Chapter 2
The Metabolic Syndrome

Matthew J. Sorrentino

Keywords  Waist circumference • Abdominal obesity • Impaired fasting glucose • HDL-cholesterol • Triglycerides

Metabolic syndrome is the designation given to a clustering of interrelated metabolic factors that increase the future risk of the development of diabetes mellitus and cardiovascular disease. Intraabdominal or visceral obesity appears to be the underlying component of the syndrome that leads to the development of an atherogenic dyslipidemia, endothelial dysfunction and hypertension, insulin resistance, a prothrombotic, and a proinflammatory state. The risk attributed to the metabolic syndrome is likely due to the sum of its individual components. As such, the designation of the metabolic syndrome is an easy and convenient way of characterizing individuals who may be at increased risk for developing diabetes and cardiovascular disease.

Definition of the Metabolic Syndrome

The National Cholesterol Educational Program (NCEP) Adult Treatment Panel III (ATP III) recognized the metabolic syndrome as a secondary target of risk-reduction therapy in the guidelines published in 2001 [1]. The ATP III suggested that a diagnosis of the metabolic syndrome can be made when three or more of five designated risk factors are present (Table 2.1). The American Diabetes Association (ADA) subsequently redefined impaired fasting glucose (IFG) as a fasting glucose from 100 to
125 mg/dl [2] and an elevated fasting glucose of ≥100 mg/dl is now an accepted criteria for the metabolic syndrome [3].

The International Diabetes Federation (IDF) produced a new set of criteria for a worldwide definition of the metabolic syndrome recognizing that the obesity epidemic is one of the main drivers of the high prevalence of this syndrome [4]. The IDF definition differs from the ATP III definition in that it requires the presence of central obesity for the diagnosis of the metabolic syndrome because it is highly correlated with insulin resistance. The IDF recommended waist circumference measurements of central obesity with gender and ethnic-group specific cut-points. The additional components of the IDF definition are otherwise the same as the ATP III definition.

Components of the Metabolic Syndrome

**Abdominal Obesity**

In 1998, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) released a clinical guideline on the identification, evaluation, and treatment of overweight and obese adults and proposed a classification of six body mass index (BMI) categories and two waist circumference categories (normal or high) (Table 2.2) [5]. The waist circumference cutoffs were taken from a study of over 2,000 individuals in North Glasgow that corresponded to a BMI of 30 or above at the point in which symptoms of breathlessness, arthritis, and increased health risk occurred [6]. The NCEP adopted these cutoffs for the definition of metabolic syndrome.

Visceral or intraabdominal adiposity is more metabolically active than subcutaneous fat accumulation. In addition, visceral adiposity correlates with markers of

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**Table 2.1** Clinical factors that define the metabolic syndrome [1]

<table>
<thead>
<tr>
<th>Component</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>1. Abdominal obesity (waist circumference)</td>
<td></td>
</tr>
<tr>
<td>a. Men</td>
<td>&gt;102 cm (&gt;40 in.)</td>
</tr>
<tr>
<td>b. Women</td>
<td>&gt;88 cm (&gt;35 in.)</td>
</tr>
<tr>
<td>2. Triglycerides</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>3. High-density lipoprotein cholesterol (HDL)</td>
<td></td>
</tr>
<tr>
<td>a. Men</td>
<td>&lt;40 mg/dl</td>
</tr>
<tr>
<td>b. Women</td>
<td>&lt;50 mg/dl</td>
</tr>
<tr>
<td>4. Blood pressure</td>
<td>≥130/≥85 mmHg</td>
</tr>
<tr>
<td>5. Fasting glucose</td>
<td>≥110 mg/dl</td>
</tr>
</tbody>
</table>

Any three of the five risk factors designate the metabolic syndrome

*American Diabetes Association [2] definition of impaired fasting glucose: fasting glucose 100 mg/dl or greater, accepted as criteria for metabolic syndrome*
dyslipidemia, hypertension, insulin resistance, and inflammation. Waist circumference correlates better than BMI or waist-to-hip ratio (WHR) to the quantity of adipose tissue in the abdominal cavity as measured by CT scanning [7]. In the Nurses Health Study, a higher waist circumference was independently associated with an increased risk of coronary heart disease (CHD) [8]. A waist circumference of 30 cm was associated with more than a twofold higher coronary risk and a waist circumference of 38 cm was associated with a greater than threefold risk. Nearly 15,000 subjects in the Third National Health and Nutrition Examination Survey (NHANES) were evaluated to determine if the NIH waist circumference cutoffs helped to identify individuals at increased health risk [9]. Within the three BMI categories of normal weight, overweight, and class I obese, individuals with high waist circumference values (men > 102 cm, women > 88 cm) were increasingly likely to have hypertension, diabetes, dyslipidemia, and the metabolic syndrome. Thus, it appears that the waist circumference cutoffs chosen for the American population are a reasonable measurement to help determine risk. Non-US populations, however, may be at increased risk at different levels of visceral obesity. The International Diabetes Federation recommends ethnic-group specific waist circumference thresholds because of emerging information on the variable relationship between waist circumference and metabolic abnormalities and has acknowledged that more research is needed to determine the optimal cutoffs [4].

**High-Density Lipoprotein Cholesterol**

A low high-density lipoprotein cholesterol (HDL-C) is a well-known independent predictor of CHD especially in women. The criteria for the metabolic syndrome uses a lower than average HDL-C as one of the major components of the syndrome. The HDL-C cutoff chosen is a value below the 50th percentile for HDL-C for the American population. Women tend to have higher HDL-C than men so the HDL threshold is higher for women. The National Health and Nutrition Surveys have

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**Table 2.2** Body mass index (BMI) and waist circumference categories – disease risk for type II diabetes, hypertension, and cardiovascular disease (adapted from [5])

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Men ≤ 102 cm</th>
<th>Women ≤ 88 cm</th>
<th>Men &gt; 102 cm</th>
<th>Women &gt; 88 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5–24.9</td>
<td>High</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>Increased</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>Obesity, class I</td>
<td>30.0–34.9</td>
<td>High</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0–39.9</td>
<td>Very high</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>Class III (extreme obesity)</td>
<td>≥40</td>
<td>Extremely high</td>
<td>Extremely high</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>
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tracked the trends in lipid levels for the USA over the last four decades. From the 1999–2002 survey, the average HDL-C for men ≥20 years of age in this country was 45.9 mg/dl and the average HDL-C for women was 56.2 mg/dl [10]. From 1988 to the present, there has been a steady decline in total and low-density lipoprotein cholesterol (LDL-C) but substantially no change in the average HDL-C levels. The HDL-C criteria used for the metabolic syndrome are an HDL-C < 40 mg/dl for men and an HDL-C < 50 mg/dl for women.

**Triglycerides**

The NCEP ATP III redefined fasting serum triglycerides and classified triglycerides values less than 150 mg/dl as normal (Table 2.3). Elevated serum triglycerides are a common lipid abnormality in the metabolic syndrome. A high triglyceride value is associated with smaller and denser LDL particles that are thought to be more atherogenic. Triglyceride levels and the ratio of triglycerides to HDL have correlated well with the presence of insulin resistance. A triglyceride/HDL ratio of 3.5 or greater predicts insulin resistance as well as the criteria for metabolic syndrome [11].

There is emerging evidence that nonfasting serum triglyceride levels are associated with an increased risk of atherosclerosis. Two recent large cohort studies found that nonfasting triglycerides were a significant risk factor for CHD and death in men and women and were a more robust indicator of risk than fasting levels [12, 13]. These data suggested that a postprandial triglyceride tolerance test can be developed with measurement of triglyceride values 2–4 h after a standard meal. A postprandial cutoff value for triglycerides has not been established although in the Danish study there appeared to be a jump in risk in individuals with a postprandial triglyceride value greater than 5 mmol/L (442.5 mg/dl) [13]. Finally, there is now evidence to suggest that patients with insulin resistance accumulate triglycerides in myocardial cells and that this is associated with diastolic abnormalities and may be an early marker for cardiac dysfunction [14].

**Elevated Blood Pressure**

The NCEP ATP III definition of metabolic syndrome uses a blood pressure of 130/85 or greater as one of the criteria for the syndrome. Although this cutoff is somewhat arbitrary, there is a clear increased prevalence of cardiovascular events

<table>
<thead>
<tr>
<th>Table 2.3 Classification of serum triglycerides (from [1])</th>
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<tbody>
<tr>
<td>Normal triglycerides</td>
</tr>
<tr>
<td>Borderline high triglycerides</td>
</tr>
<tr>
<td>High triglycerides</td>
</tr>
<tr>
<td>Very high triglycerides</td>
</tr>
</tbody>
</table>
associated with increasing blood pressure that is continuous and independent of other risk factors. For individuals aged 40–70 years, each incremental increase in 20 mmHg systolic or 10 mmHg diastolic blood pressure doubles cardiovascular risk across the entire blood pressure range beginning at 115/75 mmHg [15].

Hypertension is the most common chronic health condition associated with obesity. Insulin resistance has long been linked to essential hypertension [16] and studies suggest that the presence of hyperinsulinemia predicts the development of hypertension [17]. Visceral adiposity may contribute to the development of hypertension by releasing free fatty acids and inflammatory mediators into the circulation and change levels of adipocytokines that can lead to endothelial dysfunction. Individuals with high triglycerides and a low HDL-C and increased blood pressure are at significantly higher cardiovascular risk than those with normal pressure [18].

**Impaired Fasting Glucose**

The American Diabetes Association (ADA) has defined IFG as fasting plasma glucose levels of 100–125 mg/dl [2]. Patients with IFG are referred to as having “pre-diabetes” since they have a high risk of developing diabetes. IFG is also a risk factor for cardiovascular disease. Since this definition of IFG was proposed after the NCEP ATPIII definition of metabolic syndrome was formulated, the cutoff for fasting glucose is different in the two definitions. The current ADA definition is generally accepted as the cutoff for the metabolic syndrome designation as well.

Impaired glucose tolerance (IGT) can also be used to identify individuals with insulin resistance. IGT patients are defined as individuals who have 2-h values in the oral glucose tolerance test of ≥140 mg/dl but less than 200 mg/dl [17]. Many patients with IGT will have normal fasting glucose values and normal glycated hemoglobin levels.

A patient’s lipoprotein level may also predict insulin resistance. The triglyceride/HDL ratio has been shown to predict cardiovascular events and is associated with small, dense LDL particles. A triglyceride/HDL ratio of 3.5 or higher can identify insulin resistant individuals with a sensitivity and specificity similar to the metabolic syndrome criteria [11]. Of note, this ratio did not correlate with insulin resistance in an African American population [19]. Patients with a high triglyceride/HDL ratio and normal fasting plasma glucose values may be a group to consider further evaluation with an oral glucose tolerance test.

**Prothrombotic State**

Patients identified with the metabolic syndrome exhibit a pattern of coagulation factors that are prothrombotic. Fibrinolysis is induced by plasmin which is formed from plasminogen by tissue plasminogen activators and neutralized by plasminogen
activator inhibitor-1 (PAI-1). Increased concentrations of insulin and proinsulin in the plasma can increase plasma PAI-1 levels and is associated with decreased fibrinolytic activity in the blood [20]. The metabolic syndrome and insulin resistance has also been associated with increased coagulation factors VII–IX, von Willebrand factor, and blood viscosity [21]. The combination of all these findings may increase the potential for increased cardiovascular events.

Proinflammatory State

Visceral adiposity is highly metabolically active and produces a large number of inflammatory molecules either from the adipocytes or associated macrophages. Tumor necrosis factor-alpha (TNF-α) and Interleukin-6 are two inflammatory molecules that are increased in patients with central obesity and metabolic syndrome. These factors circulate to the liver and stimulate the production of C-reactive protein (CRP). CRP levels are directly associated with the number of metabolic syndrome factors [22]. Inflammation is thought to play a significant role in the progression of coronary atherosclerosis and plaque rupture and may be a marker for individuals at increased CVD risk.

Other Metabolic Abnormalities

The metabolic syndrome is a clustering of multiple factors that together increase the risk of developing diabetes or cardiovascular disease. Because it is not known if there is an underlying factor that ties all of these risk markers together, the syndrome was first labeled as syndrome x, where x is the unknown. It is likely that visceral obesity may be the underlying source of many of the metabolic parameters described in this syndrome. Table 2.4 lists many of the metabolic abnormalities that are thought to cluster in individuals with the metabolic syndrome.

How to Diagnose the Metabolic Syndrome

The metabolic syndrome is diagnosed when a patient has three or more of the components of the metabolic syndrome as defined by the NCEP panel. Of note, a patient would be considered to have a component of the metabolic syndrome even if one of the factors is treated and normalized. The definition of metabolic syndrome includes a fasting glucose of ≥110 mg/dl (or we can use the newer ADA definition of a fasting glucose ≥100 mg/dl). This definition includes patients with a fasting glucose
level in the diabetic range and diabetic patients can be designated as having metabolic syndrome in addition to diabetes. Metabolic syndrome can then identify a diabetic patient with additional multiple cardiovascular risk factors and therefore at higher cardiovascular risk.

Plasma lipid levels should be measured after a 9–12 h fast. This will eliminate chylomicrons from the circulation and give a fasting triglyceride value that can be used to calculate an LDL-C level. For some patients, a nonfasting triglyceride value may give additional prognostic information especially if it is greater than 400 mg/dl. Waist circumference is recommended as a measurement of visceral adiposity and correlates with the risk factors of metabolic syndrome better than BMI. Waist circumference can be measured by locating the top of the right iliac crest and placing a tape measure in the horizontal plane around the abdomen making the measurement at end expiration.

Table 2.4 Clustering of factors associated with the metabolic syndrome

<table>
<thead>
<tr>
<th>1. Prothrombotic factors</th>
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<tbody>
<tr>
<td>a. Coagulation factors VII–IX</td>
</tr>
<tr>
<td>b. von Willebrand factor</td>
</tr>
<tr>
<td>c. Fibrinogen</td>
</tr>
<tr>
<td>d. Plasminogen activator inhibitor-1 (PAI-1)</td>
</tr>
<tr>
<td>e. Increased blood viscosity</td>
</tr>
<tr>
<td>2. Inflammatory factors</td>
</tr>
<tr>
<td>a. Hs-CRP</td>
</tr>
<tr>
<td>b. Interleukins</td>
</tr>
<tr>
<td>c. High WBC</td>
</tr>
<tr>
<td>d. Tumor necrosis factor-alpha (TNF-α)</td>
</tr>
<tr>
<td>3. Renal factors</td>
</tr>
<tr>
<td>a. Microalbuminuria</td>
</tr>
<tr>
<td>b. Hyperuricemia</td>
</tr>
<tr>
<td>4. Adipocytokines</td>
</tr>
<tr>
<td>a. High leptin levels with leptin resistance</td>
</tr>
<tr>
<td>b. Decreased adiponectin levels</td>
</tr>
<tr>
<td>5. Lipoproteins</td>
</tr>
<tr>
<td>a. Increased VLDL – Triglycerides</td>
</tr>
<tr>
<td>b. Low HDL-C</td>
</tr>
<tr>
<td>c. Increased small, dense LDL and oxidized LDL</td>
</tr>
<tr>
<td>d. Increased free fatty acids</td>
</tr>
<tr>
<td>6. Endothelial dysfunction</td>
</tr>
<tr>
<td>a. Decreased endothelial-dependent relaxation</td>
</tr>
<tr>
<td>b. Increased adhesion molecules</td>
</tr>
<tr>
<td>c. Raised blood pressure</td>
</tr>
<tr>
<td>7. Insulin resistance</td>
</tr>
<tr>
<td>a. Hyperinsulinemia</td>
</tr>
<tr>
<td>b. Hyperglycemia</td>
</tr>
</tbody>
</table>
How to Use Metabolic Syndrome in Risk Assessment

The standard method for calculating an individual’s cardiovascular risk is to count traditional independent risk factors and use an algorithm based on large epidemiological studies such as the Framingham study. This analysis can predict a 10-year cardiovascular risk with an accuracy of approximately 75% [23]. Many individuals with two or more risk factors will fall into the intermediate risk group defined as a yearly cardiovascular risk between 1 and 2%. The presence of metabolic syndrome can modify this risk prediction by adding additional risk factors to the total number of factors. This may have treatment implications when considering treatment goals. As a general rule, the more risk factors that are present, the higher the possibility of a cardiovascular event suggesting a more aggressive risk factor modification treatment approach.

Prevalence of the Metabolic Syndrome

Data from the Third National Health and Nutrition Survey (NHANES) gathered between 1988 and 1994 were used to determine the prevalence of the metabolic syndrome in ambulatory Americans using the ATPIII definition of metabolic syndrome [24]. The prevalence of the metabolic syndrome is about 22% for the US population. For participants aged 60–69 years of age, the prevalence is 43%. Mexican Americans have the highest prevalence of metabolic syndrome at nearly 32%. Men and women have a similar prevalence except among African Americans where women have a 57% higher prevalence than men. Using 2000 census data, it is estimated that about 47 million Americans have the metabolic syndrome. In addition to the high prevalence in Mexican Americans, American Indians have a very high prevalence of metabolic syndrome as well. The Strong Heart Study showed a 35% prevalence of metabolic syndrome in American Indians aged 45–74 years [25].

Worldwide prevalence of metabolic syndrome approaches the prevalence in the USA especially as countries adopt a Western style diet. A study based on 11 prospective European cohorts of men and women aged 30–89 years without diabetes using a World Health Organization (WHO) definition of metabolic syndrome found a 14–15% prevalence of the condition [26]. In developing countries, the prevalence of metabolic syndrome is also approaching Western numbers. A study from eastern China using NCEP criteria and ethnic-group specific waist circumference found a 12.7% prevalence of metabolic syndrome in urban males and a 10.1% prevalence in urban females [27].

The prevalence of the metabolic syndrome will likely continue to increase as the average weight of populations increase. From NHANES data, the age-adjusted prevalence of obesity in this country was 30.5% in 1999–2000 compared with 22.9% in 1988–1994 [28]. Even more alarming is the increasing prevalence of class 3 obesity (BMI ≥ 40). In 2000, 2.2% of adults in this country have class 3 obesity
with the highest prevalence among African American women at 6.0% [29]. Epidemiological data have shown a decreased mortality from CHD with approximately half of this decline attributable to reductions in major risk factors [30]. These reductions have been partially offset by increases in BMI and the increased prevalence of diabetes which is estimated to account for an increased number of deaths (8% and 10%, respectively).

The consumption of a Western style diet may have a significant role in the obesity epidemic and promote the incidence of metabolic syndrome. Dietary intake was assessed in the Atherosclerosis Risk in Communities (ARIC) study comparing a Western and prudent diet [31]. A Western diet pattern was associated with incident metabolic syndrome with meat, fried foods, and diet soda adversely associated with metabolic syndrome and dairy consumption found to be beneficial. The Framingham Heart Study has also found that the intake of at least one regular or diet soft drink per day is associated with a >50% higher incidence of the metabolic syndrome [32]. Although it seems counterintuitive that diet drinks may lead to weight gain, individuals who consume these products may have a greater preference for the intake of sweets and fats in the diet and are more likely to have a sedentary lifestyle. To address the emerging obesity epidemic in this country, the American Heart Association has recommended reductions in added sugar intake to no more than 100–150 kcal/day for most Americans [33].

**Metabolic Syndrome and Diabetes**

The metabolic syndrome can be thought of as a prediabetic state and can predict the incidence of type 2 diabetes mellitus. A study in Finnish middle-aged men indicated that individuals with the metabolic syndrome by either the WHO or NCEP definition were seven times more likely to develop diabetes during a 4-year follow-up than age-matched controls without metabolic syndrome [34]. Middle-aged individuals of different ethnicities in the Insulin Resistance Atherosclerosis Study with metabolic syndrome had a 3.4–5.4 increased risk of developing diabetes [35]. From the Framingham Offspring cohort, the odds of developing diabetes were 6.92-fold over an 8-year period similar for men and women [36]. Metabolic syndrome accounted for about 50% of the new cases of type 2 diabetes. From this study group, a simple clinical model was developed that was able to identify subjects with an elevated risk for diabetes [37]. The variables that predict type 2 diabetes include a parental history of diabetes, obesity, hypertension, low HDL-C, elevated triglycerides, and IFG. In other words, the metabolic syndrome parameters effectively predict the development of diabetes mellitus.

Metabolic syndrome can be thought of as an earlier stage in the development of insulin resistance and diabetes mellitus in many individuals. Classification of individuals with this syndrome may allow identification of those destined to become diabetic at a time 10–15 years earlier than frank hyperglycemia. Since diabetes is a known CHD risk equivalent, the presence of metabolic syndrome may give time to
begin risk-reduction therapy that may both prevent the development of diabetes and reduce cardiovascular risk.

The diagnosis of diabetes is delayed or unrecognized in many patients. The designation of metabolic syndrome may allow earlier diagnosis and treatment of diabetes. An oral glucose tolerance test can be considered in patients with metabolic syndrome who do not reach criteria for diabetes with a fasting sugar. The criteria for the diagnosis of diabetes as outlined by the American Diabetes Associations are presented in Table 2.5.

### Metabolic Syndrome and Cardiovascular Risk

Studies have consistently shown that the metabolic syndrome is associated with an increased incidence of cardiovascular disease including an increased risk for myocardial infarction and stroke as well as increased cardiovascular and all-cause death. The NCEP ATPIII metabolic syndrome criteria was applied to the NHANES III data base of over 10,000 subjects and showed that the metabolic syndrome was significantly related in a multivariate analysis to myocardial infarction [odds ratio (OR) 2.01] and stroke (OR 2.16) [38]. This association was similar for men and women. Non-Hispanic black subjects had significantly higher odds ratios compared with non-Hispanic white subjects particularly for stroke.

Other epidemiological surveys have shown similar results. In the Framingham Offspring Study of over 3,000 middle-aged adults, the metabolic syndrome age-adjusted relative risk of cardiovascular disease was 2.88 [36]. European surveys, usually using the WHO definition of metabolic syndrome, concur with these risk assessments. In the Kuopio Ischaemic Heart Disease Risk Factor Study, middle-aged men with metabolic syndrome by NCEP criteria were 2.9 times and by WHO criteria 4.2 times more likely to die of CHD after adjustment for conventional cardiovascular risk factors than those who did not fit criteria for the syndrome [39]. A report based on 11 prospective European cohort studies using a modified WHO definition of the metabolic syndrome found an increased cardiovascular mortality of 2.26 in men and 2.78 in women after adjustment for age, blood cholesterol levels, and smoking [26].

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**Table 2.5** Diagnosis of diabetes mellitus (from [2])

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms of diabetes with a casual plasma glucose ≥ 200 mg/dl</td>
<td>symptoms include polyuria, polydipsia, and unexplained weight loss</td>
</tr>
<tr>
<td>2. Fasting plasma glucose ≥ 126 mg/dl</td>
<td></td>
</tr>
<tr>
<td>3. 2-h Postload glucose ≥ 200 mg/dl during a 75 g oral glucose tolerance test</td>
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</tr>
</tbody>
</table>

The results from each method are confirmed on a different day unless definite symptoms of hyperglycemia are present.
The different definitions of the metabolic syndrome and different populations (lower- and higher-risk groups) have led to some variability in the relative risk of having the metabolic syndrome. A large meta-analysis of 37 studies with 43 cohorts and over 170,000 individuals showed that the metabolic syndrome had a relative risk of cardiovascular events and death of 1.78 [40]. This association was stronger in women (RR 2.63 vs. 1.98, p=0.09) and if the analysis used the WHO definition of metabolic syndrome. The association remained significant after adjusting for traditional risk factors (RR 1.54, 95% CI 1.32–1.79).

How does the metabolic syndrome compare with traditional risk factor analysis in predicting cardiovascular events? A prospective study of over 5,000 middle-aged men in Britain with no history of cardiovascular disease or diabetes was observed for 20 years [41]. Using the NCEP definition of metabolic syndrome, men fitting the criteria of the syndrome at baseline had a significantly higher relative risk of developing CHD (RR 1.64), stroke (RR 1.62), and diabetes (RR 3.57). The probability of having a CHD event over 20 years increased from 7.1% for individuals with no metabolic syndrome abnormalities to 20.2% in those with three of the criteria to 24.5% in those with four or five of the abnormalities. The Framingham risk score, however, was a better predictor of CHD than the number of metabolic abnormalities. In a multivariate model, metabolic syndrome provided no additional predictive value for CHD when the Framingham risk score was included in the model but it did remain strongly associated with diabetes.

This type of analysis suggests that the designation of the metabolic syndrome does not appear to confer greater CHD risk than the sum of its individual parts. A number of additional studies have also concluded that once the individual components of the metabolic syndrome are accounted for, the predictive power of the syndrome as a discrete entity disappears [42]. In other words, no additional information regarding risk is added when considering the combination of the components of the metabolic syndrome than considering the risk factors individually in a typical Framingham-type model. This has led some groups, such as the American Diabetes Association, to question the utility of using the metabolic syndrome as a risk predictor.

Designating a patient with the metabolic syndrome, however, is a convenient way of recognizing a patient who has a clustering of cardiometabolic risk factors and is at an increased risk of developing diabetes. This designation can alert both physicians and patients that an individual is at an intermediate risk level and can focus therapy goals to reduce risk. In addition, the designation of metabolic syndrome highlights factors that are not included in the traditional Framingham risk assessment tool such as visceral obesity, elevated triglycerides, and IFG. By identifying these factors, a focused treatment plan can be formulated that addresses these components. Although there are no studies that have determined if patient motivation is improved if they are diagnosed with the metabolic syndrome, increased awareness of multiple risk factors should at least alert a physician to considering a more aggressive multifactorial treatment approach for risk reduction.

The metabolic syndrome may also predict a population that is at increased risk for other diseases as well. A prospective study in Japan of over 28,000 participants
showed that the metabolic syndrome was associated with an increased risk of atrial fibrillation [43]. Microalbuminuria has been associated with the metabolic syndrome suggesting that clinically important renal dysfunction may be an important risk for patients with the syndrome especially those individuals with increased blood pressure and IFG [44]. Elderly patients with the metabolic syndrome were more likely to have cognitive impairment than those without [45]. This emerging data support the contention that the metabolic syndrome can easily identify a high-risk cohort that should be considered for more aggressive risk management.

Management of the Metabolic Syndrome

Lifestyle Modification

The NCEP ATPIII recognized the metabolic syndrome as a secondary target for risk reduction after addressing LDL-C. The NCEP recommended that first line therapy for all of the risk factors associated with the metabolic syndrome is weight reduction and increased exercise [1]. The NCEP pointed out that weight reduction and exercise can help further lower the LDL-C as well as improve all the lipid and nonlipid components of the syndrome. The American Heart Association/National Heart, Lung, and Blood Institute published a scientific statement that recommended a general outline of the therapeutic targets and goals of a lifestyle treatment program for the long-term prevention of both CVD and diabetes for patients with the metabolic syndrome [3]. These recommendations are summarized in Table 2.6.

Abdominal obesity is a major underlying cause of many of the metabolic abnormalities of the metabolic syndrome so it should be a primary target of therapy. Individuals with the metabolic syndrome should try to reduce body weight by 7–10% in the first year of treatment. Ideally, strategies should be adopted to ultimately achieve a body weight in the normal BMI category. Calorie reduction is an essential component of any weight loss plan if any significant progress is to be achieved. Restricting high caloric products (fatty foods) and avoiding highly processed foods may help further reduce weight. Whole foods should be consumed in preference to refined products. Foods that have high fructose content may contribute to a prediabetic state by contributing to tissue insulin insensitivity [46]. Patients should be counseled to reduce or avoid heavily sweetened foods including diet products trying to reduce added-sugar to no more than 100–150 kcal/d.

The carbohydrate content of a diet and their relationship to the metabolic syndrome and diabetes is still not well defined. There is some evidence to suggest that a high intake of simple sugars may increase triglycerides. Low to moderate carbohydrate diets, especially diets that have complex nonstarchy or low glycemic index carbohydrates, may reduce triglycerides in some individuals. A Mediterranean-type diet or a low fat diet can also lower triglycerides.
Exercise is an essential component of any lifestyle modification program and can augment weight loss and help maintain weight reduction. Both total body weight and intraabdominal fat is reduced with regular moderate-intensity exercise [47]. Increased duration of exercise achieves a greater reduction in body fat. In addition, exercise has positive effects on all of the components of the metabolic syndrome. Moderate regular exercise can increase HDL-C 4–18% and decrease triglycerides 4–37% [48]. LDL-C tends not to change with exercise unless accompanied by diet change and weight reduction. Exercise, likely through changes in body composition, improves insulin sensitivity and lowers blood pressure. Exercise can improve endothelial function, reduce inflammation, and improved left ventricular diastolic function [49]. Guidelines for exercise training are summarized in Table 2.7.

In addition to the metabolic benefits of exercise, regular physical activity has been associated with a reduced risk for CVD, diabetes, and total mortality. The risk of death from CHD is nearly twofold in sedentary individuals compared with those that are active [50]. The total amount of physical activity and more intense activity shows the strongest reductions in CHD risk in both women and men [51, 52]. Data from the Framingham Heart Study indicate that moderate and high physical activity levels can lead to 1.3 and 3.7 more years in total life expectancy for men, and 1.5 and 3.5 more years for women aged 50 years and older compared with those who maintain a low physical activity level [53].

<table>
<thead>
<tr>
<th>Therapeutic target/goals of therapy</th>
<th>Therapeutic recommendations</th>
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<tbody>
<tr>
<td><strong>Abdominal obesity:</strong></td>
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</tr>
<tr>
<td>Goal – reduce body weight by 7% during first year of therapy</td>
<td>Encourage weight maintenance/reduction with physical activity, reduced caloric intake, formal behavioral programs</td>
</tr>
<tr>
<td>Goal – achieve desired weight BMI &lt; 25 kg/m²</td>
<td>Maintain/achieve waist circumference &lt; 40 in. in men, &lt; 35 in. in women</td>
</tr>
<tr>
<td>Initial reduction 7–10% weight from baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Physical inactivity:</strong></td>
<td></td>
</tr>
<tr>
<td>Goal – regular moderate-intensity physical activity, at least 30 min of continuous/ intermittent (preferably 60 min) 5 day/ week, preferably daily</td>
<td>Patients with established CVD – assess physical activity risk (history/stress test)</td>
</tr>
<tr>
<td></td>
<td>Encourage 30–60 min moderate-intensity aerobic activity daily supplemented by increase in daily lifestyle activities</td>
</tr>
<tr>
<td></td>
<td>Encourage resistance training 2 day/week</td>
</tr>
<tr>
<td></td>
<td>Medically supervised programs for high-risk patients</td>
</tr>
<tr>
<td><strong>Atherogenic diet:</strong></td>
<td></td>
</tr>
<tr>
<td>Goal – reduce saturated fat, trans fat, cholesterol</td>
<td>Saturated fat &lt; 7% total calories; reduce trans fat; dietary cholesterol &lt; 200 mg/day; total fat 25–35% of total calories</td>
</tr>
<tr>
<td></td>
<td>Most dietary fat should be unsaturated</td>
</tr>
<tr>
<td></td>
<td>Simple sugars should be limited</td>
</tr>
</tbody>
</table>

**Table 2.6** Management of the metabolic syndrome: treatment of lifestyle risk factors (adapted from [3])
A lifestyle modification program that combines exercise and weight loss has been shown to reduce the incidence of diabetes in the Diabetes Prevention Program [54]. Over 3,000 nondiabetic individuals with an elevated fasting and postload glucose were randomized to placebo, metformin, or a lifestyle modification program with the goals of at least a 7% body weight loss and 150 min of exercise per week. After nearly 3 years of follow-up, the lifestyle modification group had a 58% reduction in the incidence of diabetes compared with the placebo group. The lifestyle program was significantly more effective than metformin which achieved only a 31% decrease in the incidence of diabetes compared with placebo. This study shows that diabetes may be prevented or at least delayed in individuals at risk for the disease by an easily performed lifestyle program. The average weight loss in the lifestyle group was 5.6 kg which is an achievable goal for most individuals. The lifestyle goal targets in this study should be the minimal goals that we recommend to all patients with the metabolic syndrome.

**Pharmacological and Surgical Treatment of Obesity**

Unfortunately, dietary interventions are not successful in reducing weight in many individuals who attempt a weight loss program. A number of prescription and over the counter medications are available that may have efficacy for weight loss. Pharmacological therapy for obesity is deemed appropriate for some individuals with a BMI of 30 or greater or a BMI of 27 or greater in the presence of comorbidities [5].

Appetite suppressants such as phentermine are FDA approved for short-term weight loss. These drugs are adrenergic stimulants enhancing the release of catecholamines. A meta-analysis of short-term studies with phentermine indicated an average weight loss of about 3.5 kg was achieved with this agent [55]. These drugs
may significantly increase blood pressure which may be a problem in individuals who have prehypertension or are on hypertensive medications. Dependency may also be a concern with these agents. Since blood pressure is frequently elevated in patients with metabolic syndrome, these medications may not be the best choice for weight loss.

Sibutramine is approved by the FDA for induction and maintenance of weight loss as an adjunct to a comprehensive weight loss program. Sibutramine is a serotonin-norepinephrine reuptake inhibitor and appears to reduce appetite. Patients receiving subutramine alone achieved an average loss of 5 kg but those receiving sibutramine in combination with a lifestyle modification program were able to lose a mean of 12.1 kg of weight in a 1-year trial [56]. Sibutramine may also increase blood pressure and is not recommended for use in patients with cardiovascular disease. In January 2010, the European Medicine Agency’s Committee for Medicinal Products for Human Use recommended that sibutramine be removed from the European market because of concern about an increase in cardiovascular events in patients with CVD and diabetes using this drug [57]. The FDA added new contraindications to the label stating that this drug should not be used in patients with a history of cardiovascular disease.

Orlistat is a medication that works in the intestine to reduce the absorption of fat. It is available as a prescription medication and over the counter at a lower dose (Alli, GlaxoSmithKline). A meta-analysis of studies using orlistat for weight loss showed only a modest 2.89 kg weight loss [58]. Orlistat has been shown to reduce the incidence of diabetes in the Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study [59]. In this study, over 3,300 obese patients were randomized to a lifestyle program plus orlistat or placebo and followed for 4 years. After 4 years treatment, the incidence of diabetes was 9.0% with placebo and 6.2% with orlistat (37.3% risk reduction, \( p=0.0032 \)). Greater weight loss was achieved in the orlistat group (5.8 kg vs. 3.0 kg with placebo). Gastrointestinal side effects such as fecal urgency may limit its use for some patients.

Future medications may include agents that target the endocannabinoid system which is involved in energy homeostasis. Activation of central cannabinoid receptors stimulates eating and may contribute to obesity [60]. Rimonabant is a selective cannabinoid-1 receptor blocker and has been shown to reduce body weight in obese subjects. Both the Rimonabant in Obesity-Europe study [61] and the Rimonabant in Obesity-North America study [62] showed that rimonabant induces significant weight loss that can be sustained over a 2-year period. In addition, favorable changes in cardiometabolic risk factors such as a 12.6% increase in HDL-C and a 5.3% reduction in triglycerides may make this treatment strategy useful for patients with obesity and metabolic syndrome. Unfortunately, side effects including an increase in depression and anxiety have raised concerns about rimonabant and a large outcome trial was terminated early and the drug removed from the European market because of side effects. It is unclear if other products targeting the endocannabinoid system will be developed.

Drugs that target the serotonergic system have also been used in the management of obesity and new agents in this class are in development. Fenfluramine and
dexfenfluramine were removed from the market when reports of valvular heart disease were associated with these drugs [63]. Newer agents in development selectively target central 5-hydroxytryptamine (5-HT, or serotonin) 2C receptors without adverse effects on heart valves and without causing an increase in pulmonary artery pressures. A 1 year weight loss study with the selective serotonin 2C receptor agonist lorcaserin showed an approximately 4 kg greater weight loss with this agent compared with placebo [64].

**Bariatric Surgery**

Weight loss surgery is an option for weight reduction in patients with severe obesity (BMI 40 or greater) or in patients with a BMI of 35 or greater and comorbidities [5]. A meta-analysis of bariatric surgery showed that the different surgical techniques are highly successful in achieving significant weight loss and that diabetes completely resolved in over 76% of the patients [65]. In addition, hyperlipidemia improved in 70% of patients and hypertension resolved in over 61% of patients. Resolution of diabetes following bariatric surgery can occur days after surgery even before marked weight loss is achieved suggesting a change in gut-related hormones may play a role [66]. Evidence is accumulating that bariatric surgery may be associated with an improvement in longevity [67].

**Dyslipidemia**

The National Cholesterol Education Program recommends that the LDL-C should be the primary target of therapy in individuals at cardiovascular disease risk. Patients diagnosed with the metabolic syndrome who do not fit the criteria for diabetes and do not have clinically evident atherosclerotic disease would fit the treatment guidelines for primary prevention. The LDL-C target for primary prevention is less than 130 mg/dl. For patients who are moderately high-risk defined as two or more risk factors and a 10-year risk of a cardiovascular event between 10 and 20%, an LDL-C goal of <100 mg/dl is a therapeutic option or a reasonable clinical strategy based on more recent trial evidence [68]. LDL-C lowering therapy should achieve at least a 30–40% reduction in LDL-C. Patients with the metabolic syndrome would frequently fit the moderately high-risk category based on the clustering of multiple risk factors found in this syndrome.

The NCEP guidelines recommend an LDL-C target of <100 mg/dl for secondary prevention patients. These are individuals at high CVD risk. This category includes patients with clinical atherosclerotic disease (CHD, symptomatic carotid artery disease, abdominal aortic aneurysm, or peripheral arterial disease), diabetes, or patients whose 10-year Framingham CVD risk is greater than 20% due to multiple risk factors. When the risk is considered very high, an LDL-C goal of <70 mg/dl is a
The very high-risk category can include patients who have the metabolic syndrome in addition to the component that put them into the high-risk category.

A low HDL-C is one of the major components of the metabolic syndrome and a frequent lipid abnormality in diabetic patients. The NCEP recommends that non-HDL-C should be the second therapeutic target after LDL-C reduction. The non-HDL-C is calculated by subtracting the HDL-C from the total cholesterol value. The non-HDL-C goal is 30 mg/dl higher than the LDL-C goal. There are three strategies for further lowering the non-HDL-C; further reduction in LDL-C, raising HDL-C or reducing triglycerides.

Persons with low HDL-C levels are at increased risk of CHD. Epidemiologic studies suggest that an increase in HDL-C of 1 mg/dl is associated with a 2–3% reduction in CHD risk [69]. Strategies for raising HDL-C include lifestyle modification and pharmacological agents. The percent change in HDL-C by the different lifestyle strategies are summarized in Table 2.8. Improvement in HDL-C has been associated with regular aerobic exercise, smoking cessation, weight loss, alcohol consumption, and changes in diet that replaces saturated fat and high glycemic index carbohydrates with polyunsaturated (fish oils) and monounsaturated fatty acids. The change in HDL-C with hygienic methods is dependent on the initial HDL-C level with, unfortunately, the least improvement in individuals with the lowest HDL-C levels at baseline [70].

Several classes of lipid-lowering agents can increase HDL-C including statins, niacin, and fibrates. Statins modestly increase HDL-C by about 5–15% likely through increasing levels of apolipoprotein A-I [71]. Statins are considered first line pharmacological therapy because of their ability to lower LDL-C, the primary target of treatment, and their effectiveness in improving outcomes across the risk spectrum. Statins appear to give the greatest risk reduction among patients with the lowest HDL-C both from primary prevention studies [72] and in patients with known cardiovascular disease [73].

Niacin can increase HDL-C by 20–30% as well as reduce triglycerides by 40–50% and LDL-C by 20% at doses in the 1.5–3 g per day range [71]. Niacin may be the most effective agent currently available to raise HDL-C. The main limitation to its use is tolerability. The Coronary Drug Project, using 3.0 g of short-acting niacin per day, achieved a 27% decrease in nonfatal myocardial infarction in the treatment group after 6 years [74]. The addition of niacin to a

<table>
<thead>
<tr>
<th>Table 2.8</th>
<th>Lifestyle modification and the effect on HDL-C (from [69])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic intervention</td>
<td>Increase in HDL-C levels (%)</td>
</tr>
<tr>
<td>Aerobic exercise</td>
<td>5–10</td>
</tr>
<tr>
<td>Tobacco cessation</td>
<td>5–10</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.35 mg/dl per kg of weight loss</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>5–15</td>
</tr>
<tr>
<td>Omega 3, Omega 6, MUFA in diet</td>
<td>0–5</td>
</tr>
</tbody>
</table>

HDL-C high-density lipoprotein cholesterol, MUFA monounsaturated fatty acid
statin can bring about a further reduction in LDL-C and a significant increase in HDL-C. In the HDL-Atherosclerosis Treatment Study (HATS), a small group of patients with coronary artery disease and low baseline HDL-C levels achieved significant clinical and angiographic benefit from the combination of simvastatin and at least 2 g of niacin daily [75].

Niacin may be an important agent for patients with the metabolic syndrome since it can address both the low HDL-C values and elevated triglycerides that are a common pattern of dyslipidemia in these patients. However, there is concern that niacin may worsen insulin resistance and glycemic control. An early study using 4.5 g of niacin daily showed induction and aggravation of glucose intolerance in the subjects studied [76]. Longer-term studies suggest that these changes in glycemia may not lead to substantial glucose intolerance. The Arterial Disease Multiple Intervention Trial (ADMIT) studied 3.0 g of niacin daily to determine the efficacy and safety of niacin in diabetic and nondiabetic patients [77]. Glucose levels were modestly increased by niacin averaging 8.7 mg/dl in diabetics and 6.3 mg/dl in nondiabetics with no change in hemoglobin A1c from baseline. Some of the diabetic patients, however, increased their insulin during the course of the study. More analysis will need to be done to determine if the potential benefits of niacin are diminished by the modest change in glycemic control with niacin. Patients with metabolic syndrome may develop an increase in fasting sugars significant enough to change their diagnosis to diabetes. Since the increase in fasting glucose is modest, these patients are likely near the diabetic category and would likely warrant therapy for diabetes.

Hypertriglyceridemia is a common component of the dyslipidemia associated with insulin resistance and is one of the major criteria for the metabolic syndrome. High triglycerides correlate with the presence of small, dense LDL-C particles and reduced levels of HDL-C, especially the HDL₂ component of HDL-C. Because of this correlation with LDL and HDL, triglyceride levels are not usually found to be an independent predictor of coronary artery disease after adjustments for these factors are made [78].

The treatment of hypertriglyceridemia consists of a combination of lifestyle modification and pharmacological therapy when lifestyle changes alone cannot achieve the desired triglyceride goal. A diet that concentrates on reducing complex carbohydrates can lower triglyceride levels. In addition, a reduction or elimination of alcohol can be beneficial. Fish oils have been shown to reduce triglycerides although the dose needed to reduce triglycerides by about 35% are typically 3–4 g per day of a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [79]. Multiple brands of fish oil capsules are available over the counter and there is one branded fish oil product (Lovaza, GlaxoSmithKline) that contains 465 mg of EPA and 375 mg of DHA in each 1,000 mg capsule.

Statins, niacin, and fibrates all have triglyceride lowering effects with the fibrates having the greatest efficacy. Gemfibrozil has the most convincing outcome data. The Helsinki Heart Study was a primary prevention trial that studied 1,200 mg of gemfibrozil in over 4,000 asymptomatic men and showed a 34% reduction in the incidence of CHD compared with placebo [80]. The subgroup that achieved the
The greatest benefit, with a 71% lower incidence of CHD events, had an LDL-C/HDL-C ratio greater than 5 and a triglyceride level greater than 203 mg/dl [81]. This lipid pattern is commonly found in metabolic syndrome patients. The Helsinki Heart Study, however, did not find a reduction in total mortality because of a surprising and unexplained increase in noncardiac mortality that offset the fewer deaths due to CHD.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) treated over 2,500 men with coronary artery disease and lower than average HDL-C with either 1,200 mg of gemfibrozil or placebo [82]. The mean HDL-C increased 6% and the mean triglyceride level decreased 31% with no significant change in LDL-C. The gemfibrozil treated group achieved a 24% reduction in the combined outcome of death, nonfatal myocardial infarction, and stroke. In contrast, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study enrolled nearly 10,000 people with type 2 diabetes mellitus and only achieved a nonsignificant 11% reduction in the primary end point [83]. This disappointing finding suggests that all fibrates may not be equivalent in producing significant event reduction. It was also suggested that the high use of statins in the placebo arm of the FIELD trial may have masked the efficacy of fenofibrate in this study. Finally, combination therapy with a statin and a fibrate can be considered. There is, however, no convincing outcome data using this combination and the recent results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showing no reduction in cardiovascular events with the combination of simvastatin plus fenofibrate in comparison to simvastatin alone raised questions about the benefit of combination therapy in diabetics [84].

General recommendations on the treatment of dyslipidemia in the metabolic syndrome can be made based on these outcome studies. LDL-C should be the primary target of therapy and the percent reduction and treatment goal should be determined based on the risk level of the patient. If a statin drug is contraindicated, then niacin or fibrates can be considered depending on which lipid factor is most outside of the normal range. Combination therapy with a statin plus niacin or a statin plus a fibrate is a treatment option to consider in patients with an elevated non-HDL-C but there is little outcome data to support a strong recommendation. Combination therapy has the strongest appeal for the highest risk individuals. Further research is needed to better elucidate the risk reduction that can be achieved with combination therapy.

Blood Pressure

The Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seventh report recognized that the risk of CVD begins at a blood pressure of 115/75 mmHg and that this risk doubles with each 20/10 mmHg increment [85]. Individuals with blood pressure of 120–139 systolic or 80–89 diastolic are designated as having prehypertension and require a lifestyle modification program to prevent CVD. The blood pressure treatment goals are
blood pressure $<140/90$ mmHg or $<130/80$ mmHg for patients with diabetes or chronic kidney disease. A blood pressure of 130/85 has been designated as one of the criteria for the metabolic syndrome so many patients with this syndrome will be in the prehypertension range. If patients are being treated with an antihypertensive agent, even if the blood pressure is at the treatment goal, they would still be classified as having hypertension. Since many individuals with the metabolic syndrome may fit the criteria for diabetes, the more aggressive treatment goal of $<130/80$ would apply to this group of patients.

The JNC recommends that the choice of antihypertensive is determined by compelling indications. Although all first line agents have the potential to reduce the incidence of CVD in patients with diabetes, the angiotensin-converting enzyme (ACE) inhibitor and the angiotensin receptor blocker (ARB) based treatments favorably affect the progression of renal insufficiency and reduce albuminuria [85]. Microalbuminuria is associated with the metabolic syndrome. From the NHANES III data, 34% of women and 42% of men with microalbuminuria also have the metabolic syndrome [44]. Because of the high association of microalbuminuria and metabolic syndrome, a reasonable treatment strategy would be an evaluation for the presence of microalbuminuria and institution of an ACE inhibitor or ARB if positive. A blood pressure target of $<130/80$ would be a therapeutic goal in such patients using the same JNC treatment goal as diabetic patients.

The use of ACE inhibitors as a preventive strategy may help delay or prevent renal disease in high-risk individuals. The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) studied over 1,200 patients with diabetes and hypertension and normal urinary albumin excretion using an ACE inhibitor treatment strategy and a target blood pressure of 120/80 [86]. The use of an ACE inhibitor significantly decreased the incidence of microalbuminuria. In addition, a number of clinical trials have suggested that the use of ACE inhibitors or ARBs may reduce the incidence of diabetes compared with placebo, diuretics, or beta-blockers. A meta-analysis of 22 clinical trials of participants who did not have diabetes at randomization showed that ACE inhibitors and ARBs were the agents the least associated with diabetes [87]. Diuretics and beta-blockers apparently increased the likelihood of diabetes compared with placebo. Finally, the use of an ARB in individuals with prehypertension may prevent or postpone the development of stage I hypertension as shown in the Trial of Preventing Hypertension (TROPHY) study [88]. In this study, over 400 individuals with prehypertension were randomized to an ARB for 2 years followed by placebo for 2 years and compared with 400 participants on placebo for the 4 years of the study. Over the 4 years of the study, stage I hypertension developed in nearly two thirds of the placebo group. The ARB significantly reduced the risk of incident hypertension during the study period.

From this analysis, it is reasonable to consider the metabolic syndrome as a compelling indication for the use of an ACE inhibitor or an ARB as first line therapy for the treatment of hypertension. If microalbuminuria is present, a treatment goal of $<130/80$ as indicated for diabetic patients would be recommended. For patients in
the prehypertension category without microalbuminuria, there is compelling data to suggest treatment with an ACE inhibitor or ARB may prevent the development of stage I hypertension and diabetes. The role of direct renin inhibitors is being investigated as well. An aggressive lifestyle program may also be effective in preventing these conditions as well. Therefore, a reasonable strategy would be to recommend a lifestyle program and reserve the use of pharmacological agents if the lifestyle program is not successful. Further studies may help to modify these recommendations as to when to consider starting pharmacological therapy.

**Insulin Resistance and Hyperglycemia**

Impaired fasting glucose is one of the major criteria of the metabolic syndrome. Many patients with metabolic syndrome may fit the criteria for diabetes following a glucose tolerance test even though fasting sugars may not reach criteria (see Table 2.5 for diagnostic criteria for diabetes). Drug therapies to reduce plasma glucose or improve insulin sensitivity are FDA approved for diabetes and not for IFG. Currently, it is recommended to begin a lifestyle program with weight loss and increased physical activity to treat IFG. Drug therapy is often required once diabetes develops. How early to start hypoglycemic agents is an important question that needs further research to answer definitively.

There is emerging evidence that hypoglycemic therapy initiated in patients with IFG or metabolic syndrome can reduce the incidence of diabetes. The Diabetes Prevention Program showed that metformin reduced the incidence of diabetes by 31% compared with placebo [54]. A meta-analysis of 31 trials showed that metformin reduced BMI, improved insulin resistance, lowered triglycerides and LDL-C, and increased HDL-C compared with placebo in patients at risk for diabetes [89]. New-onset diabetes was reduced by 40% with a 6% absolute risk reduction in 1.8 years. The evidence from the Diabetes Prevention Program prompted an American Diabetes Association (ADA) consensus panel to conclude that all individuals with prediabetes should be counseled on lifestyle changes similar to those recommended in the trial [90]. The panel felt that metformin could be considered for diabetes prevention in very high-risk individuals with IFG and IGT and at least one other risk factor.

Other pharmacological agents have also been shown to reduce the incidence of diabetes. Acarbose, in the STOP-NIDDM randomized trial, was found to delay the development of diabetes by 25% in individuals with IGT although 31% discontinued therapy early most commonly due to gastrointestinal side effects [91]. In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone reduced the risk of diabetes or death by 60% in individuals with IFG or IGT and no previous cardiovascular disease [92]. Despite this emerging evidence, the ADA consensus panel felt that at the present time only metformin should be considered for diabetes prevention [90].
Prothrombotic and Proinflammatory Risk Factors

The metabolic syndrome is a prothrombotic and proinflammatory condition. Low-dose aspirin (75–160 mg/day) has been recommended by the American Heart Association Primary Prevention guidelines for individuals at higher CHD risk defined as a 10% 10-year risk or greater [93]. The majority of metabolic syndrome patients would fit this risk category and should be treated with aspirin unless contraindicated.

There is no specific therapy for inflammation and no current guidelines for treatment targets for the different inflammatory biomarkers. All of the treatments suggested for the treatment of the metabolic syndrome have the potential to significantly reduce inflammation and decrease levels of biomarkers such as CRP. Lifestyle modification including weight loss, dietary changes, exercise, and smoking cessation can reduce CRP levels [94]. Certain drugs including antidiabetic and antihyperlipidemic agents have also been shown to significantly reduce CRP [95]. Further research will need to be completed to determine if treatment goals for inflammatory biomarkers can further help reduce risk.

Conclusion

Metabolic syndrome is becoming increasingly more prevalent as the obesity epidemic is advancing worldwide. The designation of the metabolic syndrome can identify individuals who are at future risk for diabetes and cardiovascular events and may be an easy way for health care providers to determine a subset of patients at higher risk. Lifestyle modification is the underlying treatment and should be a strong focus of care that is discussed at every patient encounter. Individual risk factors can then be targeted with aggressiveness of therapy dependent on overall risk. The metabolic syndrome designation gives an opportunity to identify at risk individuals before the development of significant disease.

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