Clinical Management of Metabolic Syndrome : Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association Conference on Scientific Issues Related to Management

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The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III)[1] identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD) that is deserving of more clinical attention. Subsequently, the National Heart, Lung, and Blood Institute (NHLBI), in collaboration with the American Heart Association (AHA), convened a conference to examine scientific issues related to definition of the metabolic syndrome.[2] The present report summarizes a second conference devoted to clinical management of the metabolic syndrome, which was sponsored by the AHA in partnership with the NHLBI and cosponsored by the American Diabetes Association (ADA). This latter conference considered the following issues: (1) pathogenesis and presentation of the metabolic syndrome, (2) management of underlying risk factors, (3) management of metabolic risk factors, and (4) unresolved issues and research challenges.

The conference on definition[2] confirmed CVD as a major clinical outcome of metabolic syndrome and identified 6 major components of the syndrome: abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance ± glucose intolerance, a proinflammatory state, and a prothrombotic state. The follow-up conference on management was structured around therapies for these components. Clinical recognition of the metabolic syndrome is generally based on finding several well-recognized signs in clinical practice: abdominal obesity, elevated triglycerides, reduced HDL cholesterol, raised blood pressure, and elevated plasma glucose. In addition, research shows that other components not routinely measured commonly aggregate with the major components: elevated apolipoprotein B, small LDL particles, insulin resistance and hyperinsulinemia, impaired glucose tolerance (IGT), elevated C-reactive protein (CRP), and variation in coagulation factors (eg, plasminogen activator inhibitor [PAI]-1 and fibrinogen). The conference on definition[2] also emphasized that risk for type 2 diabetes is higher in persons with metabolic syndrome and that diabetes is a major risk factor for CVD. It also examined various criteria for a clinical diagnosis of the metabolic syndrome. The diagnostic scheme developed by ATP III is shown in the Table. Clinical criteria proposed by the World Health Organization[3] and American Association of Clinical Endocrinologists[4] also were reviewed. These latter criteria overlap with those of ATP III but differ by requiring direct evidence of insulin resistance for diagnosis. Both the World Health Organization and the American Association of Clinical Endocrinologists recommend an oral glucose tolerance test (OGTT) in patients without an elevated fasting glucose. In other words, in the absence of impaired fasting glucose (IFG), IGT detected by OGTT is considered as one metabolic risk factor defining the metabolic syndrome. ATP III does not recommend OGTT in such persons, even through IGT is a high-risk condition for type 2 diabetes (independent of IFG) and correlates with increased risk for CVD. ATP III, however, held that the information gained by OGTT does not outweigh its costs and inconvenience in routine practice. The present conference on management moved from the issue of definition of the metabolic syndrome to the wide issues of clinical management.

Presentation and Pathogenesis of Metabolic Syndrome

Presentation of Metabolic Syndrome

Characteristics of the metabolic syndrome occur in some children and adolescents, but prevalence of the metabolic

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ATP III Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*†	
Men	≥102 cm (≥40 in)
Women	≥88 cm (≥35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL‡

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, eg, 94 to 102 cm (37 to 39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

‡The American Diabetes Association has recently established a cutpoint of ≥100 mg/dL, above which persons have either prediabetes (impaired fasting glucose) or diabetes.[16] This new cutpoint should be applicable for identifying the lower boundary to define an elevated glucose as one criterion for the metabolic syndrome.

syndrome increases with age. The highest prevalence is observed in older persons, although frequency rises rapidly in middle age and parallels, with some lag time, the development of obesity in the population. In the United States, approximately one third of overweight/obese persons manifest the metabolic syndrome according to ATP III diagnosis criteria.[5] Several ethnic groups, including Hispanics and South Asians (eg, from the Indian subcontinent), seem to be particularly susceptible to the syndrome. Black men have a lower frequency of the syndrome than do white men, likely because of a lower prevalence of atherogenic dyslipidemia; nonetheless, black men are unusually susceptible to hypertension and carry a greater risk for diabetes. The genetic underpinning of metabolic syndrome is a topic of growing interest. In rare instances, patients have severe metabolic syndrome because of monogenic disorders such as adipose tissue disorders (eg, lipodystrophy caused by mutations in lamin A/C, AGPAT, and seipin). Polymorphisms in a variety of genes have been reported to associate with the metabolic syndrome, but their contributions to the syndrome in the general public remain to be determined. The metabolic syndrome increasingly is being recognized as a side effect of several commonly used drugs, mainly because some of these drugs (eg, corticosteroids, antidepressants, antipsychotics, antihistamines) can produce weight gain, which predisposes to 2 of the features of the metabolic syndrome: obesity and glucose intolerance. Protease inhibitors used in the treatment of HIV very often induce a metabolic syndrome secondary to lipodystrophy and insulin resistance. More commonly, the metabolic syndrome associates with abdominal obesity, the form of obesity that often develops in middle age. An excess of visceral fat may be particularly pathogenic, but abdominal subcutaneous adipose tissue likely contributes as well, as can total body fat.

Pathogenesis of Metabolic Syndrome

The conference on the definition of the metabolic syndrome[2] identified 3 potential etiologic categories: (1) obesity and disorders of adipose tissue, (2) insulin resistance, and (3) a constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the syndrome. Both genetic and acquired causes were determined to play a role in each. These 3 potential etiologic categories were examined in the present conference. In clinical and epidemiological studies, obesity is strongly associated with all cardiovascular risk factors. Adipose tissue is recognized as a source of several molecules that are potentially pathogenic: excess nonesterified fatty acids, cytokines (tumor necrosis factor-α), resistin, adiponectin, leptin, and PAI-1. Visceral adipose tissue may be particularly active in producing several of these factors. However, the mechanisms underlying the association between abdominal obesity (particularly visceral obesity) and the metabolic syndrome are not fully understood and likely are complex. It has been assumed that obese adipose tissue releases an excess of fatty acids and cytokines that induce insulin resistance; however, there is growing recognition that this concept, although undoubtedly containing truth, is an oversimplification of the interactions among obesity, body fat distribution, and cardiovascular risk factors.

The second pathogenic category, insulin resistance, is widely believed to be at the heart of the metabolic syndrome, even though there is as yet little clinical trial evidence that a reduction in insulin resistance will substantially improve any of the components of the metabolic syndrome other than glucose intolerance. Thus, the mechanistic link between insulin resistance and most of the components of the metabolic syndrome remains unclear. Although insulin resistance is strongly associated with atherogenic dyslipidemia and a proinflammatory state, it is less tightly associated with hypertension and the prothrombotic state. Finally, some data support the concept that insulin resistance or its associated hyperinsulinemia are independent risk factors for CVD, but this association has not yet been confirmed in controlled studies.

Much of the heterogeneity in the manifestation of the metabolic syndrome may therefore be due to the fact that many of the component factors are regulated independently of insulin resistance. Lipoprotein metabolism is regulated by genetic factors as well as by diet composition, and both can worsen atherogenic dyslipidemia. Blood pressure regulation is similarly complex and affected by dietary factors, physical activity, and renal/adrenal organ function. Only some persons with obesity and/or insulin resistance develop type 2 diabetes; for diabetes to appear, independent defects in beta-cell function must be present.

Other important modifiers also influence clinical expression of the metabolic syndrome. For example, physical inactivity promotes the development of obesity and modifies muscle insulin sensitivity. Aging is commonly accompanied by a loss of muscle mass and by an increase in body fat,

particularly accumulation of fat in the abdomen; both changes can increase insulin resistance. Moreover, recent studies suggest that aging is accompanied by specific defects in fatty acid oxidation in muscle, also enhancing insulin resistance. Hyperandrogenemia has been associated with insulin resistance in women with polycystic ovary disease. Furthermore, mild hypercorticoidism has been implicated in development of abdominal obesity.

Management of Underlying Risk Factors

The underlying risk factors that promote development of the metabolic syndrome are overweight and obesity, physical inactivity, and an atherogenic diet. All current guidelines on the management of the individual components of the metabolic syndrome emphasize that lifestyle modification (weight loss and physical activity) is first-line therapy. ATP III introduced the concept of the metabolic syndrome into its cholesterol guidelines in an attempt to highlight the need for more intensive lifestyle therapy as a means to prevent CVD in higher-risk patients. Conference participants supported this emphasis, whereas drug therapy was considered secondary, if at all, unless otherwise indicated by current CVD prevention guidelines.

Overweight and Obesity

In 1998, an expert panel was commissioned by the NHLBI and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to produce evidence-based guidelines on clinical management of overweight and obesity. This panel[6] defined overweight and obesity as body mass indexes of 25 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively. Abdominal obesity, defined as a waist circumference ≥102 cm (≥40 inches) in men and ≥88 cm (≥35 inches) in women, was identified as being particularly associated with several of the components of the metabolic syndrome. For this reason, ATP III recommended that abdominal obesity be considered one of the risk factors for the metabolic syndrome. It must be remembered that individuals can have the metabolic syndrome with a lesser degree of or no abdominal obesity if 3 of the remaining components are found. Such individuals are common in certain ethnic groups, such as Asians.

Obesity guidelines[6] stress the need for weight reduction using behavioral change to reduce caloric intake and increase physical activity. Years of study and clinical experience have revealed several key points about weight loss and weight management. The first is that "crash diets" and "extreme diets" are seldom effective in producing long-term weight reduction. Such diets include very low-calorie diets and high-fat/low-carbohydrate diets. More effective and healthful for long-term weight loss are reduced-energy diets, consisting of a modest 500- to 1000-calorie/day reduction. A realistic goal for weight reduction is to reduce body weight by ≈7% to 10% over a period of 6 to 12 months. Long-term maintenance of weight loss is then best achieved when regular exercise is included in the weight-reduction regimen. The emphasis in behavioral change should include improvements in eating habits (eg, setting goals, planning meals, reading labels, eating regular meals, reducing portion sizes, self-monitoring, avoiding eating binges). Emphasis should be placed on the benefit of social support, stress management, and the value of a regular exercise regimen. Although knowledge and education are critical, they are insufficient, and thus professional support (eg, nutrition counseling) is often very helpful. Detailed advice for weight reduction can be obtained from obesity guidelines at http://www.nhlbi.nih.gov and http://www.americanheart.org.

Physical Inactivity

Approximately 70% of the US public can be classified as being sedentary. Regular exercise and fitness have been shown to improve several metabolic risk factors and are associated with a reduction in the risk of developing many chronic diseases. For these reasons, physical inactivity must be considered to be an important contributor to the development of the metabolic syndrome.[7] Current physical activity guidelines[7] recommend practical, regular, and moderate regimens for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. Increasing the level of physical activity appears to further enhance beneficial effect. Suggestions that may help to initiate and maintain a regular exercise regimen include incorporating multiple short (10- to 15-minute) bouts of activity (brisk walking), avoiding common sedentary activities in leisure time (television watching and computer games), purchasing simple exercise equipment for the home (eg, treadmills), adding regular exercise into daily schedule (eg, brisk walking, jogging, swimming, biking, golfing, team sports), and self-monitoring of exercise. More exercise (ie, 1 hour daily) is even more efficacious for weight control.

Because of the relation between physical inactivity and the metabolic syndrome, management of the latter should include initiation of a program of regular physical activity. As already mentioned, physical activity is one modality associated with successful weight reduction, particularly for weight maintenance. Conference participants reviewed several clinical trials that showed that the combination of weight reduction and increased physical activity can halve progression to new-onset diabetes over a period of several years in persons with prediabetes, defined as IFG or IGT. Whether weight reduction together with regular exercise will reduce risk for CVD has not been adequately tested in controlled clinical trials; nonetheless, epidemiological data are supportive, and the favorable effects of weight reduction and exercise on CVD risk factors provide strong support and justification for recommending them as part of a regimen to reduce risk for CVD.

Dietary Modification

ATP III recommendations for diet composition for patients with metabolic syndrome are consistent with general dietary recommendations.[8–10] These guidelines call for low intake of saturated fats, *trans* fats, and cholesterol; reduced consumption of simple sugars; and increased intakes of fruits, vegetables, and whole grains. An important question is whether patients with metabolic syndrome will benefit from a shift to relatively more unsaturated fats. Very high-carbohydrate diets may accentuate atherogenic dyslipidemia, and this risk factor is reduced by isocalorically substituting a higher intake of unsaturated fats. The clinical significance of diet-induced

atherogenic dyslipidemia, however, is undetermined. Recent small clinical trials indicate that improvement of atherogenic dyslipidemia by increasing unsaturated fat consumption is relatively small when compared with standard dietary recommendations.[8,9]

Management of Metabolic Risk Factors

Although therapeutic lifestyle modification is first-line therapy for the metabolic syndrome and thus deserves initial attention, drug therapy may be necessary in many patients to achieve recommended goals. Risk assessment in patients with metabolic syndrome is critical for setting goals of therapy.

Risk Assessment

In the conference on definition of metabolic syndrome,[2] investigators from the Framingham Heart Study showed that the standard Framingham risk equations, which include cigarette smoking, blood pressure, total cholesterol, HDL cholesterol, and age, capture most of the risk for CVD in patients with the metabolic syndrome. Adding abdominal obesity, triglycerides, and fasting glucose to these equations provides little or no increase in power of prediction. Whether adding other parameters that contribute to the components of the metabolic syndrome—apolipoprotein B, small LDL, CRP, fibrinogen—to these risk equations will improve prediction of coronary heart disease (CHD) risk has not been tested extensively. At present, therefore, a practical approach to estimating CHD/CVD risk in patients with the metabolic syndrome is to use the standard Framingham algorithm. The risk of developing diabetes is highly dependent on the presence of obesity and IFG—2 components of the syndrome. Whether to carry out OGTT in persons with obesity and/or IFG was debated. Obtaining the 2-hour value in an OGTT may increase the likelihood of finding that a patient already has diabetes or IGT. The presence of IGT signifies increased risk for developing diabetes. Framingham data, however, fail to show independent predictive power of IGT for CVD, although diabetes definitely raises CVD risk. Therefore, OGTT adds power only for detecting or predicting diabetes but not CVD. Moreover, oral glucose testing is inconvenient and adds cost to evaluation. Finally, persons who have diabetes only diagnosed by an OGTT will likely develop diabetes diagnosed by fasting plasma glucose in a relatively short time, and it is unclear whether the hiatus will be clinically meaningful. Therefore, OGTT is not now widely recommended as routine for obese persons who have the metabolic syndrome but must be placed in the category of optional testing based on clinical judgment.

Atherogenic Dyslipidemia

Beyond lifestyle modification, several drug alternatives may be considered in patients with atherogenic dyslipidemia. ATP III emphasized that LDL cholesterol is the primary target of lipid-lowering therapy. Statins will reduce all apolipoprotein B–containing lipoproteins and often can achieve the ATP III goals for LDL cholesterol as well as for non-HDL cholesterol. Several clinical trials have confirmed the benefit of statin therapy.[1] Fibrates improve all components of atherogenic dyslipidemia and appear to reduce the risk for CVD.[1] Their use in combination with statins is particularly attractive. However, both fibrates and statins have the potential to produce myopathy, and when they are used together, risk for myopathy is enhanced.[11] The literature contains many isolated reports of severe myopathy occurring from the combination of statin plus gemfibrozil. Recent evidence further indicates that gemfibrozil interferes with catabolism of statins in the liver, which can raise statin blood levels, thereby predisposing to myopathy. Fenofibrate does not interact adversely with statin catabolism and thus may be safer to use in combination therapy. Nicotinic acid has similar features to fibrates, and the combination of nicotinic acid and statins is promising. Nicotinic acid is especially efficacious for raising HDL cholesterol levels, but higher doses can raise plasma glucose levels. Therefore, if nicotinic acid is used in patients with IFG, IGT, or diabetes, its dose should be kept relatively low (eg, 1 to 2 g per day).

Elevated Blood Pressure

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[12] introduced a new category of "prehypertension" (120 to 139/80 to 89 mm Hg), in recognition of the fact that underlying risk factors raise blood pressure to ranges that increase risk for CVD. This recognition accords with ATP III's adding of blood pressures $\geq$130/$\geq$85 mg/dL to the list of risk factors comprising the metabolic syndrome. In persons with categorical hypertension (blood pressure $\geq$140/$\geq$90 mm Hg), drug therapies are required according to JNC 7 recommendations. In patients with established diabetes, antihypertensive drugs should be introduced at even lower blood pressures ($\geq$130/$\geq$80 mm Hg). No particular antihypertensive agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome. Diuretics and β-blockers in high doses can worsen insulin resistance and atherogenic dyslipidemia. For thiazide diuretics, doses should be kept relatively low in accord with current recommendations. β-Blockers are cardioprotective in patients with established CHD and are no longer contraindicated in patients with type 2 diabetes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, and some clinical trials (but not all) suggest that they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials indicate that most of the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering alone.

Insulin Resistance and Hyperglycemia

There is growing interest in the possibility that drugs that reduce insulin resistance will delay onset of type 2 diabetes and will reduce CVD risk when the metabolic syndrome is present. The Diabetes Prevention Program showed that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes. Data on use of the thiazolidinedione troglitazone suggested a similar effect, but this drug has been withdrawn from commercial use. Although insulin resistance is associated with increased CVD risk, neither metformin nor any of the thiazolidinediones now on the market have been shown to reduce the risk of CVD in those with the metabolic syndrome, prediabetes, or diabetes.

Thus, there is insufficient evidence to recommend these drugs for anything other than their glucose-lowering action.

The presence of the metabolic syndrome in patients with type 2 diabetes conveys a particularly high risk for CVD. When both are present, appropriate treatment of dyslipidemia and hypertension is essential. Good glycemic control is also important because of the evidence suggesting that a reduction in A1C level to 7.0% or less will reduce CVD events. Choice of drug therapy beyond lifestyle changes to achieve this glycemic goal depends on clinical judgment.

Prothrombotic State

A prothrombotic state in patients with the metabolic syndrome is characterized by elevations of fibrinogen, PAI-1, and possibly other coagulation factors. However, these are not measured routinely in clinical practice. The risk for thrombotic events can be reduced by aspirin therapy. The AHA currently recommends use of aspirin prophylaxis in most patients whose 10-year risk for CHD is ≥10% as determined by Framingham risk scoring.[13] Including patients with metabolic syndrome when their 10-year risk for CHD is ≥10% is appropriate.

Proinflammatory State

This condition is characterized by elevated cytokines (eg, tumor necrosis factor-α and interleukin-6) as well as by elevations in acute-phase reactants (CRP and fibrinogen). Measurement of CRP is the most practical way to assess the presence of an inflammatory state. CRP levels tend to be higher than normal in patients with the metabolic syndrome. An elevated CRP (≥3 mg/L) is an emerging risk factor for CVD.[1] The AHA and Centers for Disease Control and Prevention (CDC)[14] recently issued guidelines for measurement of CRP in clinical practice. They suggested that such measurements can be made at the physician's discretion, but testing should be limited to individuals assessed to be at intermediate risk by Framingham scoring, ie, those whose 10-year risk for CHD is in the range of 10% to 20%. The purpose of CRP testing in an intermediate-risk patient is to find those with high CRP levels whose risk category should be raised to high. The practical consequences of elevating the risk category would be to intensify lifestyle therapies, make certain that low-dose aspirin is used, and set lower LDL goals. AHA/CDC guidelines emphasized that CRP testing still belongs in the category of *optional based on clinical judgment* rather than *recommended routinely* because the magnitude of its independent predictive power remains uncertain.[15]

Major Conclusions

The metabolic syndrome consists of a constellation of factors that raise the risk for CVD and type 2 diabetes. Because of the increasing prevalence of obesity in the United States, the metabolic syndrome has increased in frequency. ATP III introduced the metabolic syndrome into its clinical guidelines in the effort to achieve CVD risk reduction beyond LDL-lowering therapy. Other clinical guidelines likewise have emphasized the need for more clinical attention to the metabolic syndrome.

Although not all obese, sedentary persons acquire the metabolic syndrome, a significant subgroup of the population is susceptible to worsening of important contributors to the metabolic syndrome in the presence of energy imbalance. Several factors appear to contribute to this susceptibility, especially genetic predisposition and aging. Certain ethnic groups are particularly susceptible to the syndrome. Insulin resistance is a common feature of many of the components of the metabolic syndrome, and some investigators believe that it plays a key pathogenic role. Although genetic susceptibility is essential, the metabolic syndrome is relatively uncommon in the absence of obesity and physical inactivity. For this reason, lifestyle modification leading to weight reduction and increased physical activity represents first-line clinical therapy of the metabolic syndrome. Practical approaches to both were considered in depth in the conference. Smoking cessation, of course, is paramount. A realistic goal for overweight/obese persons is to reduce body weight by ≈7% to 10% over a period of 6 to 12 months. Weight reduction should be combined with a daily minimum of 30 minutes of moderate-intensity physical activity. Nutritional therapy calls for a low intake of saturated fats, *trans* fats, and cholesterol; reduced consumption of simple sugars; and increased intakes of fruits, vegetables, and whole grains. Extremes in intakes of either carbohydrates or fats should be avoided.

In addition, it was recognized that when genetic influences are particularly strong or when lifestyle changes fail to reduce risk sufficiently, drug therapy might be required to achieve treatment goals recommended in current guidelines. Particular attention must be given to adequately controlling the other major CVD risk factors: cigarette smoking, hypertension, elevated LDL cholesterol, and diabetes. Standard therapies for each apply in patients with the metabolic syndrome. Use of combination therapy with fibrates or nicotinic plus a statin is attractive for metabolic-syndrome patients with atherogenic dyslipidemia; even so, efficacy over statins alone has not been documented through clinical trials. Low-dose aspirin to modify the prothrombotic–proinflammatory state is justified for patients at intermediate risk and high risk. To date, management of insulin resistance with insulin-sensitizing agents in the absence of diabetes has not been shown to reduce CVD risk; therefore, they cannot be recommended for this purpose.

Unresolved Issues: Future Research Challenges

The conference highlighted several unresolved issues that should receive attention. These include the following for patients with the metabolic syndrome:

1. Improved strategies for successful weight reduction and maintenance and increased physical activity
2. A better understanding of the genetic and metabolic contributions leading to the development of the syndrome
3. Improved risk assessment for CVD
4. The value of treating atherogenic dyslipidemia beyond LDL-lowering therapy
5. The efficacy of treating insulin resistance for reducing the risk of CVD

6. A better understanding of the relationship between a proinflammatory state and the metabolic syndrome and the efficacy of intervention on this state for the prevention of both CVD and diabetes
7. Establishment of benefit and cost-effectiveness of specified goals for drug therapies directed toward the metabolic syndrome as a whole or particular risk components

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