Metabolic Syndrome: Epidemiology and Consequences

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Psychiatry is constantly faced with challenges related to the medical status of its patients and comorbid effects of pharmacologic treatment for psychiatric disorders. Other articles in this supplement review how obesity, diabetes, and dyslipidemia play a role in the treatment of schizophrenia, but these issues are by no means limited to schizophrenia. As the population of the United States becomes more obese and sedentary over time, risk factors for cardiovascular disease and diabetes are increasing in prevalence and affect the treatment of any psychiatric condition. As our understanding of how metabolic factors contribute to disease grows, it has become clear that a clustering of individual dysmetabolic factors, now known as metabolic syndrome, can contribute to significant morbidity and mortality and should be accounted for in the treatment of psychiatric conditions.

(J Clin Psychiatry 2004;65[suppl 18]:3–12)

The metabolic syndrome is a clustering of metabolic abnormalities within a single individual that is associated with an increased risk of cardiovascular disease. These abnormalities include dysregulation of glucose metabolism, abdominal or visceral obesity, dysregulation of plasma lipids (specifically low plasma levels of high-density lipoprotein cholesterol [HDL-C] and high plasma levels of triglycerides), and elevated blood pressure. Whereas each of these components of the metabolic syndrome is itself a risk factor for cardiovascular morbidity and mortality, when they exist in concert, the increased risk appears to be at least additive.[1] Prothrombotic and proinflammatory states are also considered part of the metabolic syndrome, but are not currently used in its diagnosis.[2]

This clustering of risk factors has been recognized for many years and has previously been referred to as "syndrome X," or the insulin resistance syndrome,[3,4] and indeed the World Health Organization (WHO) required impaired glucose tolerance for the diagnosis.[5] However, insulin resistance is not invariably present with obesity or dyslipidemia, leading U.S. national guidelines to take a broader view of the metabolic syndrome, considering abdominal obesity and insulin resistance equally as potential causes.

The importance of metabolic syndrome as a cardiovascular risk factor has led the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) and WHO to publish definitions of the metabolic syndrome to be used in its diagnosis.[2,5] These definitions are presented in Table 1. Using the NCEP/ATP III definition, a diagnosis of metabolic syndrome is made when an individual has any 3 of the components listed. The WHO definition is similar and differs mainly in that it requires a diagnosis of diabetes, impaired glucose regulation, or insulin resistance in addition to 2 or more of the other components for a diagnosis of metabolic syndrome. Despite the differences in the definitions, the NCEP/ATP III and WHO definitions identify the same individuals about 85% of the time.[6] The National Heart, Lung, and Blood Institute and the American Heart Association recently sponsored a conference to examine scientific issues related to definition of the metabolic syndrome.[7] The conference confirmed cardiovascular disease as a major clinical outcome of metabolic syndrome and highlighted the 6 major components of the syndrome identified in ATP III: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance with or without glucose intolerance, a proinflammatory state, and a prothrombotic state.[7] While the conference participants noted that there were some differences between the diagnostic criteria for metabolic syndrome developed by different groups, there was full agreement that therapeutic lifestyle change constituted first-line therapy, with pharmacologic therapy added as needed to treat specific components of the syndrome.

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Supported by an unrestricted educational grant from Bristol-Myers Squibb Company.

Dr. Sacks has been a consultant for Bristol-Myers Squibb and Eli Lilly and has received honoraria from Bristol-Myers Squibb.

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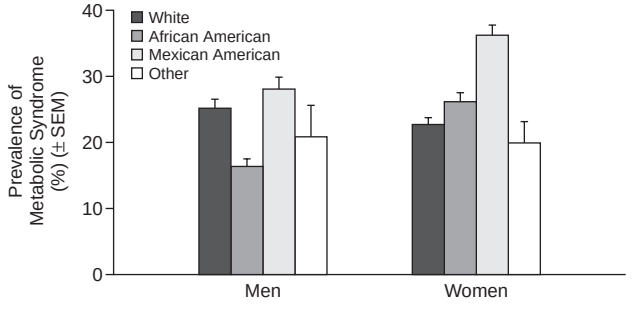
Table 1. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and World Health Organization (WHO) Definitions of Metabolic Syndrome

NCEP/ATP III Definition[2]	WHO Definition[5]
Three or more of the following:	Diabetes, IGT,[a] IFG,[b] or insulin resistance plus 2 or more of the following:
Waist circumference	BMI > 30 kg/m^2 and/or WHR > 0.90 in men, > 0.85 in women
> 102 cm (> 40 in) in men	
> 88 cm (> 35 in) in women	
Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg/dL and/or HDL-C < 35 mg/dL in men, < 39 mg/dL in women
HDL-C	
< 40 mg/dL in men	
< 50 mg/dL in women	
BP ≥ 130/85 mm Hg	BP ≥ 140/90 mm Hg
FPG ≥ 110 mg/dL	Microalbuminuria (UAE ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g)

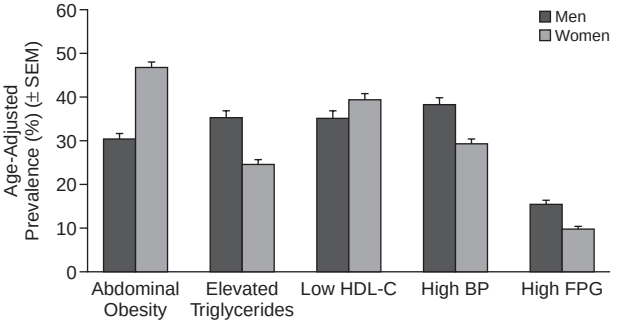
[a]Normal fasting glucose plus plasma glucose ≥ 120 mg/dL 2 hours after 75-g glucose load.
[b]Plasma glucose ≥ 100 and < 110 mg/dL after overnight fast.
Abbreviations: BMI = body mass index, BP = blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, UAE = urinary albumin excretion, WHR = waist-to-hip ratio.

Figure 1. Age-Adjusted Prevalence of Metabolic Syndrome Among 8608 Adult Participants in NHANES III by Sex and Race[a]



[a]Data from Ford and Giles.[6] No statistical analysis was reported.
Abbreviation: NHANES III = Third National Health and Nutrition Examination Survey.

Figure 2. Age-Adjusted Prevalence of the Individual Components of the Metabolic Syndrome as Defined by NCEP/ATP III[a]



[a]Data from Ford and Giles.[6] No statistical analysis was reported.
Abbreviations: ATP III = Adult Treatment Panel III, BP = blood pressure, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, NCEP = National Cholesterol Education Program.

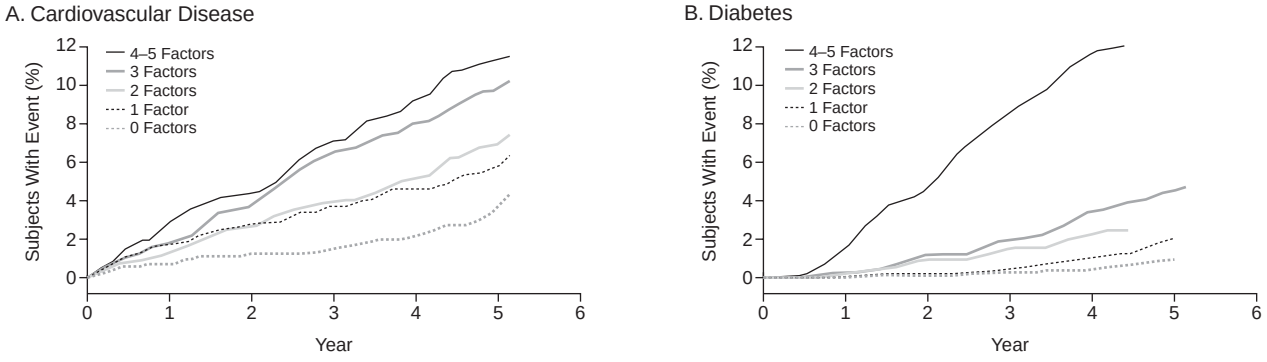
EPIDEMIOLOGY OF METABOLIC SYNDROME

Metabolic syndrome is a common finding in the U.S. population. Data from the Third National Health and Nutrition Examination Survey (NHANES III) have recently been used to evaluate the epidemiology of metabolic syndrome in the United States. The overall prevalence of metabolic syndrome using the NCEP/ATP III definition was 23.9% for the 8608 participants ≥ 20 years old who had complete information for the metabolic syndrome components.[6] As illustrated in Figure 1, the prevalence of metabolic syndrome depends on sex and ethnic background. In this study, African American men had the lowest mean ± SE age-adjusted prevalence, 16.5 ± 1.0%, and Mexican American women had the highest age-adjusted prevalence, 36.3 ± 3.1%.[6] The prevalence of metabolic syndrome increases with age, from about 7% in those between the ages of 20 and 29 years to over 40% in those over 60 years old.[6]

The age-adjusted prevalence of the individual components of the metabolic syndrome is presented in Figure 2. It is clear that abdominal obesity is a key component of metabolic syndrome, especially in women. In men with a body mass index (BMI) between 30 and 35 kg/m^2, the risk of metabolic syndrome is increased 25-fold ($p < .001$) compared with men who have a BMI between 18.5 and 25 kg/m^2.[8] In men with a BMI ≥ 35 kg/m^2, the risk is 68-fold greater ($p < .001$). It is important to note that these estimates of metabolic syndrome prevalence used data that were collected between 1988 and 1994. Between 1991 and 2001, the prevalence of obesity (BMI ≥ 30 kg/m^2) has increased from 12% to 20.9%,[9] and this increase would be expected to increase the prevalence of metabolic syndrome substantially.[8]

Because many consider abnormalities in glucose metabolism and insulin sensitivity to be key elements linking the components of metabolic syndrome,[10] it is surprising that elevated fasting plasma glucose is the least common component of the metabolic syndrome. However, fasting glucose is a relatively insensitive measure of glucose and

Figure 3. Cardiovascular Disease (A) and Diabetes (B) Incidence According to Number of Metabolic Syndrome Components[a]



[a]Reprinted with permission from Sattar et al.[1]

insulin dysregulation. The important role of abnormalities in glucose metabolism in the prevalence of metabolic syndrome was recently reported by Alexander et al.[11] In NHANES III participants more than 50 years old, a clear stepwise increase in the prevalence of metabolic syndrome was found as glucose tolerance worsened, increasing from 26% in those with normal fasting glucose, to 33% in those with impaired glucose tolerance and normal fasting glucose, to 71% in those with impaired fasting glucose, to 86% in those with type 2 diabetes.

EVIDENCE OF INCREASED MORBIDITY AND MORTALITY

The impact of metabolic syndrome on cardiovascular morbidity and mortality as well as on the incidence of new-onset diabetes has been shown in several studies. In the NHANES III data analyses, metabolic syndrome was associated with a significantly increased odds ratio for self-reported myocardial infarction, stroke, and congestive heart failure.[6] In survey participants over 50 years old without diabetes, the age-adjusted prevalence of coronary heart disease (CHD) was increased from 8.7% to 13.9% by metabolic syndrome.[8] Prospective studies yield evidence that is more convincing. In a study of families with type 2 diabetes, metabolic syndrome was associated with a relative risk of CHD, myocardial infarction, or stroke of 2.96, 2.63, and 2.27, respectively, during the median 6.9-year follow-up ($p < .001$ for all values).[12] The Kuopio Ischemic Heart Disease Risk Factor Study followed a cohort of Finnish men without a history of cardiovascular disease, cancer, or diabetes at baseline for a median of 11.6 years. The presence of metabolic syndrome was associated with a 4.2-fold increased risk of CHD mortality (95% CI = 1.6 to 10.8). In addition, a 5.0- to 8.8-fold increase in the incidence of type 2 diabetes was observed in those men with metabolic syndrome during a 4-year follow-up study of the original study population.[13] Similar results were reported for a retrospective analysis of the West of Scotland Coronary Prevention Study in which baseline metabolic syndrome in moderately hypercholesterolemic men was associated with a relative risk of CHD of 1.76 (95% CI = 1.44 to 2.15) and of new-onset diabetes of 3.51 (95% CI = 2.47 to 4.98).[1] Each component of the metabolic syndrome increased risk of CHD stepwise, while diabetes risk was synergistically increased when at least 4 factors were present (Figure 3).

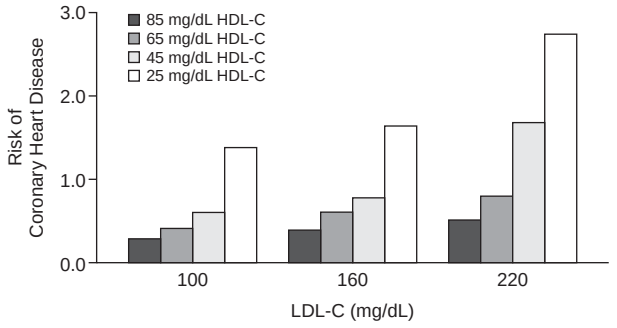
CAUSES OF METABOLIC SYNDROME

The causes of metabolic syndrome are not well understood but clearly involve many factors, including visceral or central obesity and insulin resistance. Modifiable environmental factors, such as sedentary lifestyle, are involved,[14] as is genetic susceptibility, quite likely involving multiple genes. Evidence of the genetic component comes from family studies that have shown that components of the metabolic syndrome are more likely to occur when each parent has diabetes, hypertension, or both.[15] Similarly, twin studies have shown a higher coprevalence of components of the metabolic syndrome in monozygotic than in dizygotic twins.[16] Visceral or central obesity and insulin resistance, arising from either modifiable or genetic factors, appear to be likely proximal causes of metabolic syndrome.

Role of Central Obesity

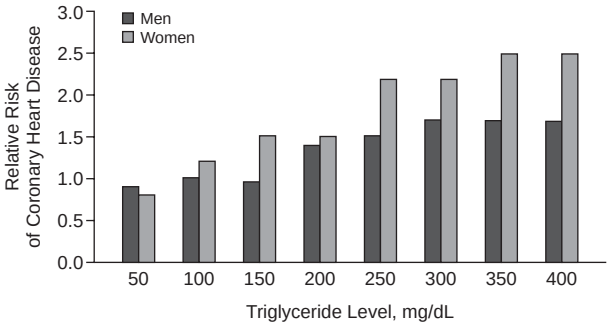
Both the NCEP/ATP III and WHO definitions of metabolic syndrome include parameters relating to central obesity, with NCEP/ATP III using a waist circumference cutoff of > 102 cm (> 40 in) for men and > 88 cm (> 35 in) for women and WHO using a BMI of > 30 kg/m^2 and/or a waist-to-hip ratio of > 0.90 in men and > 0.85 in women. Even for subjects with similar BMIs, waist circumference

Figure 4. Low HDL-C: Independent Predictor of Coronary Heart Disease Risk, Even When LDL-C Is Low[a]



[a]Data from Gordon et al.[21]
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Figure 5. Risk of Coronary Heart Disease by Triglyceride Level: The Framingham Heart Study (N = 5127)[a]



[a]Reprinted with permission from Castelli.[23]

is correlated with the risk for hypertension, diabetes, dyslipidemia, and metabolic syndrome. In a study utilizing almost 15,000 participants from NHANES III, Janssen and colleagues[17] found that for participants with a normal BMI (18.5–24.9 kg/m^2), the risk of hypertension, hypercholesterolemia, hypertriglyceridemia, and metabolic syndrome was significantly higher for patients with high waist circumference. A similar pattern was evident in participants who were overweight (BMI of 25.0–29.9 kg/m^2) or class I obese (BMI of 30.0–34.9 kg/m^2). The localized compartmentalization of adipose tissue appears to be an important factor in the development of insulin resistance. In a study[18] of 51 overweight or obese men, intraperitoneal, anterior, and posterior subcutaneous fat mass was assessed using magnetic resonance imaging and correlated with metabolic parameters including insulin resistance and triglyceride concentrations. Intraperitoneal fat mass correlated best with insulin resistance, very-low-density lipoprotein (VLDL)–apolipoprotein B (apoB) concentrations, and VLDL production by the liver.

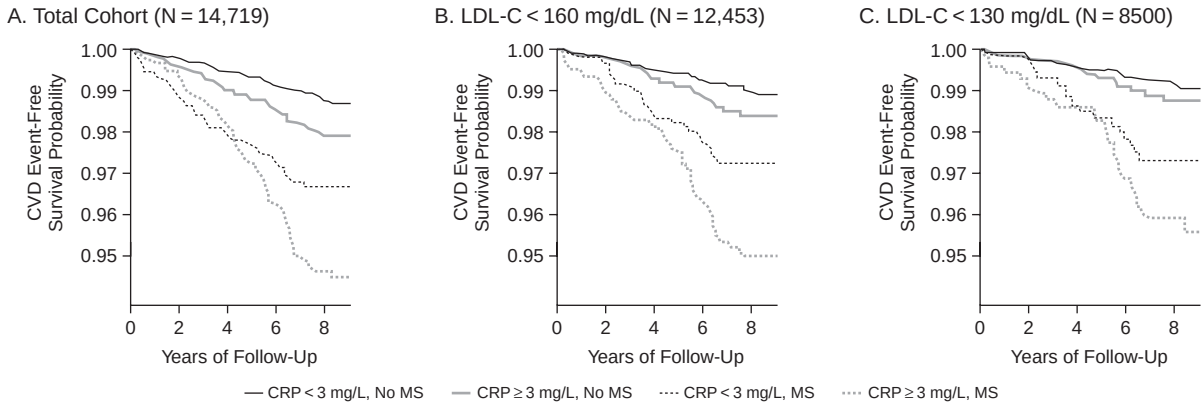
In an analysis utilizing data from 1087 nondiabetic patients enrolled in the Insulin Resistance Atherosclerosis Study, 2 underlying "factors" were identified that contributed to the intercorrelational nature of metabolic syndrome.[19] One factor was labeled the "blood pressure factor" and included both systolic and diastolic blood pressure. However, the authors suggested that this factor was secondary to a "metabolic factor," which included variables such as insulin resistance, obesity, low concentration of HDL-C, and high triglyceride concentration.

Role of Dyslipidemia

Some of the factors that contribute to central obesity (e.g., poor diet and insufficient exercise) also contribute to the atherogenic dyslipidemia exhibited in the metabolic syndrome. This dysregulated lipid profile is characterized by factors including low serum concentrations of HDL-C, high concentrations of serum triglycerides, and small low-density lipoprotein cholesterol (LDL-C) particle size. Low HDL-C concentrations have been linked to increased risk for CHD, even when other risk factors are not present. Data from the Prospective Cardiovascular Munster Study indicated that the risk for developing CHD was 4-fold higher in men over 40 years of age whose HDL-C was < 35 mg/dL than in men whose HDL-C was ≥ 35 mg/dL.[20] Among men and women over 50 years old from the Framingham Heart Study, HDL-C concentration exhibited a strong inverse relationship with the incidence of CHD in both men and women, even among those subjects whose LDL-C or triglyceride concentration was not elevated (Figure 4).[21] In fact, HDL-C may be a stronger predictor of CHD development among patients with low LDL-C concentrations. A pooled analysis of patients enrolled in the Cholesterol and Recurrent Events and the Long-Term Intervention With Pravastatin in Ischemic Disease studies found that the occurrence of CHD events was almost 3 times higher among those patients who had the lowest compared with the highest quintile of HDL-C concentration (28 vs. 50 mg/dL) and who had LDL-C levels of < 125 mg/dL.[22]

In addition to HDL-C, serum triglyceride concentration is associated with the development of and mortality associated with CHD. The relative risk of CHD among men and women in the Framingham Heart Study increased as serum triglyceride levels increased, although relative risk plateaued at roughly 300 mg/dL and higher (Figure 5).[23] In addition, hypertriglyceridemia in patients with non–insulin-dependent diabetes (NIDDM) is associated with an increased risk of mortality due to CHD.[24] The association between hypertriglyceridemia and diabetes has long been recognized. For example, Olefsky and colleagues[25] found that serum triglyceride concentrations correlated closely with insulin response to oral glucose tolerance tests. The mechanisms behind this association

Figure 6. C-Reactive Protein Adds to Prediction of Cardiovascular Disease in Metabolic Syndrome (MS) in U.S. Women[a]



[a]Reprinted with permission from Ridker et al.[34]

are related to several aspects of triglyceride metabolism. Howard and colleagues[26] examined triglyceride metabolism in matched diabetic and control patients and found that those subjects with diabetes not only had higher mean serum concentrations of triglyceride, but also exhibited reduced catabolism of triglyceride compared with controls. Another study[27] found that patients with NIDDM exhibited an impaired ability of insulin to suppress the release of large, triglyceride-rich particles from the liver.

Lewis and Steiner performed several studies that examined the association between serum triglyceride and insulin. In one study[28] of insulin-sensitive individuals, they found that production of plasma free fatty acids (FFAs), triglycerides, and apoB was suppressed in response to insulin. When insulin-induced suppression of plasma FFA levels was prevented, triglyceride production was still inhibited, although less than with insulin alone. The authors concluded that insulin suppressed triglyceride production in insulin-sensitive subjects partly by suppressing plasma FFA levels and partly by a non-FFA mediated mechanism such as suppression of VLDL secretion. Pont and colleagues[29] examined the metabolism of different lipids in female volunteers and found that insulin-resistant women who had abdominal obesity but normal fasting triglyceride levels exhibited increased serum lipid production (including triglyceride) relative to control subjects. Therefore, there are several mechanisms through which insulin resistance, NIDDM, and serum triglyceride levels are associated.

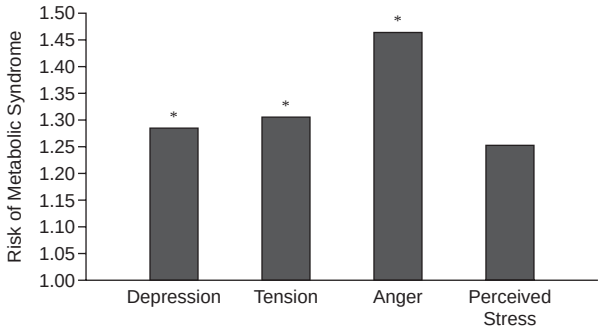
Role of Inflammation

More recently, inflammation has been suggested as a risk factor in the development of atherosclerosis and, although not part of the definition of the metabolic syndrome per se, appears to be associated with each of the components of the metabolic syndrome and the development of NIDDM.[30–32] In a subset of nondiabetic patients from the Insulin Resistance Atherosclerosis Study, C-reactive protein (CRP) level, an indicator of inflammatory activity, was correlated with several parameters, including BMI, waist circumference, and insulin sensitivity.[33] As the number of metabolic disorders (dyslipidemia, abdominal obesity, insulin resistance, hypertension) present increased, CRP levels increased in a linear fashion. In a large population from the Women's Health Study, CRP levels were also found to increase with an increasing number of components of the metabolic syndrome, such that median CRP levels were over 8 times higher in subjects who exhibited all 5 components of the metabolic syndrome compared with subjects who exhibited no component.[34] Furthermore, CRP levels of ≥ 3.0 mg/L afforded an additional predictive value with respect to events related to cardiovascular disease over the presence of metabolic syndrome alone (Figure 6).

Role of Psychological Status

In addition to the more obvious physical parameters associated with the metabolic syndrome, it is likely that several other parameters relating to emotional status, including hormones, behavioral status, and stress, contribute to the components of metabolic syndrome. For example, in a population of nondiabetic Finnish men, testosterone levels were significantly lower in men with the metabolic syndrome (WHO definition).[35] Even after adjustment for age and BMI, testosterone was inversely associated with concentrations of insulin, glucose, triglycerides, and CRP. Men with the lowest testosterone levels were almost 3 times more likely to have the metabolic syndrome and almost 2 times more likely after adjusting for BMI. The relationship between psychological state and metabolic health is even more evident in women. A cohort of 425 women was followed for over 7 years and assessed for several psychological factors and components of the metabolic syndrome.[36] Women who exhibited high scores on the

Figure 7. Psychological Symptoms and the Risk of Metabolic Syndrome During 7-Year Follow-Up in Postmenopausal Women[a]



[a]Data from Raikkonen et al.[36]
*p < .05.

Beck Depression Inventory at baseline had a greater risk for developing the metabolic syndrome during follow-up (Figure 7). Conversely, women who exhibited the metabolic syndrome at baseline had a greater mean increase in Spielberger Trait Anger and Trait Anxiety scores during follow-up. These results are not surprising considering the vast literature examining the association between psychological health, stress, and eating disorders.

Even among children and adolescents, psychological health may contribute to future metabolic status. A study[37] utilizing a cohort of 134 children assessed whether hostility at study entry predicted the appearance of metabolic syndrome risk factors an average of 3 years later and found that children who exhibited high hostility scores at baseline were likely to exhibit the metabolic syndrome at the follow-up.

Some of the association between psychological state and metabolic syndrome may be related to chronic stress responses. In a study of working men aged 45 to 63 years, metabolic syndrome was associated with higher levels of urinary cortisol and catecholamine output and higher levels of CRP.[38] Interestingly, subjects who had formerly exhibited the metabolic syndrome had cortisol output similar to control subjects, suggesting that some changes associated with psychological contributions to the development of the metabolic syndrome might be reversible.

RELEVANCE TO PSYCHIATRY

An association between several psychiatric disorders and the prevalence of metabolic syndrome and its components has been reported. For example, abdominal obesity, elevated fasting glucose, and impaired glucose tolerance were associated with an increase in depressive symptoms in men.[39] In women, an increased waist-hip ratio is reported to be associated with an increase in anxiety and depression.[40] The directionality of this association is not established; a recent prospective study[41] of 2123 subjects ≥ 50 years old suggests that obesity at baseline is significantly associated with incident depression 5 years later, but depression at baseline was not associated with incident obesity during the same 5-year period. Another recent prospective study[36] showed that middle-aged women with high scores for depression, anger, anxiety, and tension at baseline had an increased risk of developing metabolic syndrome during the 7-year follow-up period. Interestingly, metabolic syndrome at baseline was a risk factor for increasing anxiety and anger. Depression may also be associated with disorders of glucose metabolism and has been shown to be more common in patients with type 2 diabetes than in those without diabetes.[42] At least one prospective study[43] indicated that depression at baseline predicted the development of type 2 diabetes over a 13-year follow-up period. It is not clear whether all of the increased cardiovascular morbidity and mortality observed in subjects with anxiety disorders or depression can be explained by these associations with components of the metabolic syndrome.[44,45]

Recent studies of bipolar patients have found higher rates of obesity compared with reference control subjects. Elmslie and colleagues[46] studied 89 euthymic bipolar (DSM-IV) patients and compared them with 445 reference subjects matched for age and sex and found higher rates of obesity in both male and female bipolar patients, with a significantly larger waist-hip ratio in both men and women. McElroy and coworkers[47] compared 644 bipolar patients in the Stanley Foundation Bipolar Treatment Outcome Network and found that both men and women had higher rates of obesity than those observed in the NHANES III study. Of interest in the present discussion is the observation that the prevalence of hypertension and diabetes was significantly associated with increasing BMI, suggesting an increased prevalence of metabolic syndrome.

Patients with schizophrenia have a high prevalence of the components of metabolic syndrome, and a recent study suggests that the prevalence of metabolic syndrome is 37% in patients with schizophrenia.[48] However, because most patients are drug-treated, it is difficult to separate abnormalities associated with the disease from those that may be drug-induced. However, several studies suggest that schizophrenia patients may have metabolic abnormalities associated with metabolic syndrome prior to beginning drug treatment. For example, Ryan et al.[49] studied 26 patients experiencing their first episode of schizophrenia. Compared with an age- and sex-matched control group, this drug-naive patient group had a higher prevalence of impaired fasting glucose (15.4% vs. 0%, p < .02) and a higher level of insulin resistance as assessed by homeostasis model assessment (p < .01). However, waist circumference and plasma triglycerides were similar in

the 2 groups. Other investigators have reported that drug-free and drug-naive schizophrenia patients have more than 3 times as much intra-abdominal fat as control subjects.[50]

Patients with schizophrenia have a higher rate of mortality from cardiovascular disease compared with the general population,[51] and many think that atypical antipsychotic drugs may contribute to this increased risk. Indeed, drug-induced weight gain, new-onset diabetes and changes in glucose metabolism, and lipid dysregulation have all been reported with this class of pharmacotherapy. However, these metabolic changes are not equivalent among different antipsychotic agents. Four national organizations recently published a consensus statement regarding the metabolic liability profile of several antipsychotics and found that the risk for weight gain, diabetes, and dyslipidemia was not uniform among antipsychotics, but that certain drugs (e.g., clozapine and olanzapine) were associated with greater weight gain and risk for diabetes and dyslipidemia than aripiprazole and other newer atypical antipsychotics.[52–57]

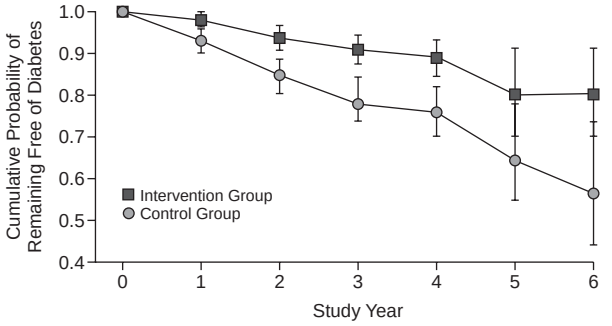
TREATMENT OF METABOLIC SYNDROME

No treatment algorithm for metabolic syndrome currently exists, and current recommendations are to treat the individual abnormalities with an emphasis on lifestyle modification to reduce weight in overweight or obese individuals.[58,59] Because overweight and obesity are also risk factors for hypertension and dysregulation of glucose metabolism, reducing weight can positively influence many components of the metabolic syndrome.[59,60] Two recent studies[61,62] have shown that intensive lifestyle modification focusing on diet and exercise in overweight subjects with impaired glucose tolerance can reduce the incidence of diabetes, one of the major consequences of metabolic syndrome (Figure 8). More aggressive approaches, including drug and surgical therapy for obesity, may be indicated for those patients unable to lose weight.[59]

Treatment Goals

Treatment goals for patients with the metabolic syndrome should take into consideration each of the components of the syndrome: for patients with coronary artery disease (CAD) or CAD equivalent risk (e.g., patients with diabetes), LDL-C levels should be brought below 100 mg/dL; for patients with multiple risk factors, LDL-C should be brought to < 130 mg/dL. Serum triglycerides should be brought below 150 mg/dL, blood pressure should be 120/80 mm Hg or less, plasma glucose should be below 110 mg/dL, and HDL-C should be raised to at least 40 mg/dL. Reaching these goals will require significant lifestyle changes for many patients and may require pharmacologic interventions as well.

Figure 8. Lifestyle Changes to Prevent Type 2 Diabetes Among Subjects With Impaired Glucose Tolerance[a]



[a]Reprinted with permission from Tuomilehto et al.[61] Data shown are for the Finnish Diabetes Prevention Study Group, 522 middle-aged, overweight subjects with impaired glucose tolerance. The intervention consisted of individualized counseling aimed at reducing weight and intake of total and saturated fat, increasing intake of fiber, and performing physical activity.

Dietary Approaches

The relationship between abdominal obesity and the other components of the metabolic syndrome makes sensible weight loss a critical requirement for many patients. There are several common-sense considerations with regard to developing a dietary approach in the treatment of the metabolic syndrome, the first of which is to develop or follow a plan that designates a list of foods to eat (or avoid), specifies times and places for consumption, and controls the number and size of servings. Changing habits to emphasize eating foods lower in sugars, saturated fats, and calories and introducing regular physical activity are also important. There are several dietary approaches that have been assessed for their ability to modify different components of the metabolic syndrome.

The Dietary Approaches to Stop Hypertension (DASH) study assessed the effects of maintaining a diet rich in fruits, vegetables, and low-fat dairy products on blood pressure and found that systolic and diastolic blood pressure could be reduced in normotensive and hypertensive patients with the study diet compared with a usual U.S. diet.[63] Additional studies[64,65] found that by restricting sodium levels in addition to following the dietary guidelines of the DASH study, blood pressure could be further reduced, with the greatest reductions evident when combining the DASH diet with a sodium limit of 1.5 g/day.

Other studies have assessed the Mediterranean diet, which typically features abundant fresh fruit and vegetables and moderate amounts of cheese, yogurt, fish, poultry, and wine; utilizes olive oil as a fat source (total fat, 25%–43%); and is low in sugar and red meats. The Lyon Diet Heart Study found that a Mediterranean-type diet was associated with a reduced incidence of all-cause mortality, cardiac mortality, and nonfatal myocardial infarction.[66,67]

Other studies examined the role of dietary fat source in metabolic parameters. Mensink and Katan[68] conducted a meta-analysis of 27 controlled trials to calculate the effect of changes in carbohydrate and fatty acid intake on serum lipid and lipoprotein levels and found that replacing saturated fat with monounsaturated or polyunsaturated fats was associated with reductions of 10% to 12% in LDL-C concentrations, as well as smaller reductions in LDL-C concentrations. Other trials have assessed different ways of replacing saturated fat and noted significant reductions in cholesterol and cardiovascular disease. For example, when saturated fats are replaced with monounsaturated or polyunsaturated fats from vegetable oils, LDL-C decreases, and, equally important, the ratio of LDL-C to HDL-C decreases, leading to reduced cardiovascular disease.[69]

The comparative benefits of dietary plans are subject to substantial debate, although some studies have assessed different dietary plans in parallel. For example, a diet featuring moderate fat intake was compared with a low-fat diet over 18 months in a population of overweight men and women.[70] Patients in the moderate-fat group exhibited significantly greater reductions in body weight, BMI, and waist circumference compared with the low-fat group. Furthermore, patient retention was better in the moderate-fat group. Another study[71] assessed the effects of a low-carbohydrate, high-protein, high-fat diet versus a conventional (low-calorie, high-carbohydrate, low-fat) diet and found that patients on a low-carbohydrate diet lost more weight than subjects on the conventional diet at 3 and 6 months, but not at 12 months. However, at 12 months, patients on the low-carbohydrate diet exhibited significantly greater reductions in serum triglycerides and greater increases in HDL-C. There were no significant differences between the groups at month 12 for percentage change in total cholesterol or LDL-C.

There is substantial evidence that implementing lifestyle and dietary changes can reduce the risk of developing NIDDM. In the Finnish Diabetes Prevention Study, overweight patients were assigned either to an intervention group, which received individualized counseling aimed at reducing weight and total intake of fat, increasing intake of fiber, and performing physical activity, or to a control group.[61] By the end of year 2, patients in the intervention group experienced a mean weight loss of 3.5 kg, compared with 0.8 kg in the control group. Most importantly, the risk for developing diabetes was reduced by 58% for the intervention group compared with control patients (Figure 8). Stampfer and colleagues[72] assessed the relationship between lifestyle risk factors and their association with CHD in a population of women participating in the Nurses' Health Study. Subjects were defined as low risk if they were nonsmokers, had a BMI < 25 kg/m^2, engaged in moderate alcohol consumption, participated in moderate-to-vigorous exercise for at least half an hour per day, and scored in the highest 40% of the population for consumption of a diet that included high fiber and folate and a high ratio of polyunsaturated to saturated fat and was low in trans fat. The risk of coronary events or stroke was reduced by 51% for patients who met 3 of the 5 aforementioned criteria and by 74% for patients who met all 5 of the criteria.

Pharmacologic Intervention

There are several guidelines and recommendations regarding treatment of the individual components of the metabolic syndrome. For example, the American Diabetes Association has recommended specific options for the treatment of diabetic dyslipidemia in adults.[73] The recommendations are based on the characteristics of the dyslipidemia, so, for example, if a patient exhibits elevated LDL-C concentrations, the first-line pharmacologic treatment choice is a statin, with bile acid sequestrants or fibrates added as second-line therapy. Diabetic patients with hypertriglyceridemia should first establish glycemic control and then add a fibrate or a statin, particularly if they also have elevated LDL-C. Raising HDL-C is often difficult, but improvement may be achieved through behavioral interventions or by using nicotinic acid or fibrates.

The American Heart Association and the American College of Cardiology published guidelines for the prevention of heart attack and cardiovascular-related mortality in patients with cardiovascular disease.[74] The primary goals of dyslipidemia management within these guidelines focus on LDL-C, where an LDL-C concentration of < 100 mg/dL is the treatment goal. For patients with LDL-C concentrations of > 100 mg/dL, pharmacologic management should begin with a statin or bile acid sequestrant, with a fibrate or niacin added if patients exhibit low HDL-C or high triglyceride levels. All interventions should include dietary therapy and behavioral interventions.

Since NIDDM is often associated with hypertriglyceridemia, considerations should be given to interventions that specifically target triglycerides. The National Cholesterol Education Program Expert Panel recommended that for patients with triglyceride concentrations > 200 mg/dL, treatment should begin with dietary and behavioral interventions and can include pharmacologic interventions that target specific lipid components.[2]

SUMMARY

Metabolic syndrome is a clustering of metabolic abnormalities that is associated with an increased risk of cardiovascular disease and NIDDM and is characterized by abdominal obesity, elevated blood pressure, impaired glucose metabolism, and dysregulation of plasma lipids. The dyslipidemia associated with metabolic syndrome features low concentrations of HDL-C, high plasma triglycerides, and

average to low concentrations of LDL-C. While the causes of metabolic syndrome are not completely elucidated, there can be several contributing factors, including visceral obesity, insulin resistance, chronic inflammation, stress, and hormonal imbalances.

Metabolic syndrome is of particular importance in the psychiatric community, because many psychiatric disorders are associated with individual components of the metabolic syndrome. In addition, many psychiatric medications adversely affect body weight and may adversely affect plasma lipids and glucose regulation. Recognizing that some antipsychotics, for example, may carry a metabolic liability requires that clinicians consider the metabolic risks before starting therapy with these agents, as well as conduct regular monitoring when patients do require these medications. It is most important that the treatment needs of the individual patient guide treatment.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, Fazaclo, and others), olanzapine (Zyprexa), pravastatin (Pravachol).

REFERENCES

1. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414–419
2. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
3. Reaven GM. Banting Lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
4. Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41:715–722
5. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications, pt 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, Switzerland: World Health Organization; 1999:1–59
6. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. Diabetes Care 2003;26: 575–581
7. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–438
8. Park Y-W, Zhu S, Palaniappan L, et al. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 2003;163:427–436
9. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289:76–79
10. Modan M, Halkin H, Almog S, et al. Hyperinsulinemia: a link between hypertension obesity and glucose intolerance. J Clin Invest 1985;75: 809–817
11. Alexander CM, Landsman PB, Teutsch SM, et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003; 52:1210–1214
12. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24:683–689
13. Laaksonen DE, Lakka HM, Niskanen LK, et al. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156:1070–1077
14. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790–797
15. Liese AD, Mayer-Davis EJ, Tyroler HA, et al. Familial components of the multiple metabolic syndrome: the ARIC study. Diabetologia 1997;40: 963–970
16. Edwards KL, Newman B, Mayer E, et al. Heritability of factors of the insulin resistance syndrome in women twins. Genet Epidemiol 1997;14: 241–253
17. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. Arch Intern Med 2002;162:2074–2079
18. Chan DC, Watts GF, Barrett PH. Comparison of intraperitoneal and posterior subcutaneous abdominal adipose tissue compartments as predictors of VLDL apolipoprotein B-100 kinetics in overweight/obese men. Diabetes Obes Metab 2003;5:202–206
19. Hanley AJG, Karter AJ, Festa A, et al. Factor analysis of metabolic syndrome using directly measured insulin sensitivity: the Insulin Resistance Atherosclerosis Study. Diabetes 2002;51:2642–2647
20. Assmann G, Schulte H, von Eckardstein A, et al. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk: the PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis 1996;124(suppl):S11–S20
21. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. Am J Med 1977;62:707–714
22. Sacks FM, Tonkin AM, Craven T, et al. Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors. Circulation 2002;105:1424–1428
23. Castelli WP. Epidemiology of triglycerides: a view from Framingham. Am J Cardiol 1992;70:3H–9H
24. Laakso M, Lehto S, Penttila I, et al. Lipids and lipoproteins predicting coronary heart disease mortality and morbidity in patients with non-insulin-dependent diabetes. Circulation 1993;88:1421–1430
25. Olefsky JM, Farquhar JW, Reaven GM. Reappraisal of the role of insulin in hypertriglyceridemia. Am J Med 1974;57:551–560
26. Howard BV, Reitman JS, Vasquez B, et al. Very-low-density lipoprotein triglyceride metabolism in non-insulin-dependent diabetes mellitus: relationship to plasma insulin and free fatty acids. Diabetes 1983;32: 271–276
27. Malmstrom R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. Diabetologia 1997;40:454–462
28. Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans: implications for the insulin-resistant state. Diabetes Care 1996;19:390–393
29. Pont F, Duvillard L, Florentin E, et al. Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity. Arterioscler Thromb Vasc Biol 2002;22:1726–1732
30. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–334
31. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–843
32. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–979
33. Festa A, D'Agostino R Jr, Howard G, et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–47
34. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107: 391–397
35. Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol 2003;149:601–608
36. Raikkonen K, Matthews KA, Kuller LH. The relationship between psychological risk attributes and the metabolic syndrome in healthy women: antecedent or consequence? Metabolism 2002;51:1573–1577

37. Raikkonen K, Matthews KA, Salomon K. Hostility predicts metabolic syndrome risk factors in children and adolescents. Health Psychol 2003; 22:279–286
38. Brunner EJ, Hemingway H, Walker BR, et al. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. Circulation 2002;106:2659–2665
39. Ahlberg A-C, Ljung T, Rosmond R, et al. Depression and anxiety symptoms in relation to anthropometry and metabolism in men. Psychiatry Res 2002;112:101–110
40. Wing RR, Matthews KA, Kuller LH, et al. Waist to hip ratio in middle-aged women: associations with behavioral and psychosocial factors and with changes in cardiovascular risk factors. Arterioscler Thromb 1991; 11:1250–1257
41. Roberts RE, Deleger S, Strawbridge WJ, et al. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord 2003;27:514–521
42. Nichols GA, Brown JB. Unadjusted and adjusted prevalence of diagnosed depression in type 2 diabetes. Diabetes Care 2003;26:744–749
43. Eaton WW, Armenian H, Gallo J, et al. Depression and risk for onset of type II diabetes: a prospective population-based study. Diabetes Care 1996;19:1097–1102
44. Kubzansky LD, Kawachi I, Weiss ST, et al. Anxiety and coronary heart disease: a synthesis of epidemiological, psychological, and experimental evidence. Ann Behav Med 1998;20:47–58
45. Ford DE, Mead LA, Chang PP, et al. Depression is a risk factor for coronary artery disease in men: the precursors study. Arch Intern Med 1998; 158:1422–1426
46. Elmslie JL, Silverstone JT, Mann JI, et al. Prevalence of overweight and obesity in bipolar patients. J Clin Psychiatry 2000;61:179–184
47. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002; 63:207–213
48. Heiskanen T, Niskanen L, Lyytikäinen R, et al. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry 2003;64:575–579
49. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. Am J Psychiatry 2003;160:284–289
50. Thakore JH, Mann JN, Vlahos I, et al. Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. Int J Obes Relat Metab Disord 2002;26:137–141
51. Brown S. Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997;171:502–508
52. American Diabetes Association. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 2004; 27:596–601
53. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002;63:856–865
54. Gianfrancesco F, Grogg A, Mahmoud R, et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. Clin Ther 2003;25:1150–1171
55. Hedenmalm K, Hagg S, Stahl M, et al. Glucose intolerance with atypical antipsychotics. Drug Saf 2002;25:1107–1116
56. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003;160:290–296
57. Lean ME, Pajonk FG. Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. Diabetes Care 2003;26:1597–1605
58. Hill JO, Bessesen D. What to do about the metabolic syndrome? Arch Intern Med 2003;163:395–397
59. Wilson PWF, Grundy SM. The metabolic syndrome: practical guide to origins and treatment, pt 1. Circulation 2003;108:1422–1424
60. Wilson PWF, Grundy SM. The metabolic syndrome: a practical guide to origins and treatment, pt 2. Circulation 2003;108:1537–1540
61. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
62. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
63. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997;336:1117–1124
64. Sacks FM, Svetkey LP, Vollmer WM, et al, for the DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10
65. Vollmer WM, Sacks FM, Ard J, et al. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med 2001;135:1019–1028
66. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99: 779–785
67. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. Arch Intern Med 1998;158:1181–1187
68. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. Arterioscler Thromb 1992;12: 911–919
69. Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. Am J Med 2002;113(suppl 9B):13S–24S
70. McManus K, Antinoro L, Sacks F. A randomized controlled trial of a moderate-fat, low-energy diet compared with a low fat, low-energy diet for weight loss in overweight adults. Int J Obes Relat Metab Disord 2001; 25:1503–1511
71. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–2090
72. Stampfer MJ, Hu FB, Manson JE, et al. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 2000; 343:16–22
73. American Diabetes Association. American Diabetes Association: Clinical Practice Recommendations 2002. Diabetes Care 2002;25(suppl 1): S1–S147
74. Smith SC, Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001;104:1577–1579