Obesity, the metabolic syndrome, and cardiovascular disease

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The prevalence of overweight and obesity has increased significantly in the United States and worldwide. In the United States alone, >97 million adults are obese, and more than half the population is overweight. The incidence of obesity is also increasing at alarming rates in the pediatric population. At the turn of the 21st century, overweight and obesity have reached epidemic proportions. Both pediatric and adult populations are at increased risk of morbidity from chronic diseases, and it is projected that the cost of treatment of obesity-related diseases will increase proportionally.

The impact of obesity-related diseases on medical care and disability costs is a major concern. In 1995 it was estimated that spending for the treatment of obesity represented about 5.7% of the national health costs. The total cost of obesity care was $99.2 billion; 51% of this amount was devoted to medical costs associated with diseases attributable to obesity. The highest cost associated with medical treatment of obesity was diabetes mellitus ($32.4 billion), followed by coronary heart disease (CHD) ($7 billion). The prevalence of diabetes mellitus has increased by 33%, and CHD will likely follow this trend. The health care community thus needs to make major efforts to contain the epidemic of obesity and overweight. For example, multiple risk factor management that includes weight control should be considered for patients with established CHD or conditions with equivalent risk. For patients at risk for CHD, it is necessary to establish programs of public education that include lifestyle modification.

Because of the increased morbidity and mortality associated with obesity, the condition has recently been reclassified as a disease. The first stages of the disease include metabolic changes; there are also neuroendocrine changes that worsen the metabolic balance. If untreated, the disease progresses from asymptomatic metabolic alterations to clinical manifestations of chronic diseases such as hypertension, dyslipidemia, and diabetes mellitus.

This review provides an estimate of the relative risk for CHD that can be attributed to the “metabolic syndrome.” It also summarizes the guidelines recently released by the third Adult Treatment Panel (ATP) III on detection and treatment of the syndrome.

Metabolic syndrome

A desirable content of body fat for men ranges from 12% to 20% of total body weight. For women it ranges from 20% to 30%. Obesity is defined as a body fat content >25% or >33% of total body weight in men and women, respectively. This means that obesity is characterized by excess fat weight; body mass index (BMI) is used as an alternative measure of body fat. BMI (calculated as weight in kilograms/height in meters squared) has been used extensively in epidemiologic studies to assess the relationship between fat weight and mortality. The relationship has a U or J shape.

Low BMIs are associated with high mortality rates, principally from pulmonary and gastrointestinal diseases. In contrast, high BMIs impart a high risk of mortality from cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, stroke, and cancer. High BMIs are also associated with gallstone disease, sleep apnea, and osteoarthritis. These conditions compromise significantly a person’s quality of life and ability to work. For this reason it is desirable to monitor BMI as part of the routine clinical assessment of patients.

The term “metabolic syndrome” describes a cluster of metabolic alterations associated with excess fat weight. The typical abnormalities include impaired glucose tolerance, dyslipidemia, insulin resistance (hyperinsulinemia), hypertension, upper body obesity, coagulation abnormalities, hyperuricemia, and polycystic ovary syndrome in women. To have a “metabolic syndrome,” an individual must have excess fat weight and at least 2 comorbidities such as dyslipidemia and hypertension or dyslipidemia and impaired fasting glucose. The excess fat must be truncal rather than gynoid. Typical features of the metabolic syndrome are summarized in Table I.

Impaired fasting glucose

An elevated fasting blood sugar or a high postprandial glucose level 2 hours after ingestion of 75 g of glucose (Table I) is a common feature of the metabolic syndrome. The levels of glucose are intermediate between desirable ranges and the levels that define type 2 dia-
Diabetes mellitus. The role of impaired glucose in atherogenesis remains unclear; however, a large body of data supports the contention that prolonged elevation of plasma glucose can induce alterations in plasma proteins and lipoproteins. An example of such alterations can be found in an increased concentration of glycated hemoglobin. Some investigators suggest that high blood glucose levels induce a nonenzymatic modification of plasma proteins and that the end products of the reaction are called advanced glycosylated end products (AGE). These glycosylated proteins and lipoproteins may be involved in organ damage and in the atherogenic process; however, determining the role of AGEs in atherosclerosis will require a prospective study in humans that examines the relationship of AGEs and CHD risk.

Dyslipidemia
The prevalent lipoprotein phenotype of the metabolic syndrome includes moderate elevation of plasma triglycerides and reduced high-density lipoprotein (HDL) cholesterol levels. Levels of low-density lipoprotein (LDL) cholesterol are not markedly elevated in individuals with the metabolic syndrome (Table I). However, LDL has abnormal physicochemical properties. A fraction of the LDL is typically “small” and “dense” because it has a low content of total cholesterol. Consequently, each component of dyslipidemia imparts a risk for CHD as detailed below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Metabolic syndrome range</th>
<th>Desirable range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired glucose tolerance</td>
<td>≥110 and &lt;126</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>≥140 and &lt;200</td>
<td>&lt;140</td>
</tr>
<tr>
<td>2-h Postprandial glucose (mg/dL)</td>
<td>≥150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>100-139</td>
<td>≤100*</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>Men &lt;40, women &lt;50</td>
<td>Men &gt;40, women &gt;50</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>≥140/≥90.99</td>
<td>≤102 (≤40)</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139/85-89</td>
<td>Optimal: &lt;120/≤80</td>
</tr>
<tr>
<td>Stages 1, 2, 3</td>
<td>1≤88 [35]</td>
<td>≤88 (≤35)</td>
</tr>
<tr>
<td>Central obesity (waist circumference in cm [inches])</td>
<td>&gt;20</td>
<td>12-20</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;30</td>
<td>20-30</td>
</tr>
</tbody>
</table>

*See Table IV for ATP III recommendations.

A few methods have been developed to quantify remnants and small, dense LDL. These are not currently standardized as required for clinical practice but they are likely to be fully developed in the near future. However, the total amount of small, dense LDL and remnant cholesterol can be estimated by use of accepted methods of β-estimation or β-quantitation in which total cholesterol and HDL cholesterol are measured. Accordingly, for plasma triglycerides ranging between 200 to 499 mg/dL, the difference between total cholesterol and HDL cholesterol levels is the sum of all atherogenic lipoprotein cholesterol. This difference is designated

Small, dense LDL and CHD risk. Normally VLDL is a metabolic precursor of LDL. However, when VLDL remnants accumulate in blood, fewer lipoproteins are converted to LDL. This leads to lower LDL cholesterol levels. In addition, remnants become precursors of small, dense LDL through the action of hepatic lipase. The enzyme seemingly mediates the formation of small, dense LDL. There is an inverse relationship between LDL size and hepatic lipase levels. Once formed, dense LDL is more prone to oxidative damage than is buoyant LDL. Oxidized LDL is taken up by macrophages once the lipoproteins bind to “scavenger” receptors located on the surface of macrophages. Excess influx of these lipoproteins into macrophages also can lead to foam cell formation and local inflammation. These processes facilitate plaque formation.
“non–HDL cholesterol,” and it represents VLDL plus IDL plus LDL cholesterol. In cases of moderate elevations of plasma triglyceride such as the metabolic syndrome, non–HDL cholesterol levels are probably superior to LDL cholesterol levels for risk assessment. This, of course, remains to be proved with certainty.

**Low levels of HDL and CHD risk.** Reduced levels of HDL cholesterol impart a risk for CHD independently of LDL and triglyceride levels. The risk is increased by the presence of high levels of LDL or increased plasma triglycerides. Therefore low HDL can be an independent risk factor for CHD or it can worsen the risk in the presence of other risk factors. Assmann et al9 have shown that low HDL cholesterol is associated with 2 different risk categories. First, isolated low HDL has a relatively low risk for CHD. In the Prospective Cardiovascular Munster Study (PROCAM) population,9 isolated low HDL represents the 1st decile of the HDL cholesterol distribution. This fraction of the population includes subjects who have a low HDL cholesterol level as the only risk for CHD. The second risk category is low HDL in association with a cluster of risk factors. This subgroup is represented by the upper 10th decile of the HDL distribution for the PROCAM population. In this subgroup, low HDL has a risk that is increased by 2- to 3-fold above the risk for isolated low HDL. The data suggest that a low HDL cholesterol level in association with other risk factors for CHD imparts a greater than does isolated low HDL alone; therefore low HDL levels should be treated to reduce CHD risk.

A low level of HDL appears to be a persistent lipoprotein phenotype of the metabolic syndrome (Table I). In contrast, serum triglyceride varies widely; it has a greater coefficient of physiologic variation than does HDL. A low level of HDL cholesterol has been previously defined as ≤35 mg/dL. Recently, the definition was extended to HDL ≤40 mg/dL. In the PROCAM study, the incidence of CHD was 3 times greater in men who had HDL cholesterol levels ≤40 mg/dL compared with men with HDL cholesterol levels ≥49 mg/dL. Still, low HDL cholesterol and the clustering of other risk factors were prevalent in men with HDL cholesterol levels ≤35 mg/dL. The risk for CHD also was increased significantly. In addition, there are sex differences in levels of HDL cholesterol that should be considered in the definition of a low HDL. An indication of an abnormal HDL in women may be ≤50 mg/dL. This area is another that needs more investigation.

Low levels of HDL cholesterol result from increased levels of hepatic lipase,11 decreased production of apolipoprotein A-I,12 deficiency of apolipoprotein C-III,13 deficiency of the ABC-1 cassette,14 reduced levels of lipoprotein lipase, or increased numbers of VLDL particles that lead to enhanced activity of cholesterol ester transfer protein. In the metabolic syndrome, it is very likely that increased hepatic lipase and reduced synthesis of apolipoprotein A-I account for persistently low levels of HDL cholesterol.

The role of low HDL in atherosclerosis is not well understood. Normally, HDL has a function in the cellular efflux of cholesterol that is part of its function in “reverse cholesterol transport.” HDL also may play a significant role as an antioxidant and as an anti-inflammatory agent. If these functions pertain to HDL, a low HDL in the metabolic syndrome could be proatherogenic. Few HDL particles would be available for reverse cholesterol transport or for protection against oxidative damage of remnants and LDL lipoproteins.

**Hypertension and CHD risk**

Subjects with the metabolic syndrome are likely to have high blood pressure (BP) (Table I). A desirable BP is ≤120/<80 mm Hg. That this is a desirable range is partially supported by the results of the Hypertension Optimal Treatment (HOT) Study,16 which involved 18,000 subjects with hypertension who were treated to 3 targets of diastolic BP. The study showed that subjects reaching a goal of 83 mm Hg had the lowest incidence of cardiovascular events. Among patients with diabetes mellitus recruited for the study, it was shown that those attaining a diastolic BP <80 mm Hg had a 51% reduction in cardiovascular events.

A number of epidemiologic studies show that hypertension is associated with risk factors such as dyslipidemia and central obesity. It is still unclear how excess body weight leads to hypertension. However, hypertension and dyslipidemia are associated with stroke or transient ischemic attacks, and hypertension in the presence of diabetes mellitus leads to nephropathy. In individuals ≥60 years old, hypertension is associated with peripheral arterial disease. Moreover, a combination of hypertension and smoking leads to heart disease.

It is possible that elevated BP may be responsible for organ damage. Hypertension in the presence of dyslipidemia most likely leads to increased filtration of small lipoproteins across the capillaries. If so, this would result in an increased concentration of atherogenic lipoproteins in the interstitial fluid. In turn, this would lead to increased deposition of cholesterol in the artery wall and in macrophages. However, more work needs to be done to determine the mechanisms of atherosclerosis during hypertension.

**Central obesity and excess fat weight**

Excess fat weight is a requirement for the metabolic syndrome (Table I). Abdominal obesity precipitates dyslipidemia, hypertension, or high fasting blood sugar levels. The current guidelines on obesity1 define overweight as a BMI of 25 to 29.9 kg/m² and obesity as a BMI ≥30 kg/m². However, a criterion for fat weight based on percent of total weight has been included in
the current review as an index of the metabolic syndrome (Table I). BMI is a practical tool for assessment of fat weight, but it must be recognized that this instrument has limitations. A direct assessment of fat weight may be a more sensitive indicator of excess fat weight than is BMI, particularly in populations at high risk for CHD.

Waist circumference is used to estimate abdominal fat content, and a large circumference is typical of the metabolic syndrome (Table I). Waist circumference correlates with abdominal fat content (visceral and subcutaneous). This type of fat distribution is associated with a high risk for CHD. However, more sensitive indicators of central obesity than a waist circumference measure are still needed; biochemical markers of increased abdominal obesity would be preferable to the measure of waist circumference.

Prevalence of risk factors for CHD in overweight and obese subjects

The National Heart, Lung, and Blood Institute and the World Health Organization have introduced a weight classification for BMI. According to their classification, a normal weight range is a BMI of 18.5 to 24.9 kg/m², overweight ranges from 25.0 to 29.9, and obesity is a BMI ≥30 kg/m². There are 3 classes of obesity—class 1: 30.0 to 34.9, class 2: 35.0 to 39.9, and class 3 > 40 kg/m². Recently, Must et al. used data from the third National Health and Nutrition Examination Survey (NHANES III) to determine the prevalence of comorbidities associated with obesity (Table II). These authors observed a strong association between excess fat and type 2 diabetes mellitus or hypertension. The prevalence ratios of these comorbidities are noteworthy, given that overweight is prevalent in the United States. The study also showed that the frequency of having 2 or more diseases increased with increasing weight, regardless of sex or ethnicity.

CHD risk imparted by the metabolic syndrome

Algorithms for estimation of CHD risk have been developed from longitudinal trials such as the Framingham Heart Study and the PROCAM study. The Framingham risk factor assessment includes age, total or LDL cholesterol, HDL cholesterol, BP, and the presence or absence of type 2 diabetes mellitus or smoking. CHD risk estimation is sex specific. The PROCAM algorithm includes age, LDL cholesterol, HDL cholesterol, triglycerides, smoking, type 2 diabetes mellitus, and family history of CHD. The equation is predictive of CHD risk in men.

An estimate of the risk for CHD can be made by use of the algorithm developed from the Framingham Heart Study. To estimate CHD risk, a score sheet has been developed; this score sheet was used in the current review to construct a plot of 10-year risk for CHD for the “metabolic syndrome” in men at an age range of 30 to 74 years (Figure 1). The score was calculated for an LDL in the range of 100 to 159 mg/dL, an HDL <40 mg/dL, a BP ranging from 140 to 159/90 to 99 mm Hg, either a positive or negative history of smoking, and no history of type 2 diabetes mellitus. These criteria are typical of the metabolic syndrome (Table I). The risk for CHD for an individual with the metabolic syndrome is compared with the low risk for CHD calculated for a person of the same age who has a BP in the range of <120/80 mm Hg, an LDL cholesterol in the range of 100 to 129 mg/dL, and an HDL cholesterol >45 mg/dL for men or 55 mg/dL for women, as detailed by Wilson et al. The 10-year risk associated with aging alone ranges from 3% to 14% over a 44-year life span (low-risk profile, Figure 1, curve C). In contrast, the 10-year risk for CHD for the metabolic syndrome starts at 11% to 47% for smokers over the same life span (Figure 1, curve A). That is, the risk is greatly increased because smoking contributes significantly to overall risk. If smoking is not part of the risk score for the metabolic syndrome, then the risk is still much higher than is the low-risk profile (Figure 1, curve B).

Recently, ATP III introduced a new version of the Framingham score sheet for risk assessment. With use of the new score table, risk for the metabolic syndrome differs in absolute value compared with the original Framingham score table (Figure 1, B, curves B vs D). Curve D represents the estimated risk for the metabolic syndrome according to the revised Framingham score.
The difference between curves B and D results from the subtraction of the baseline risk for aging alone (Figure 1, B). That is, the estimated 10-year risk is adjusted for baseline risk associated with aging.

Both versions of the Framingham score sheets for risk assessment of the metabolic syndrome are limited because neither algorithm includes fat weight, triglycerides, or glucose in the scoring system. Similarly, the PROCAM risk assessment is not directly applicable to the metabolic syndrome because it does not take into account fat weight or glucose. In addition, neither algorithm (Framingham or PROCAM) weighs the clustering of 2 or more risk factors. Grundy et al21 have addressed this limitation in a recent review, and Wilson et al22 recently examined the “clustering of metabolic factors” and CHD risk (Table III). These authors defined metabolic risk factors in terms of quintiles for their distribution. The factors included the lowest sex-specific quintile for HDL cholesterol and the highest quintiles for BMI, systolic BP, triglycerides, glucose, and serum cholesterol. Data were based on a prospective community sample of 2569 women and 2406 men, ranging from 18 to 74 years of age. Clusters of 3 or more risk factors were associated with 2.39 and 5.90 times greater CHD risk in men and women, respectively (Table III). In the same study it was noted that an increase of 2.25 kg in weight over a 16-year period markedly increased the risk factor sum in men and women.

Isomma et al23 have also examined the morbidity and mortality associated with the metabolic syndrome in persons in Finland. The study showed that cardiovascular mortality was greatly increased in individuals with
the metabolic syndrome (12.0% vs 2.2%, \( P < .001 \)). The single most important marker of risk in those in the Finnish population who have the metabolic syndrome was microalbuminuria (relative risk 2.8, \( P = .002 \)). Clearly, more work is needed to define an algorithm for CHD risk assessment of the metabolic syndrome that can be used in a clinical setting. The algorithm should be sex and age specific and should be extended to children by at least including coefficients for patterns of BMI, HDL cholesterol levels, or other risk factors within families.

### Putative role of nonesterified fatty acids in the metabolic syndrome

An excess fat weight is associated with increased release of nonesterified fatty acids (NEFAs) from the adipose tissue.\(^4\) Increased serum levels of NEFAs are likely an integral component of the metabolic syndrome. Still, the association of NEFAs with risk for CHD is not well documented. In recent years more attention has been given to the role of NEFAs in the etiology of type 2 diabetes mellitus. A view has emerged that dysregulation of NEFA release by the adipose tissue, particularly abdominal adipose tissue, induces steatosis (Figure 2). The hypothesis is that with increasing fat weight abdominal adipose tissue becomes less sensitive to the regulation of NEFA release by insulin. This insulin insensitivity leads to increased serum levels of NEFA and increased uptake of NEFA by the liver, skeletal muscle, and pancreas (Figure 2). Normally NEFAs entering these organs are channeled to the mitochondria for oxidation. However, it has become apparent that in type 2 diabetes mellitus and perhaps in the prediabetic state NEFAs are channeled to triglyceride synthesis rather than to oxidation. The result is an increased concentration of triglyceride within organs that have low capacity for storage or release of triglyceride. The accumulation of triglyceride leads to steatosis (Figure 2). Evidence supporting this contention has been obtained in animal studies\(^23\) but its relevance to human disease remains to be demonstrated. However, if NEFA dysregulation is a “typical” feature of the metabolic syndrome, it will be necessary to determine its relative contribution to the clustering of metabolic factors. In addition, appropriate therapies targeted to regulation of NEFA metabolism will also be necessary.

### Table III. Age-adjusted risk factor sum and 16-year CHD risk\(^{22}\)

<table>
<thead>
<tr>
<th>Risk factor sum</th>
<th>Prevalence (%)</th>
<th>CHD events (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n = 2406)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33</td>
<td>18</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>27</td>
<td>1.54 [1.01-2.35]</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>25</td>
<td>2.02 [1.31-3.12]</td>
</tr>
<tr>
<td>≥3</td>
<td>18</td>
<td>30</td>
<td>2.39 [1.56-3.66]</td>
</tr>
<tr>
<td><strong>Women (n = 2569)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32</td>
<td>9</td>
<td>1 [referent]</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>13</td>
<td>1.21 [0.45-3.23]</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>23</td>
<td>2.89 [1.17-7.13]</td>
</tr>
<tr>
<td>≥3</td>
<td>19</td>
<td>56</td>
<td>5.90 [2.54-13.73]</td>
</tr>
</tbody>
</table>

Figure 2

**Excess Truncal Fat Weight**

**Increased Nonesterified Fatty Acid Release from Abdominal Adipose Tissue**

**Increased Steatosis:**
1. Pancreas
2. Muscle
3. Liver
4. Kidney

Metabolic scheme showing the relationship of truncal fat to steatosis. Increased abdominal adipose tissue leads to increased influx of nonesterified fatty acid (NEFA) into pancreas, muscle, liver, and kidney. Accumulation of triglyceride occurs, most likely as a result of reduced NEFA oxidation. Steatosis causes beta cell dysfunction in the pancreas and abnormal glucose metabolism in liver, muscle, and kidney.
Summary of ATP III guidelines for the treatment of the metabolic syndrome

ATP III\(^3\) included the metabolic syndrome as a secondary target of risk reduction therapy along with treatment of LDL cholesterol. The goal of treatment for LDL cholesterol varies according to the severity of risk factors for CHD. Table IV summarizes the ATP III recommendations on treatment for the metabolic syndrome. Persons with the metabolic syndrome are considered candidates for intensified therapeutic lifestyle changes. The centerpiece of treatment is LDL cholesterol. The goals of LDL treatment depend on the severity of risk (Table IV). Accordingly, subjects with established CHD or CHD equivalence may begin drug therapy in conjunction with lifestyle modification. The second priority of treatment is weight reduction along with institution of moderate physical activity (Table IV); nonlipid risk factors such as hypertension should show improvement and should be monitored progressively during treatment. Finally, treatment of elevated triglycerides and low HDL can be addressed to improve the lipoprotein profile as needed. ATP III introduced a goal of cholesterol treatment for subjects with triglycerides ranging between 200 and 499 mg/dL (Table IV). The goal of treatment is based on non–HDL cholesterol levels for each of the 3 categories of CHD risk (Table IV). Non–HDL cholesterol is the sum of VLDL + IDL + LDL cholesterol. As triglycerides increase, levels of VLDL and IDL cholesterol increase. These lipoproteins are as atherogenic as is LDL; for this reason non–HDL cholesterol is a reasonable index of all atherogenic lipoproteins.

The goal of treatment for low HDL was not defined in ATP III because data on which to base recommendations were insufficient. However, low HDL cholesterol is a risk factor for CHD, especially in association with other risk factors, as was demonstrated in the Framingham and the PROCAM studies. Treatment options include lifestyle modification and drugs such as niacin. Treatment of isolated low HDL or low HDL in the presence of the metabolic syndrome requires individual assessment of the patient and his or her clinical history. However, ATP III has recommended therapeutic lifestyle changes in persons whose levels of triglyceride are elevated and whose HDL cholesterol is low.

Prioritizing risk factor management during treatment of the metabolic syndrome

Because persons with the metabolic syndrome have a cluster of risk factors, it is interesting to speculate about how the treatment of these risk factors should be prioritized. For example, for individuals with a 10-year risk of >20%, instituting therapeutic lifestyle modification and pharmacotherapy for dyslipidemia may be the first priority. The target of treatment for dyslipidemia may be non–HDL cholesterol because most persons with the metabolic syndrome have serum triglycerides between 200 and 499 mg/dL. The goal of treatment for non–HDL cholesterol is to achieve a level of <130 mg/dL. For patients with a 10-year risk ranging from 10% to 20%, the goal of treating non–HDL cholesterol is to achieve a level <160 mg/dL. How best to achieve these goals is another question to consider. Physical activity and diet modification are indicated for long-term treatment of the metabolic syndrome. However, therapeutic lifestyle changes require patient education and commitment, and the treatment will probably require a stepwise approach. Emphasis on physical

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**Table IV. ATP III guidelines for treatment of the metabolic syndrome**

<table>
<thead>
<tr>
<th>Goal</th>
<th>T}reat LDL cholesterol first</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD* and CHD risk equivalent (10-y risk for CHD &gt;20%)</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Multiple (2+) risk factors and 10-y risk ≤20%</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Institute weight control</td>
<td>-10% from baseline‡§</td>
</tr>
<tr>
<td>Institute physical activity</td>
<td>30 to 45 min/d for 3 to 5 d/wk§</td>
</tr>
<tr>
<td>Monitor treatment of hypertension</td>
<td>&lt;130/85 mm Hg</td>
</tr>
<tr>
<td>Treat elevated triglycerides and low HDL cholesterol†</td>
<td>High CHD risk: &lt;130 mg/dL</td>
</tr>
<tr>
<td>≥200 mg/dL and ≤499 mg/dL</td>
<td>Intermediate CHD risk: &lt;160 mg/dL</td>
</tr>
<tr>
<td>Goal of non–HDL cholesterol for patients with triglycerides</td>
<td>Low CHD risk: &lt;190 mg/dL</td>
</tr>
</tbody>
</table>

*CHD: ATP III recommends monitoring compliance to aspirin intake by patients with CHD.
†HDL cholesterol: ATP III does not specify goals of treatment for HDL cholesterol because data available at the time of the release of ATP III were insufficient to specify a goal of therapy.
‡If the weight goal is achieved, additional weight loss can be attempted if indicated after clinical evaluation.
§Recommendations from Clinical Guidelines for Overweight and Obesity¹ and cited in the ATP III executive summary.³

(Non–HDL cholesterol = VLDL + IDL + LDL cholesterol.)
activity may be a reasonable first step. Physical activity should promote a gradual weight loss; it also will likely have an effect on serum triglycerides, HDL cholesterol, and glucose. Pharmacotherapy of dyslipidemia is also indicated in this high-risk group of subjects. Statins are probably more appropriate than are bile acid sequestrants for this patient population because the latter increase hepatic secretion of VLDL and are likely to increase the serum triglyceride level. Also, statins lower LDL cholesterol and its precursors effectively. Most statins produce a modest increase in HDL cholesterol; however, statins are specific for LDL reduction as the main mechanism of action. Therefore it is likely that the preferred drug treatment may be a combination of a statin and nicotinic acid or fibrate, in contrast to very high doses of statins. Careful assessment of the patient is required before a physician institutes polypharmacy and decides the particular drug combinations to be used. Lipid specialists should probably institute treatment and determine the precise titration of drug regimens.

The rationale for polypharmacy as opposed to monotherapy is to target the metabolic pathways affected by excess fat weight. Nicotinic acid may be considered because it reduces NEFA release from adipose tissue; it reduces hepatic secretion of VLDL and increases HDL better than do the hypolipidemic drugs currently available. The immediate-release and extended-release forms of the drug seemingly have a relatively safe profile when used in combination with statins. The concern with this drug is its potential for increasing basal glucose levels. However, low doses of niacin can be considered for treatment. Fibrates effectively reduce triglycerides and have other highly desirable mechanisms of action that include regulating the expression of genes such as lipoprotein lipase and apolipoprotein C-III and regulating fatty acid oxidation. Fibrate monotherapy has been shown to reduce the risk of CHD in persons whose characteristics fit the criteria of the metabolic syndrome. Unfortunately, fibrates in combination with statins require that patients be carefully monitored for possible myositis.

For patients with a low 10-year risk, therapeutic lifestyle modification may be the first indication, and the target of treatment may be to reduce waist circumference. Treatment of metabolic abnormalities in these patients may be prioritized according to the clinical presentation of the individual. However, the lipoprotein phenotype should also be a focus of treatment, and the goal of treatment is a non–HDL cholesterol level <190 mg/dL.

Conclusion

This review has summarized typical features of the metabolic syndrome and presented estimates regarding the relative risk for CHD in persons with this syndrome. It is important to note that systematic work is still required to develop algorithms specific for risk assessment with respect to the metabolic syndrome. Wilson et al2 have made a step in this direction by developing an algorithm that includes traditional risk factors and BMI, insulin, and glucose levels, but algorithms specific to the metabolic syndrome are still needed. These new risk equations must also be tested for specificity and sensitivity in a variety of populations with the metabolic syndrome. Studies that measure fat weight by dual-energy x-ray absorptiometry or other direct methods of fat weight quantitation are preferred to those that use BMI as an alternative measure of fat weight.

This review has also presented evidence that indicates the prevalence of the metabolic syndrome; this evidence points to new areas that require investigation because they may be important to the etiology of the syndrome and the rationale for its treatment. A summary of the ATP III recommendations concerning the diagnosis and management of the metabolic syndrome has been given, and the ranking of risk factors in the treatment of this condition have been discussed. It is hoped that this brief review will help physicians to advance their understanding of the metabolic syndrome and assist them in their assessment of therapeutic strategies for patients with this complex disorder.

References

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