The Complex Metabolic Mechanisms Relating Obesity to Hypertriglyceridemia

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The importance of hypertriglyceridemia as a cardiovascular disease risk factor continues to be a controversial topic,1 and patients with obesity frequently exhibit hypertriglyceridemia. In the Framingham Heart Study, the incidence of coronary heart disease was significantly greater with than without insulin resistance at either the lowest plasma high-density lipoprotein cholesterol values or the highest triglyceride values.2 The mechanism of hypertriglyceridemia in the setting of obesity has been linked to insulin resistance, wherein an increased flux of adipose tissue–derived free fatty acids (FFAs) gives rise to increased rates of hepatic triglyceride synthesis and secretion of very-low-density lipoprotein (VLDL) triglycerides (Figure).3,4 A recent report has also related increased FFA flux to the secretion of apolipoprotein CIII (apoCIII)-containing VLDL.4 Moreover, there is additional evidence that the hyperinsulinemia that ensues in the setting of insulin resistance is associated with increases in intrahepatic gene expression of genes of triglyceride biosynthesis, eg, sterol regulatory element-binding protein-1C.5 In the presence of increased intrahepatic triglycerides, nonalcoholic fatty liver disease or hypertriglyceridemia often occur, yet not all patients with obesity are insulin resistant.

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In the study by Taskinen et al published in the current issue of *Arteriosclerosis, Thrombosis and Vascular Biology,*6 both overproduction of large VLDL (VLDL1) and reduced VLDL1 fractional catabolic rate (FCR) were found to be associated with hypertriglyceridemia in obese subjects. A sophisticated multicompartmental model was used to simultaneously determine the kinetics of apoB and triglycerides in VLDL after a bolus injection of [2H3]leucine and [2H5]glycerol.7 Although the sample size was small, there were associations between large VLDL1 secretion and the amount of subcutaneous abdominal adipose tissue (measured by magnetic resonance imaging) + intrahepatic fat, and between VLDL1 FCR and plasma levels of apoCIII. The finding that <20% of the hypertriglyceridemia in these obese men was associated with increases in VLDL1 secretion but almost 50% related to impaired FCR is somewhat consistent with the literature. However, VLDL triglyceride overproduction is more emphasized as the pathophysiology of hypertriglyceridemia than defects in VLDL FCR.5,9 The association of plasma levels of apoCIII with reductions in VLDL1 FCR was of particular interest, noting the well-appreciated inhibitory effect of apoCIII on lipoprotein lipase (LPL).10 ApoCIII is a 79-amino-acid glycoprotein synthesized by the liver and intestines that is mostly associated with triglyceride-rich lipoproteins (VLDL and chylomicrons) and high-density lipoprotein, with rapid exchange of the apoprotein between these lipoprotein classes during lipolysis.11 Increased hepatic production of VLDL apoCIII is characteristic of subjects with higher body weights and insulin resistance and is strongly related to the plasma concentration and level of production of VLDL triglycerides.12,13 Because insulin is known to inhibit apoCIII gene transcription,14 overproduction of apoCIII may be a further manifestation of hepatic insulin resistance. Moreover, recent evidence indicates that once glucose intolerance develops, activation of apoCIII gene transcription by hyperglycemia could lead to worsening hypertriglyceridemia.15 Not to be dismissed is the role of insulin in increasing apoB degradation in the liver.16 Once insulin resistance occurs, this is another mechanism that could relate to the overproduction and secretion of VLDL in patients with obesity.

The fact that the inverse relationship between VLDL1 FCR and apoCIII appeared to extend across the entire cohort suggests that a continuous relationship exists between apoCIII production and plasma triglycerides.6 However, not stated was whether or not levels of apoCIII also related to VLDL1 production or hepatic fat. There was, however, no evidence of any apoCIII variants in the study participants that have recently been linked to fatty liver.17 Although it is presumed that the effect on clearance of VLDL1, in the obese hypertriglyceridemic group was an inhibitory effect on LPL, only LPL mass was quantified. Because most of the LPL in plasma is inactive mass and there is no predictability of postheparin LPL activity by LPL activity in preheparin plasma,18 additional studies are needed to discern whether or not the presumed inhibitory effect of apoCIII on LPL as a contributor to the hypertriglyceridemia can be distinguished from simply a defect in FCR related to VLDL pool size.

The debate continues as to the relative importance of increases in intraabdominal or visceral fat versus subcutaneous fat in hepatic FFA delivery. Although in this study the subcutaneous adipose tissue depot appeared to relate to VLDL1 secretion rate more than visceral adipose tissue, increases in lipolysis and fatty acid flux from the visceral depot seems more etiologic in explaining fatty liver and hypertriglyceridemia. Despite the direct link between the visceral depot and the liver, intraabdominal adipose tissue...
quantitatively remains a relatively minor contributor. In one study in obese men, splanchnic FFA levels ranged from <10% to almost 50%, with an increasing contribution as visceral adipose tissue volume increased. When obese subjects with nonalcoholic fatty liver disease were compared with those with normal levels of intrahepatic fat, the increased VLDL triglyceride secretion was primarily due to fatty acid sources other than the systemic circulation, ie, from visceral or intrahepatic sites.

Both obese groups appeared to be hyperinsulinemic, although the sample size limited the distinction between the nonobese fasting insulin of 5.7±0.8 mU/L in the nonobese normotriglyceremic group from 10.0±1.9 mU/L in the obese normotriglyceridemic group. The fasting insulin of 12.9±1.7 mU/L in the hypertriglyceridemic obese group was clearly not different from that in the obese normotriglyceridemic group, as was the homeostasis model assessment of insulin resistance. Thus, these crude assessments of insulin sensitivity do not appear to be related to the mechanism of the hypertriglyceridemia. Despite the sample size and lack of robust tests of insulin action, some attempt to relate VLDL kinetics to fasting insulin and homeostasis model assessment of insulin resistance may have helped clarify whether a gradient or threshold relationship existed. Moreover, a euglycemic clamp with stepwise increments in the insulin infusion rate assessing both the effects of insulin on antilipolysis and FFA flux, in addition to hepatic and peripheral insulin resistance in glucose metabolism, would be informative.

Overall, Taskinen et al appropriately stress a simplistic approach to identifying patients at high cardiometabolic risk by measuring waist circumference and fasting triglycerides, revisiting the hypertriglyceridemic waist, a concept developed by the Després group more than a decade ago. Defined as a waist circumference of ≥90 cm and a triglyceride level of ≥2.0 mmol/L in men and a waist circumference of ≥85 cm and a triglyceride level of ≥1.5 mmol/L in women, this easily quantified metric has been used to identify patients with added metabolic disturbances related to insulin resistance and higher risk for coronary heart disease. Finally, apoCIII remains a fascinating lipoprotein constituent that...
demands further characterization and epidemiology before its measurement is ready for prime time.

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Disclosures

None.

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