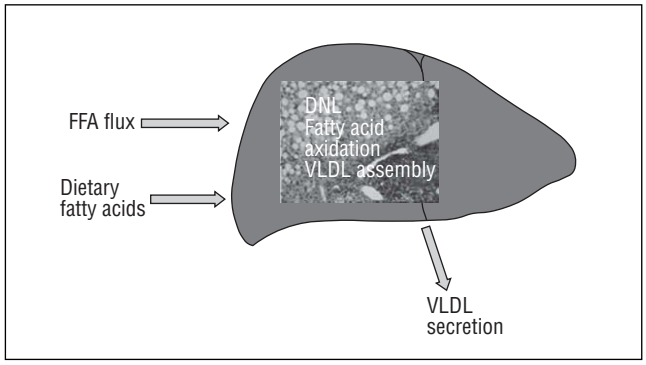

Figure 2 Imbalance in dynamics of lipid betabolism results in fatty liver.

that intestinal peptides (GLP1 and GLP2) may play a seminal role in the regulation of lipid metabolism in enterocytes. Thus the intestine is not a passive absorption site but assembly and secretion of chylomicrons are regulated by hormones (insulin, incretins) and fatty acid input.

We have reported that large VLDL 1 particles (Sf 60 – 400) are the principal component of VLDL species that accumulates in plasma as the triglyceride level rises[5]. Available data indicates that overproduction of VLDL 1 is more important than decreased removal of VLDL 1 in determining the actual VLDL 1 level in type 2 diabetes with mild to moderate hypertriglyceridemia[6]. We also reported that VLDL 1 production rate correlated inversely with LDL size and HDL cholesterol. Thus overproduction of large VLDL 1 particles initiates a sequency of events leading to the atherogenic lipid triad. We conclude that overproduction of VLDL particles is the hallmark of the atherogenic dyslipidemia in Type 2 diabetes and in the metabolic Syndrome.

This raises the question which factors predict over-production of VLDL 1 particles? The key regulators of the normal assembly of VLDL in the liver are free fatty acid flux (FFA) from systemic FFA pool and from dietary fat, de novo lipogenesis (DNL) lipid oxidation and VLDL secretion[6,7] (Fig. 2.) Accumulation of liver fat results from the imbalance between these factors. Both intra-abdominal fat volume and liver fat content correlate with VLDL 1 production rate in univariate analyses but only liver fat remains significant in a multivariate regression model including also subcutaneous fat volume, adiponectin and HOMA index as a surrogate marker of insulin resistance[6]. A physiological action of insulin is to directly suppress VLDL 1 synthesis in the liver in analogy to suppression of glucose production. In patients with type 2 diabetes insulin action to suppress VLDL 1 production is defective resulting to overproduction of VLDL particles. Our recent studies demonstrated that insulin suppressed the production of VLDL particles in people with low liver fat content but failed to suppress VLDL 1 production in people with high liver fat content[8].

The dynamics of fatty acid fluxes into the liver and DNL seems to play a critical role as a determinant of liver fat and VLDL secretion. Emerging evidence suggest that the impact of DNL may have been overlooked. Transcription factors LXR, SREBP1- C and ChREBP mediate the actions of insulin and glucose on the transcriptional activation of enzymes involved in fatty acid synthesis[9]. Recently fructose – sweetened beverages has been reported to increase DNL more than glucose —sweetened beverages in man and increase both fasting and postprandial lipemia, intra-abdominal fat deposit and to impair insulin sensitivity[10,11]. This raises the urgent need to examine the contribution of dietary sugars as well as fats as sources for hepatic triglycerides and secreted VLDL TG. The failure of liver to export excess TG in secreted VLDL particles will result in fat accumulation in the liver. Thus the overproduction of large VLDL 1 particles can be considered as a compensatory mechanism in obese subjects to maintain the integrity of lipid metabolism at hepatocytes (Fig. 3).

The key question is how much overconsumption of dietary sugars and fats can directly contribute to both liver fat accumulation and VLDL overproduction by enhancing DNL beyond the obesity linked excessive FFA flux[12,13].

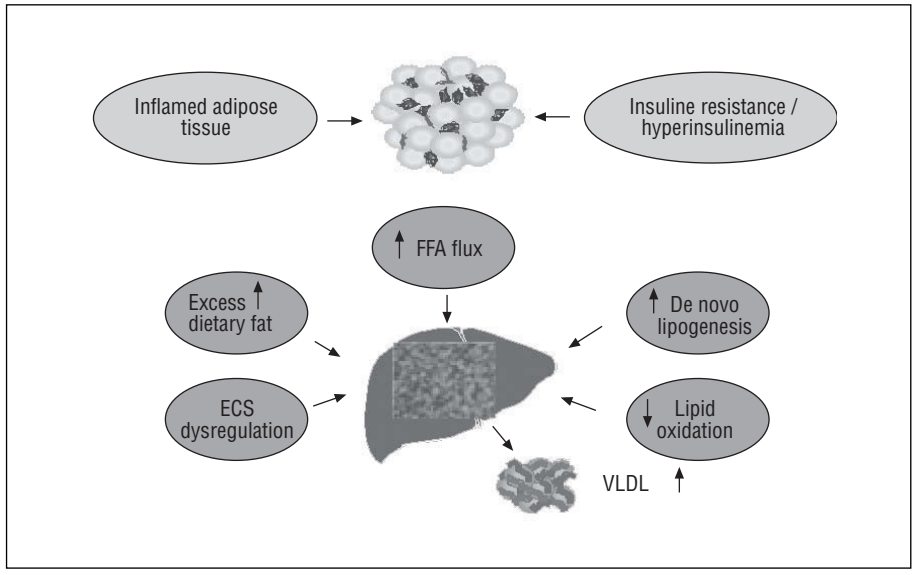

Figure 3 Imbalance of liporegulation: the culprit of fatty liver and dyslipidemia.

Conflict of interest

M.R. Taskinen declares associations with the following companies: Eli Lilly, Kowa, Merck Sharpe & Dohme, Merck Schering-Plough, Novartis, Sanofi-Aventis, and Takeda.

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