

OBESITY AND CARDIOVASCULAR RISK: METABOLIC SYNDROME

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Abstract: Increased abdominal fat distribution is a risk factor for coronary artery disease, dyslipidemia, hypertension, stroke and type 2 diabetes. Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity. Intraabdominal fat increases with age in both overweight and normal weight individuals. Men have twice as much abdominal fat as women, due to hormonal effect. Two groups of patients with abdominal obesity are at high risk for premature CAD, one with Type 2 diabetes and second, familial combined hyperlipidemia. Familial combined hyperlipidemia is characterized by metabolic syndrome in addition to disproportionate elevation of apolipoprotein B. Individuals with metabolic syndrome may have normal LDL levels but their LDL particles are small and dense, so current lipid lowering guidelines may underestimate their risk. Studies have shown prevalence of metabolic syndrome to be in the range of 20-30% in developed countries. The presence of metabolic syndrome is estimated to increase the risk of CAD by 1.6 to 3.0 fold. Individuals with combination of metabolic syndrome and diabetes have a higher prevalence of CAD (19.2%) as compared to diabetics without metabolic syndrome (13.2%). Metabolic syndrome patients with elevated Apo B levels (> 90th percentile for age) have Familial combined hyperlipidemia and should be targeted for aggressive lipid lowering therapy. Apo B levels increase with age therefore age appropriate apo B levels must be used in diagnosis. Apo B level is a better predictor for future cardiovascular events than LDL cholesterol. Apo B is better predictor for CAD risk in individuals with low LDL level. In addition of Apo B measurement of non HDL cholesterol is recommended as it quantifies the atherogenic Apo B containing lipoproteins. So there is increasing requirement of aggressive lipid lowering in patterns of metabolic syndrome. Therapy targeting LDL and Apo B are recommended. But rising of HDL is also an important target to be achieved. So the combination of lipid lowering therapy in form of statins and fibrates or niacin is recommended, only if lifestyle modifications are not sufficient. A word of caution is needed in administering niacin therapy in diabetes, though recent studies have found it to be safe.

INTRODUCTION

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 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. Multiple environmental and genetic factors are thought to influence the manifestation of abdominal obesity. Intraabdominal fat increases with age in both overweight and normal weight individuals independently of changes in total body fat¹. Sex steroid hormones appear to contribute to body fat distribution, as men have twice as much abdominal fat as women^{2,3}, and estrogen deficiency (at menopause) is associated with a preferential increase in intraabdominal fat, which is blunted by estrogen replacement therapy^{4,5}. There is also evidence that increased abdominal adipose tissue is associated with physical inactivity, increased plasma cortisol, and intrauterine environment⁶. Inheritance clearly plays a role in body fat distribution, as family studies have shown that genetic factors account for about 50% of the variance in intraabdominal fat

after adjusting for age, sex, and total body fat⁷. Genetic factors that predispose individuals to gain weight centrally may explain the susceptibility of certain ethnic groups to DM^{2,8,9}.

LINK BETWEEN OBESITY AND METABOLIC ABNORMALITIES

Two subgroups of patients with the abdominal obesity 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. 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.⁽¹¹⁾

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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.

METABOLIC SYNDROME

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)^{12,13}. 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. This has been given many names such as syndrome X or metabolic syndrome; criteria proposed to diagnose are: *National Cholesterol Education Programme/Adult Treatment Panel III (NCEP/ATP III) diagnostic criteria for the metabolic syndrome* — *Diagnosis is made when 3 or more of the following are present:*

- Waist circumference : Men > 102 cm , women > 88 cm.
(For Indians – Men - 90 cm, women - 80 cm)
- Fasting triglycerides > 150 mg/dl
- Blood pressure > 130/85 mmHg
- HDL cholesterol < 50 mg/dl for women; < 40 mg/dl for men
- Fasting glucose > 110 mg/dl

WHO criteria for the metabolic syndrome, as identified by one of the following:

- Type 2 diabetes
- Impaired fasting glucose (101-125 mg/dl)
- Impaired glucose tolerance (140-199 mg/dl 2 hours after 75g of glucose)
- If normal fasting glucose, glucose uptake below the lowest quartile for background population under hyperinsulinaemic, euglycaemic conditions Plus 2 of the following :
- Antihypertensive medication and/or blood pressure > 140 mmHg systolic or > 90mmHg diastolic
- Triglycerides > 150 mg/dl
- HDL < 35 mg/dl for men or < 39 mg/dl for women
- BMI > 30 kg/m² and/or waist-hip ratio > 0.9 men, > 0.85 women
- Urinary albumin excretion > 20 µg/minute or albumin-creatinine ratio > 30 µg/mg

AACE clinical criteria for diagnosis— Risk factors are as follows :

Overweight/obesity : BMI > 25 kg/m²
Elevated triglycerides : > 150 mg/dl
HDL cholesterol : Men < 40 mg/dl, women < 50 mg/dl
Blood pressure : > 130/85 mmHg
2-hour post 75 g glucose challenge : > 140 mg/dl
Fasting glucose : Between 110 and 126 mg/dl
Additional risk factors :

- Family history of type 2 diabetes
- Hypertension
- Coronary heart disease (CHD)
- Polycystic ovary syndrome
- Sedentary lifestyle
- Advanced age
- Ethnic groups at high risk for type 2 diabetes or CHD

Of all these criteria, ATP III criteria to diagnose IRS seems to be more practical during an office visit. This also has some shortcomings such as inadequate measure of glucose tolerance, and inability to detect prothrombotic (PAI), pro-inflammatory C-reactive protein (CRP) and adipocytokines (adiponectins).

PREVALENCE AND RISK OF 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^{14,15}. It is now clear that the metabolic syndrome is very common in westernized countries and varies with age, ethnicity, and body mass index^{16,17}. Ford et al.¹⁸ 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.¹⁹ 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%). 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 syndrome²⁰. Recently published American Heart Association guidelines describe the presence of the metabolic syndrome, without diabetes, as a moderate CAD risk factor²¹. No study to date has established the contribution of familial combined hyperlipidemia to CAD

risk in nondiabetic individuals with the metabolic syndrome

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. 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)²².

Metabolic syndrome patients with elevated apo B levels (>90th percentile for age) have FCHL and should be targeted for aggressive lipid-lowering therapy. Apo B levels increase with age; therefore, age-appropriate apo B levels must be used in diagnosis. Several large prospective studies have shown that the apo B level is a better predictor of future cardiovascular events than the LDL cholesterol level²³. 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. 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.

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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 syndrome²⁴. Recent *post hoc* 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 risk²⁵.

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Current *guidelines* recommend that patients with DM2 should be aggressively treated for dyslipidemia with the goal to maintain (i) LDL < 2.6 mmol/liter (100 mg/dl); (ii) triglyceride < 1.7 mmol/liter (150 mg/dl); and (iii) HDL > 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. Apo B levels increase with age; therefore, age-appropriate apo B levels must be used in diagnosis⁽²⁶⁾. Several large prospective studies have shown that the apo B level is a better predictor of future cardiovascular events than the LDL cholesterol level. 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 cholesterol²⁷. 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.

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 (28). 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. 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 (29).

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. 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 (30). Several groups have recently shown that niacin use in diabetic individuals was safe and effective, resulting in only a transient worsening of glycemic control^{31,32}.

CONCLUSION

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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