Hypertriglyceridemia Associated With Abdominal Obesity
Getting Contributing Factors Into Perspective
André C. Carpentier

Abdominal obesity is associated with a number of important metabolic and cardiovascular abnormalities, including among others ectopic fat accumulation (including liver steatosis), insulin resistance, low-grade inflammation and increased oxidative stress, impaired glucose homeostasis, hypertriglyceridemia, low high-density lipoprotein cholesterol level, hypertension, and abnormalities of hemostasis, contributing to the increased risk of type 2 diabetes mellitus and cardiovascular diseases (ie, cardiometabolic risk).1 The hypertriglyceridemia associated with this condition involves metabolic abnormalities of all triglyceride-rich lipoproteins (chylomicrons, very-low density lipoproteins [VLDL], and their remnants) caused by a complex interplay between environmental factors, such as food intake and physical activity, and cumulative, multiple gene variants.2 Some factors may predominantly increase triglyceride-rich lipoprotein secretion, for example, excessive food intake and insulin resistance.3-5 Other factors, such as lipoprotein lipase (LPL), apolipoprotein E, and apolipoprotein A5 polymorphisms, may predominantly affect triglyceride-rich lipoprotein clearance either or both through transfer into less buoyant particles or through direct removal of the particle from the circulation.2 The present view is that hypertriglyceridemia associated with abdominal obesity stems from a combination of enhanced triglyceride-rich lipoprotein secretion with some impairment of clearance.2

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Borén et al6 report VLDL1 triglyceride and apolipoprotein B100 kinetics in 46 (37 men and 9 women) middle-aged, insulin-resistant subjects with abdominal obesity and mild hypertriglyceridemia (ie, fasting triglyceride between 1.7 and 4.5 mmol/L) or low high-density lipoprotein cholesterol. This study found VLDL fractional clearance rate to be a more important determinant of plasma triglycerides than VLDL triglyceride lipolysis from these lipoproteins.15 This is further illustrated by the poor diagnostic reliability of postheparin LPL activity for the diagnosis of genetic functional abnormalities of LPL.16 A large fraction of circulating LPL mass is also inactive, making this assay unreliable to predict function in vivo.17

The strengths of the study by Borén et al15 include the application of standard, state-of-the-art stable isotopic methods and modeling used for the determination of VLDL-triglyceride and apolipoprotein B100 kinetics, liver and abdominal fat and plasma apolipoproteins, and LPL mass and activity in a relatively large cohort of subjects with abdominal obesity. The selection criteria and absence of healthy controls may, however, have favored a stronger correlation between apoCIII levels and VLDL, kinetics compared with other lipoproteins, such as apolipoprotein E given that apoCIII-rich VLDL secretion is increased in hypertriglyceridemic individuals.18 The small number of women is also a limitation given that sex is an important determinant of VLDL metabolism in healthy subjects.3 In addition, there is a marked sexual dichotomy in cardiac and adipose tissue–specific chylomicron fatty acid uptake in subjects with impaired glucose tolerance,18 suggesting that sex may influence...
the direct clearance pathways of triglyceride-rich lipoproteins. More mechanistic studies are clearly needed on these important sex-related differences in triglyceride metabolism.

The study by Borén and colleagues contributes to the remarkable and rapid recent advances in our understanding of the factors leading to hypertriglyceridemia associated with abdominal obesity. This relatively large mechanistic study has provided more support to the important roles of hepatic steatosis and increased apoCIII for the development of hypertriglyceridemia in abdominal obesity (Figure). The precise contribution of total lipoprotein removal versus lipoprotein triglyceride removal by tissues and LPL versus apoCIII-mediated catabolism remains to be defined. Furthermore, the contributing role of disordered metabolism of triglyceride-rich lipoproteins at the end organ level to the dyslipidemia associated with the cardiometabolic risk is still poorly understood in humans. Application of novel therapies using apoCIII inhibition and LPL gene transfer and the recent development of innovative methods able to more directly measure end-organ metabolism of triglyceride-rich lipoproteins offer outstanding opportunities to bridge these knowledge gaps in the near future.

Acknowledgments
Warm thanks to Monique Sullivan for editing the text and Anick Turgeon for editing the figure.

Disclosures
Dr. Carpentier received significant grant funding (>10k) from UniQure for studies on Alipogene tiparvovec effect on chylomicron metabolism. He also received modest honorarium (<10k) from UniQure for Advisory Board services.

References


**Key Words**: abdominal obesity ■ apolipoprotein CIII ■ hepatic steatosis ■ hypertriglyceridemia ■ lipoprotein lipase ■ VLDL
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Arterioscler Thromb Vasc Biol. 2015;35:2076-2078
doi: 10.1161/ATVBAHA.115.306412
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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