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Abdominal Obesity and Dyslipidemia in the Metabolic Syndrome: Importance of Type 2 Diabetes and Familial Combined Hyperlipidemia in Coronary Artery Disease Risk

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Regional body fat distribution has an important influence on metabolic and cardiovascular risk factors. Increased abdominal (visceral) fat accumulation is a risk factor for coronary artery disease (CAD), dyslipidemia, hypertension, stroke, and type 2 diabetes. The recent emphasis on treatment of the dyslipidemia of the metabolic syndrome (hypertriglyceridemia, reduced high-density lipoprotein, and increased small, dense low-density lipoprotein particle number) has compelled practitioners to consider lipid-lowering therapy in a greater number of their patients, as one in two individuals over age 50 has the metabolic syndrome. Individuals with the metabolic syndrome typically have normal low-density lipoprotein cholesterol levels, and current lipid-lowering guidelines may underestimate their cardiovascular risk. Two subgroups of patients with the metabolic syndrome are at particularly high risk for premature CAD. One, individuals with type 2 diabetes, accounts for 20–30% of early cardiovascular disease. The second, familial combined hyperlipidemia, accounts for an additional 10–20% of premature CAD. Familial combined hyperlipidemia is characterized by the metabolic syndrome in addition to a disproportionate elevation of apolipoprotein B levels. The measurement of fasting glucose and apolipoprotein B, in addition to the fasting lipid profile, can help to estimate CAD risk in patients with the metabolic syndrome.

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DISTINCT METABOLIC FEATURES are seen in individuals with increased amounts of abdominal (visceral) adipose tissue. Hypertriglyceridemia, reduced high density lipoprotein (HDL), and small, dense low density lipoprotein (LDL) particles characterize the dyslipidemia associated with increased abdominal fat. Individuals with the metabolic syndrome typically have normal LDL cholesterol levels, but their LDL particles are small and dense, and current lipid-lowering guidelines may underestimate their coronary artery disease (CAD) risk. Further evaluation of apolipoprotein B (apo B) in patients with the metabolic syndrome can help detect patients with familial combined hyperlipidemia (FCHL) and identify them as candidates for aggressive lipid lowering. As the prevalence of the metabolic syndrome rises with increasing obesity and sedentary lifestyle, so does the disease burden of increased type 2 diabetes mellitus and cardiovascular disease.

Link between abdominal obesity and metabolic abnormalities

Regional body fat distribution has an important influence on metabolic and cardiovascular risk factors. Many prospective studies have shown that increased abdominal (visceral) fat accumulation is an independent risk factor for CAD, hypertension, stroke, and type 2 diabetes (DM2) (1–3). The strong link between increased abdominal (visceral) fat and hyperinsulinism, insulin resistance, elevated plasma free fatty acid (FFA) levels, hypertension, predisposition to thrombosis, hypertriglyceridemia, small, dense LDL particles, and reduced HDL has been recognized for decades, but until recently there has been no uniform definition of this disease complex. The National Cholesterol Education Program (NCEP) and others have recently suggested the use of the term metabolic syndrome to identify the common cluster of metabolic abnormalities, defined as three or more of five criteria: 1) abdominal obesity (waist circumference, >102 cm in men and >88 cm in women), 2) hypertriglyceridemia ([≥1.69 mmol/liter ([≥150 mg/dl]), 3) low HDL (<1.04 mmol/liter (<40 mg/dl)) in men and <1.29 mmol/liter (<50 mg/dl) in women), 4) hypertension (≥130/85 mm Hg), and 5) elevated fasting glucose ([≥6.1 mmol/liter ([≥110 mg/dl]) (4, 5). Even normal weight individuals with increased amounts of abdominal adipose tissue can be metabolically obese, with insulin resistance and dyslipidemia (6, 7).

Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity. Intra-abdominal fat increases with age in both overweight and normal weight individuals independently of changes in total body fat (8). Sex steroid hormones appear to contribute to body fat distribution, as men have twice as much abdominal fat as women (9, 10), and estrogen deficiency (at menopause) is associated with a preferential increase in intraabdominal
Dyslipidemia of abdominal adiposity

The increased focus on the metabolic syndrome has drawn attention to the identification and treatment of the dyslipidemia associated with abdominal fat accumulation. The changes in lipid metabolism seen with abdominal fat accumulation have been well characterized and include hypertriglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles. Elevated LDL cholesterol is not a feature of the dyslipidemia seen with abdominal obesity. Other features of the dyslipidemia of abdominal adiposity include elevated very low density lipoproteins (VLDL), and reduced HDL, which are the large buoyant antiatherogenic subspecies of total HDL. In some individuals, apo B levels may be elevated, reflecting an increase in the number of small, dense lipoprotein particles (VLDL and LDL).

The hypertriglyceridemia seen with abdominal obesity and insulin resistance is related to the oversecretion of triglyceride-rich VLDL particles (see Fig. 1). An increased rate of hepatic FFA uptake stimulates the secretion of apo B-100, leading to increased numbers of apo B-containing particles and possibly hypertriglyceridemia (17). Apo B is the structural protein of atherogenic lipoproteins, including VLDL, intermediate density lipoproteins (IDL), and LDL. Each of these lipoproteins contains one apo B molecule, and the plasma apo B level reflects the total number of atherogenic particles in the blood. VLDL particles are exposed to lipoprotein lipase in the peripheral circulation, which hydrolyzes the triglyceride in VLDL particles, generating FFA. Under normal conditions, these FFA are taken up by muscle and adipose tissue for energy use or storage. The resultant remnant particles are then processed by the liver to form LDL.

An increased number of small, dense LDL particles is a constant feature of the dyslipidemia of abdominal adiposity, as they are associated with insulin resistance, intraabdominal fat, and hypertension (18–20). LDL comprises a spectrum of particles that vary in size, density, chemical composition, and atherogenic potential. In conditions of elevated triglycerides, LDL particles become enriched in triglycerides and depleted of core cholesteryl esters (see Fig. 2). Hepatic lipase then acts to hydrolyze these triglyceride-rich LDL, forming smaller, denser LDL particles. The presence of small, dense cholesterol-depleted LDL particles is associated with an increased risk of myocardial infarction (21–23) and worsened severity of CAD (24–26). The Familial Atherosclerosis Treatment Study showed that the strongest predictor of coronary artery stenosis regression, induced by aggressive lipid lowering, was the increase in LDL buoyancy, not the change in LDL cholesterol level (27).

Although the mechanisms underlying the association of small, dense LDL with increased risk of CAD are not clear, several hypotheses have been proposed. One explanation is that the presence of small, dense LDL particles is a marker of an atherogenic lipoprotein phenotype comprised of elevated triglycerides, reduced HDL, and elevated apo B, which together increase CAD risk (28). Mechanistically, small, dense LDL particles enter the arterial wall more easily (29), bind to arterial wall proteoglycans more avidly (30), and are highly susceptible to oxidative modification, leading to macrophage uptake (31, 32), all of which may contribute to increased atherogenesis.

HDL and VLDL metabolism are closely linked, which explains why increased plasma triglyceride is almost always associated with reduced HDL levels. Cholesteryl ester trans-
fer protein mediates the exchange of triglyceride in VLDL for cholesteryl ester in LDL and HDL, leading to the production of triglyceride-rich LDL and HDL particles. Subsequent hepatic lipase-mediated hydrolysis of these particles leads to the generation of small, dense LDL particles and a decrease in HDL cholesterol (the large buoyant and antiatherogenic subspecies of total HDL; see Fig. 2) (33).

**Prevalence and risk of the metabolic syndrome**

Many studies have shown significantly increased CAD risk with the features of the metabolic syndrome, described under different names, but until recently limited information was available about the prevalence of the syndrome in the general population (20, 23, 34, 35). It is now clear that the metabolic syndrome is very common in westernized countries and varies with age, ethnicity, and body mass index (36–41). Ford et al. (38) studied 8814 men and women (>20 yr old) and found a 24% prevalence of the NCEP-defined metabolic syndrome (in individuals with and without diabetes) using National Health and Nutrition Examination Survey III (NHANES III) data. The prevalence increased with age, and 33–45% of subjects over 50 yr met the criteria for the metabolic syndrome. Alexander et al. (40) studied a subset of NHANES III participants (>50 yr old) and confirmed a 43.5% prevalence of the metabolic syndrome (in subjects with and without diabetes) using NCEP criteria. As expected, the concordance of the metabolic syndrome with diabetes was high, as the majority of individuals with diabetes (86%) or impaired fasting glucose ≥6.1 mmol/liter (≥110 mg/dl), 71% met the criteria for the metabolic syndrome. In contrast, diabetes without the metabolic syndrome was uncommon (13% of individuals with diabetes), and the prevalence of the metabolic syndrome in normoglycemic individuals was 26%.

The presence of the metabolic syndrome is estimated to increase the risk of coronary heart disease by 1.6- to 3.0-fold. Although individuals with the combination of the metabolic syndrome and diabetes have a high overall age-adjusted prevalence of CAD (19.2%), the presence of the metabolic syndrome in subjects without diabetes appears to convey a moderate risk of CAD (13.9%) compared with those with neither (8.7%; see Fig. 3) (40). Several groups have recently shown that individuals with the metabolic syndrome (without diabetes) had a 12-14% risk of CAD compared with a 6-9% risk in individuals without the metabolic syndrome (37, 40, 41). Recently published American Heart Association guidelines describe the presence of the metabolic syndrome, without diabetes, as a moderate CAD risk factor (42). No study to date has established the contribution of familial combined hyperlipidemia to CAD risk in nondiabetic individuals with the metabolic syndrome (see below).

**Metabolic syndrome: targeting high risk patients**

The recent emphasis on treatment of the dyslipidemia of the metabolic syndrome has compelled practitioners to consider lipid-lowering therapy in a greater number of their patients, as epidemiological studies have shown that one in two individuals over 50 yr of age has the metabolic syndrome. It is not yet clear whether all of these patients should be treated with lipid-lowering medications, and the economic impact of such a decision is enormous.

Although the primary focus on CAD prevention remains on LDL lowering, LDL cholesterol levels may underestimate CAD risk in the metabolic syndrome. Studies investigating the lipid profiles of men with premature CAD have shown that approximately 50% had normal LDL cholesterol levels, but these men had low HDL and elevated triglyceride levels and may have had the metabolic syndrome (43). Recent posthoc analyses of the placebo-treated groups in the 4S and AFCAPS/TexCAPS trials showed that nondiabetic individuals with the metabolic syndrome (21% of 4S and 46% of AFCAPS/TexCAPS) had an increased risk of major coronary events during follow-up compared with those without the metabolic syndrome. Importantly, the increased event rate with the metabolic syndrome remained significant after adjustment for the Framingham 10-yr risk score, implying independent contributions of the metabolic syndrome and the Framingham score in predicting future CAD risk (44).

The evaluation of apo B in the metabolic syndrome can help target patients for aggressive lipid-lowering therapy. High levels of LDL cholesterol are generally accepted to be one of the strongest risk factors for CAD, but there is now significant evidence that the measurement of apo B may be an even better predictor of future CAD (45–48). Insulin resistance is associated with increased numbers of small VLDL, IDL, and LDL particles, reflected by higher apo B levels, with decreased triglyceride to apo B ratios compared with those in individuals with normal insulin sensitivity. These particles are associated with increased coronary heart disease. Studies have shown that increased apo B and apo B-containing lipoproteins (VLDL and IDL) are related to an increased risk of CAD (45–47) and that particle quantity (absolute number) and quality (small, dense) both contribute to cardiovascular risk (23) (see Fig. 4). Bonora et al. (49) recently found signif-

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The underlying process in FCHL appears to be the overproduction of apo B in lipoproteins (VLDL, IDL, and LDL), which is not seen in other forms of hypertriglyceridemia (60, 61). The variable clinical lipid presentation of FCHL in patients has made their identification difficult, but the demonstration of elevated apo B and small, dense LDL particles has been shown to be a consistent feature across the variable lipid phenotypes (62–64). Patients with FCHL present with elevated total and LDL cholesterol and/or hypertriglyceridemia, reduced HDL, and elevated plasma apo B (>90th percentile). Often one can identify affected relatives, and it is important to screen siblings and children of individuals with FCHL.

FCHL is an oligogenic disorder that is not fully expressed until the third decade of life, possibly associated with the accumulation of central abdominal fat (65). Children who have inherited FCHL usually do not have hyperlipidemia (52). The metabolic features of FCHL are very similar to those of the metabolic syndrome, as individuals with FCHL are also characterized by insulin resistance, increased abdominal obesity, and hypertension (65–68). Hopkins et al. (51) recently found that most FCHL patients met the NCEP criteria for the metabolic syndrome, but abdominal adiposity and insulin resistance do not fully account for the elevated apo B levels in FCHL. Purnell et al. (65) found that subjects with FCHL had significantly higher apo B levels compared with age-, body mass index-, and abdominal fat-matched controls. Further, apo B levels and small, dense LDL particles have been shown to segregate independently in families with FCHL (69). FCHL is a subtype of the metabolic syndrome, with higher apo B levels. The identification of FCHL patients at high risk for CAD within the large population of individuals with the metabolic syndrome can help identify individuals as candidates for aggressive lipid-lowering interventions.

**Screening of metabolic syndrome patients**

The metabolic syndrome is a common population trait comprised of a heterogeneous group of oligogenic disorders, such as DM2 and familial combined hyperlipidemia (see Fig. 5). The identification of these metabolic syndrome subtypes by measuring fasting glucose and apo B can help target these high risk patients for lipid-lowering therapy. Patients with the metabolic syndrome should be screened for DM2, as individuals with DM2 and the metabolic syndrome are at
high risk for CAD. Current guidelines recommend that patients with DM2 should be aggressively treated for dyslipidemia with the goal to maintain LDL below 2.6 mmol/liter (100 mg/dl), triglyceride below 1.7 mmol/liter (150 mg/dl), and HDL above 1.02 mmol/liter (40 mg/dl) (50).

Metabolic syndrome patients with elevated apo B levels (>90th percentile for age) have FCHL and should be targeted for aggressive lipid-lowering therapy (see Fig. 6). Apo B levels increase with age; therefore, age-appropriate apo B levels must be used in diagnosis (70). Several large prospective studies have shown that the apo B level is a better predictor of future cardiovascular events than the LDL cholesterol level (45, 71, 72). Recently, the Apolipoprotein-Related Mortality Risk Study published prospective data in 175,553 men and women and found that the total apo B level was a better predictor of future CAD risk than LDL cholesterol (47). Importantly, they also found that apo B was a better predictor of CAD risk in individuals with low LDL levels, supporting the idea that patients with low LDL cholesterol levels and increased quantities of small, dense atherogenic particles (VLDL, IDL, and LDL) are at risk for CAD.

In addition to apo B, the measurement of non-HDL cholesterol (total cholesterol minus HDL cholesterol) can be used to assess the quantity of atherogenic apo B-containing lipoproteins (VLDL, IDL, and LDL). Some investigators have proposed that non-HDL cholesterol could replace the LDL measure in patients with hypertriglyceridemia (dyslipidemia with DM2 or FCHL), because these patients have more cholesterol in VLDL particles, and LDL cholesterol alone can underestimate their CAD risk (73). The current NCEP guidelines recommend a non-HDL cholesterol goal of less than 3.4 mmol/liter (<130 mg/dl) in hypertriglyceridemic patients (>2.3 mmol/liter (>200 mg/dl)) (5). Total apo B and non-HDL cholesterol levels are generally highly correlated, but less so at higher triglyceride levels.

**Treatment of dyslipidemia**

Comprehensive treatment of patients with the metabolic syndrome has recently been described in detail (74). The treatment of the dyslipidemia of the metabolic syndrome should be focused on lowering LDL and apo B and increasing HDL. Statin treatment has been shown to reduce cardiovascular events in persons with low LDL cholesterol levels at baseline (75). The percent reduction in LDL cholesterol and apo B by statin medications is similar, but apo B may be a better marker of treatment efficacy in metabolic syndrome patients with normal LDL cholesterol (76).

Although LDL cholesterol has remained the primary target of lipid-lowering therapy, raising HDL levels is now an important secondary target to reduce CAD risk (5). Combination lipid-lowering therapy is frequently needed to treat the dyslipidemia of the metabolic syndrome (increased triglyceride, reduced HDL, and small, dense LDL particles), if lifestyle changes (weight loss and exercise) are inadequate. Nicotinic acid and fibric acid derivatives both act to reduce triglyceride and increase HDL cholesterol. They are frequently used with statin medications. Although fibrate monotherapy lowers plasma triglyceride levels, it can lead to increases in LDL levels. Bile acid resin binders lower LDL cholesterol levels, but can increase triglyceride levels in individuals susceptible to hypertriglyceridemia. Although niacin is an inexpensive monotherapeutic agent that corrects the dyslipidemia of the metabolic syndrome, it may increase glucose levels in some patients (77). Several groups have recently shown that niacin use in diabetic individuals was safe and effective, resulting in only a transient worsening of glycemic control (78–80).

**Conclusions**

The decision to initiate lipid-lowering therapy in nondiabetic individuals with the metabolic syndrome can be difficult using current guidelines, as LDL levels may underestimate CAD risk in this population. The large population of individuals with the metabolic syndrome appears to be comprised of a heterogeneous group of disorders, and the identification of disease subtypes at high risk for CAD can help identify individuals as candidates for aggressive lipid-lowering interventions. Two subgroups of patients with the metabolic syndrome, those with DM2 or FCHL, are at particularly high risk for premature CAD. FCHL is characterized by the metabolic syndrome in addition to a disproportionate elevation of apo B levels. The measurement of fasting glucose and apo B in addition to the fasting lipid profile can help to
estimate CAD risk and guide treatment decisions in patients with the metabolic syndrome.

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