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The apoB-to-PCSK9 ratio: A new index for metabolic risk in humans

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BACKGROUND: Proprotein convertase subtilisin/kexin type 9 (PCSK9) shuttles low-density lipoprotein (LDL) receptors for degradation, thus upregulates LDL plasma clearance. Although PCSK9 loss of function is cardioprotective, its role in metabolic risks remains unknown. Increased apoB-lipoproteins uptake into nonhepatic tissues such as white adipose tissue (WAT) induces their dysfunction, which may be favored by lower plasma PCSK9. We hypothesized that lower plasma PCSK9 relative to apoB, or higher apoB-to-PCSK9 ratio, is a better predictor of metabolic disturbances than PCSK9 alone in humans.

METHODS: Thirty-three men and 48 postmenopausal women (>27 kg/m^2, aged 45–74 years, normoglycemic) underwent in-depth assessment of glucose and fat metabolism using high-fat meals, WAT biopsies, intravenous glucose-tolerance tests, and hyperinsulinemia clamps.

RESULTS: Plasma apoB correlated positively with fasting and postprandial triglycerides and chylomicron clearance (R = 0.44–0.66) and glucose-stimulated insulin secretion (R = 0.24) and negatively with insulin sensitivity (R = −0.28) and gynoid WAT in situ lipoprotein lipase activity (ie, ex vivo WAT function, R^2 = 0.34). Neither PCSK9 nor LDL cholesterol associated with these risks. In regression analysis that adjusted for body mass index, lower plasma PCSK9 strengthened the association of apoB to WAT dysfunction and insulin resistance. Moreover, plasma apoB-to-PCSK9 ratio correlated positively with all these metabolic risks and further associated positively with android-to-gynoid fat ratio (R = 0.41) and negatively with gynoid fat mass (R = −0.23, all $P \leq .05$). No significant sex differences existed in these associations.

CONCLUSIONS: Lower plasma PCSK9 relative to apoB associates with metabolic risks and WAT dysfunction in normoglycemic obese subjects. We hypothesize that the plasma apoB-to-PCSK9 ratio provides a better clinical index than PCSK9 alone for monitoring early metabolic disturbances that may be promoted by reduction in plasma PCSK9.

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Introduction

Normal fasting plasma glucose is maintained by the balance between insulin sensitivity and secretion.[1] "Prediabetic" metabolic abnormalities that promote insulin resistance (IR), such as impaired glucose tolerance, increase the risk for type II diabetes (T2D) before the rise of fasting glucose. In time, these abnormalities are believed to promote hyperinsulinemia, β-cells exhaustion, apoptosis, and hypoinsulinemia, followed by fasting hyperglycemia and progression to T2D.[1] Although the etiology of IR is multifaceted, dysfunctional gynoid white adipose tissue (WAT) is believed to favor delayed clearance of triglyceride-rich lipoproteins (TRLs) and increased lipid influx into peripheral tissues inducing lipotoxicity and IR.[1,2]

We previously reported that elevated numbers, but not cholesterol content, of apoB-lipoprotein particles, measured as plasma apoB concentrations, are strongly associated with risks factors for T2D, namely IR, chronic inflammation and dysfunctional WAT in obese women.[3–5] Although the mechanisms behind these associations are not fully elucidated, we demonstrated that native human low-density lipoprotein (LDL) have an acute inhibitory effect of lipoprotein lipase (LPL) activity in vitro and on in situ LPL activity in murine adipocytes and human WAT.[5] Native human LDL also have a negative chronic effect on the differentiation and function of murine preadipocytes.[5] Similarly, oxidized LDLs (oxLDLs) were reported to decrease adipocytes differentiation in a scavenger receptor (CD36)-dependent mechanism.[6,7] In line, epidemiologic evidence confirmed that the risk of T2D is related to elevated plasma apoB in several populations such as Canadian[8] and Korean,[9] independent of traditional risk factors such as central adiposity,[8] fasting glycemia,[8,9] and glycated hemoglobin (HbA1c).[9]

Of importance to note, however, is that the abnormalities in the functions of WAT,[5–7] skeletal muscle,[10,11] and pancreas[12] induced by apoB-lipoproteins are dependent on receptor-mediated tissue uptake of these particles. On the other hand, the lack of LDL receptors (LDLRs) was suggested to protect against new onset T2DM in patients with familial hypercholesterolemia (FH) compared with unaffected relatives after correcting for confounders such as age, gender, body mass index (BMI), statin use, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG).[13] Taken together, these findings suggest that increasing or decreasing receptor-mediated uptake of apoB-lipoproteins into peripheral tissue increases or decreases T2D risks, respectively.

Receptor-mediated uptake of apoB-lipoproteins is controlled, in part, by proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is the last member of a novel family of enzymes, proprotein convertases, whose existence was proposed after the prohormone theory published in 1967.[14] It is an endoproteolytic enzyme that forms a heterodimer with its cleaved prosegment and becomes an escort protein for hepatic LDLR.[15] PCSK9 is a key regulator of LDL uptake as it shuttles LDLR to lysosomal degradation.[16] Plasma PCSK9 associates positively with plasma LDL cholesterol (LDLC), and variants that cause gain or loss of function of PCSK9 are associated with hypercholesterolemia or hypocholesterolemia, increasing or decreasing cardiovascular disease (CVD) risk, respectively[17,18]

The association of PCSK9 with metabolic risks is, to date, suggestive but not conclusive in both mice[19,20] and humans.[21,22] However, as LDLRs are expressed by WAT,[6,23] muscle,[10] and pancreas,[24] reducing plasma PCSK9 may reduce the "barrier" against apoB-lipoproteins uptake into peripheral tissues promoting their dysfunction. Given that the concentrations of PCSK9 does not always reflect its function,[25] the interplay between plasma PCSK9 and apoB-lipoproteins may be a better indication of PCSK9 function and the overall clearance of apoB-lipoproteins. Accordingly, we hypothesized that lower plasma PCSK9 relative to apoB, or increased apoB-to-PCSK9 ratio, was associated with reduced WAT function ex vivo and delayed TG and chylomicron clearance, hyperinsulinemia, and IR in vivo in nondiabetic obese subjects. Knowledge of plasma PCSK9 alone is unlikely to reveal these early "prediabetic" risks.

Material and methods

Study population

Metabolic studies measuring insulin sensitivity and secretion in vivo were conducted between 2010 and 2014 at the Institut de recherches cliniques de Montréal (IRCM). Subjects were recruited by newspaper advertisement with the following inclusion criteria: BMI >27 kg/m^2; age, 45 to 74 years; confirmed menopausal status (FSH ≥ 30 U/L or more than 1 year without menses); nonsmoker; sedentary (less than 2 hours of structured exercise/wk); and low alcohol consumption (<2 alcoholic drinks/day). The exclusion criteria were present or prior history of CVD and hypertension requiring medication, diabetes (or fasting glucose >7 mmol/L), cancer (within the last 3 years), untreated thyroid disease, kidney disease (or creatinine >100 μmol/L), hepatic disease (or aspartate transaminase and/or alanine transaminase >3 times normal limit), claustrophobia, anemia (hemoglobin <120 g/L), blood coagulation problems, current or past 3-month use of drugs affecting metabolism (hormone replacement therapy except thyroid hormone at a stable dose, systemic corticosteroids, antipsychotic and/or psychoactive drugs, anticoagulant, weight loss, and adrenergic agonist), known substance abuse, exceeding the annual allowed radiation dose exposure, and all other medical or psychological conditions deemed inappropriate according to the physician.

One hundred ten subjects were recruited, of whom 82 were eligible for inclusion in the principal study (49 women and 33 men). One woman felt malaise during the measurement of insulin secretion by an intravenous glucose tolerance test (IVGTT) and was excluded from continuing the test and study. Included subjects (N = 81) were invited to be part of a