Unmet Needs in Controlling Metabolic Disease

Steven M. Haffner, MD

Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, TX

In the past 10 years, there has been interest in a "metabolic syndrome" that might be associated with cardiovascular disease or diabetes. The first sets of criteria differed markedly, and their accuracy was equivocal. More recent definitions may be an improvement over previous ones. The metabolic syndrome may be most useful as a predictor of cardiovascular disease in nondiabetic subjects. It encourages healthcare providers who are confronted with a single risk factor to look for others. When multiple risk factors are found, it promotes consideration of behavioral interventions, such as weight loss and increased physical activity, instead of a pharmacological treatment for each risk factor. Such behavioral interventions were more effective than metformin in reducing the incidence of diabetes and of other components of the metabolic syndrome in one randomized, controlled study.

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Cardiovascular disease (CVD) is the single greatest cause of morbidity and mortality in the United States. Major risk factors identified for coronary heart disease (CHD) include increased age, male sex, cigarette smoking, high low-density lipoprotein cholesterol (LDL-C) or total cholesterol, low high-density lipoprotein cholesterol (HDL-C), diabetes, and high systolic blood pressure.[1] These risk factors have been shown to be independent, statistical predictors of major CHD events (fatal and nonfatal myocardial infarctions). However, established risk factors probably explain only about 50% of CVD cases.

Moreover, very effective therapies, such as the use of statins in the Scandinavian Simvastatin Survival Study Group (4S),[2] the Collaborative Atorvastatin Diabetes Study (CARDS),[3] and the Heart Protection Study,[4] prevent or delay only 25% to 40% of coronary events, leaving 60% to 75% of "at-risk" patients subject to them. Even the more aggressive LDL-C reduction in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study[5] and Treating to New Targets (TNT) study[6] reduced events by 16% to 22% over standard statin therapies. Other treatments, such as hypertension therapy and, particularly, multi–risk factor interventions, as were used in the Steno-2 Study,[7] may produce even larger reductions—although only slightly exceeding 50%. The question thus can be asked: What additional strategy might be used?

Obesity, although not found to be a statistical predictor of CHD in trials such as the Framingham Study[1] (perhaps because its effect on CHD may be mediated through other risk factors, such as hypertension and low HDL-C), may be a possible target. Several groups have emphasized the importance of obesity to cardiovascular disease.[8-11]

Over the past 10 years, several groups have focused on the concept of metabolic risk. The risk factors included are not usually considered a part of traditional global risk models.[1,11] These variables include visceral fat, insulin resistance, atherogenic dyslipidemia (elevated triglycerides; lowered HDL-C; small, dense LDL-C), hypertension, glucose intolerance (impaired glucose tolerance, diabetes mellitus), impaired fibrinolysis (elevated plasminogen activator inhibitor 1, fibrinogen), inflammation (elevated creatinine reactive protein), polycystic ovarian syndrome (lowered sex hormone–binding globulin, lowered free testosterone), and nonalcoholic fatty liver disease (Table 1). Because many of these factors, such as insulin resistance, inflammation, impaired fibrinolysis, and glucose tolerance, are not commonly assessed in routine clinical practice, a number of groups have developed operational definitions for the metabolic syndrome, which are meant to be a clinical tool. These definitions will be discussed in the next section.

Table 1
Cardiometabolic Risk

Visceral fat
Insulin resistance
Atherogenic dyslipidemia (increased triglycerides; decreased high-density lipoprotein cholesterol; small, dense low-density lipoprotein cholesterol)
Hypertension
Glucose intolerance (impaired glucose tolerance, diabetes mellitus)
Impaired fibrinolysis (increased plasminogen activator inhibitor 1, fibrinogen)
Inflammation (increased creatinine reactive protein)
Polycystic ovarian syndrome (decreased sex hormone–binding globulin, decreased free testosterone)
Nonalcoholic fatty liver disease

The Metabolic Syndrome

In the past 10 years, increased interest in the "metabolic syndrome" has been based on the development of 2 operational definitions: one proposed by the World Health Organization (WHO)[12] and the other by the National Cholesterol Education Program (NCEP).[1] These definitions differ markedly. The NCEP criteria require at least 3 out of 5 risk factors, whereas the WHO definition requires insulin resistance as an underlying factor for diagnosis. In addition, the NCEP definition uses waist circumference as a measure of obesity, whereas the WHO definition uses body mass index or the waist-to-hip ratio.

Many studies have compared the accuracy of these definitions. In some cases, the NCEP criteria were better than the WHO criteria at predicting cardiovascular disease,[13] but in other cases, the WHO criteria were superior.[14] In a study by Lakka and colleagues[14] in Finland, the increased risk of CVD mortality was 3.5 times higher in subjects with the metabolic syndrome than in subjects without it. In a study by Hunt and colleagues[13] of data from the San Antonio Heart Study, the increase in CVD mortality seen in patients with the metabolic syndrome was lower by about 2.0 in nondiabetic subjects (Table 2). Although both the WHO and the NCEP criteria predict the presence of insulin resistance, WHO was superior in the Insulin Resistance Atherosclerosis Study (IRAS).[15] The NCEP criteria were believed to have too-high cutpoints for waist circumference for Asian populations in Singapore[16] and Japan.[17] One of the major criticisms from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) is that there are several competing definitions and that the definitions presuppose different

Table 2
Hazard Ratio for CVD Mortality in the San Antonio Heart Study*†

Baseline Status	Women	Men
No DM, did not meet NCEP criteria	1.00	1.00
No DM, met NCEP criteria	2.07 (0.72, 6.00)	1.96 (0.99, 3.88)
Yes DM, did not meet NCEP criteria	3.53 (0.75, 16.7)	2.34 (0.70, 7.82)
Yes DM, met NCEP criteria	8.19 (3.15, 19.1)	3.09 (1.49, 6.43)

*Adjusted for age and ethnicity.
†No CVD at baseline.
CVD, cardiovascular disease; DM, diabetes mellitus; NCEP, National Cholesterol Education Program.
Adapted with permission from Hunt KJ et al.[13]

underlying etiologies (WHO presupposes insulin resistance and NCEP presupposes visceral fat).[18]

Because of the problems in having 2 rival definitions of the metabolic syndrome, an international committee under the leadership of the International Diabetes Federation (IDF) attempted to develop a consensus definition. This effort was not completely successful because the NCEP definition remains commonly used. The IDF definition was published in *Lancet* in September 2005.[19] It identifies the same components as NCEP, but with 2 exceptions. First, IDF requires an elevated waist circumference, much like the older WHO definition. Second, IDF introduces different waist circumferences for different regions. Of interest is that in Japanese populations, the waist cutpoint for women is higher than for men, in contrast to the cutpoints in other regions for IDF and NCEP. There are now a few published papers on the IDF definition. Sone and colleagues[20] suggest that the new IDF definition is not superior to the older NCEP definition in predicting cardiovascular disease. Hanley and colleagues[21] showed that the IDF definition is not superior to the NCEP definition or the WHO definition in predicting diabetes.

Even more recently, a slightly modified version of the NCEP was published. These criteria are called the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition[11] (Table 3). They recognize a lower level for impaired fasting glucose (> 100 mg/dL). They also include patients who take pharmacological therapy for hypertension or lipids (fibric acid or nicotinic acid), even if treatment maintains these conditions below the cutpoint. In addition, the NCEP suggests in a footnote that a lower cutpoint for waist circumference of 90 cm in men and 80 cm in women may be appropriate for subjects of Asian descent.

The new definitions (IDF and AHA/NHLBI) may be an improvement because they are much more similar than are the WHO and the NCEP definitions. It is likely that future studies will not find major differences in the ability of these definitions to predict CVD and diabetes because they use similar components. There is still the question about whether use of the required components, such as waist circumference in the IDF definition, improves the ability to predict outcome. An analysis of the IRAS data[21] requiring a high waist circumference did not improve either the odds ratio or the area under the receiver operated curve (AROC) in predicting diabetes. Furthermore, it is possible that the waist cutpoints for Japanese

Table 3
American Heart Association/National Heart, Lung, and Blood Institute: The Metabolic Syndrome*

Risk Factor	Defining Level
Waist circumference†	
Men	≥ 102 cm (> 40 in)
Women	≥ 88 cm (> 35 in)
Triglycerides‡	≥ 150 mg/dL
High-density lipoprotein cholesterol‡	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure‡	≥ 130 (systolic) or ≥ 85 (diastolic) mm Hg
Fasting glucose‡	≥ 100 mg/dL

*Diagnosis is established when 3 or more risk factors are present.
†Some US adults of non-Asian origin with marginal increases should benefit from lifestyle changes. There are lower cutpoints (≥ 90 cm in men and ≥ 80 cm in women) for Asian Americans.
‡Or on drug treatment for the risk factor.
Adapted with permission from Grundy SM et al.[11]

Table 4
Potential Concerns With the Metabolic Syndrome Classification

Data are lost with use of dichotomous variables Are the cutpoints developed in the United States applicable to countries with different lifestyles? There is low body mass index in Asia and low high-density lipoprotein cholesterol with high carbohydrate diets.
Components of the metabolic syndrome differ in their ability to predict diabetes and cardiovascular disease
Does the metabolic syndrome predict cardiovascular disease independently of its components?
Does the metabolic syndrome have a single etiology? (Is a single etiology necessary for a syndrome?)

subjects may have to be changed after additional evaluation. Nevertheless, these new definitions, particularly the refinements made to the NCEP by the AHA/NHLBI (the decreased waist circumference cutpoint for Asian populations and the recognition that use of pharmacological therapy meets the lipids and blood pressure component cutpoints), are an improvement.

The ADA/EASD Critique of the Metabolic Syndrome

The metabolic syndrome has been shown to be a risk factor for CVD and diabetes.[13,14] Because many of the published papers are relatively uncritical of this association, the recent ADA/EASD statement[18] provides a useful counterbalance to the unbridled enthusiasm of many metabolic syndrome advocates (Table 4). The ADA/EASD statement offers a number of critiques of the metabolic syndrome. The statement questions the value of including subjects with diabetes in the metabolic syndrome. About 85% of diabetic subjects in the National Health and Nutrition Examination Survey (NHANES) have the metabolic syndrome.[22] The metabolic syndrome may be most useful as a predictor of CVD in nondiabetic subjects.[13] Additionally, not all components of the metabolic syndrome predict CHD equally well. For instance, in the NHANES data,[22] diabetes, hypertension, and low HDL-C are significant predictors of the prevalence of CHD, whereas the other factors are not statistically significant independent predictors (Table 5). The observation that obesity is not a *significant* independent predictor does not, of course, preclude it from being a target of intervention. The ADA/EASD also suggests that the metabolic syndrome does not predict CHD or CVD independently of their individual components. This observation is true in almost all studies, including the NHANES data.[22] The latter 2 critiques are probably the most cogent ones in the ADA/EASD statement.

There are other potential critiques of the metabolic syndrome. In recent Framingham data,[23] there is a stepwise increase in the risk of both CVD and diabetes as one goes from no metabolic syndrome factors to 1 or 2 factors to 3 or more factors. This association suggests that information is lost when only a dichotomous cutpoint for the number of Framingham factors is used. This limitation also applies when one dichotomizes variables such as HDL-C or hypertension, instead of using continuous variables or categories with 4 levels (as are used in Framingham Global Risk). Much has been written about whether the cutpoints used in the NCEP or WHO are applicable to populations around the world. This consideration has been best recognized with the proposed use of lower BMI or waist circumference cutpoints in

Table 5
Prediction of Coronary Heart Disease Prevalence Using Multivariate Logistic Regression: NHANES

Variable	Odds Ratio	Lower 95% Limit	Upper 95% Limit
Waist circumference	1.13	0.85	1.51
Triglycerides	1.12	0.71	1.77
High-density lipoprotein cholesterol*	1.74	1.18	2.58
Blood pressure*	1.87	1.37	2.56
Impaired fasting glucose	0.96	0.60	1.54
Diabetes*	1.55	1.07	2.25
Metabolic syndrome	0.94	0.54	1.68

*Significant predictors of prevalent coronary heart disease.
NHANES, National Health and Nutrition Examination Survey.
Adapted with permission from Alexander CM et al.[22]

Asian countries. In fact, the more recent AHA/NHLBI[11] and the IDF criteria[19] employ different cutpoints for obesity in different regions.

It should be mentioned that many concerns of the ADA/EASD have considerably less merit. The ADA/EASD has suggested that the metabolic syndrome criteria are ambiguous, incomplete, or conflicting. This assessment may have been true of the earlier WHO[12] and NCEP[1] criteria, but the newer IDF[19] and AHA/NHLBI[11] criteria in fact have similar cutpoints. The ADA/EASD supports insulin resistance as a common underlying etiology,[18] while criticizing the metabolic syndrome definitions for being uncertain about the value of insulin resistance as an underlying factor. The NCEP,[1] AHA/NHLBI,[11] and the IDF[19] all suggest that obesity and/or visceral fat are underlying components.

The metabolic syndrome appears to be a stronger predictor of diabetes than of cardiovascular disease.[23,24] The ADA/EASD faulted the current operational definitions of the metabolic syndrome for omitting important variables. The existing definitions were devised so that clinicians could use them with readily available tools, and thus measurements for inflammation, insulin concentrations, and insulin resistance were purposefully excluded. The addition of factors such as creatinine reactive protein and directly measured insulin resistance has not been shown to improve the AROC for the incidence of diabetes.[21] It is curious that the ADA/EASD ignored a number of important areas in current diabetes research, such as nonalcoholic fatty liver disease. Elevated liver function tests have been shown to predict the development of diabetes and the metabolic syndrome even independently of directly measured insulin resistance.[25] Because liver function tests are often obtained by physicians, their use as a component of operational definitions of the metabolic syndrome should be considered.

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The metabolic syndrome, in spite of its limitations, still has considerable usefulness (Table 6). It encourages healthcare providers who are confronted with a single risk factor to look for others. When multiple risk factors are found, it promotes consideration of behavioral interventions, such as weight loss and increased physical activity, instead of uncritically suggesting that each risk factor be treated with a different pharmacological intervention—an approach that might be undertaken when the focus is purely on global risk. Lastly, global risk may be superior to metabolic risk at predicting CVD (because it includes demographic information such as age, sex, and smoking), but few healthcare providers actually calculate global risk. The metabolic syndrome was not designed for use as a tool to predict risk. If it had been, use would be restricted to older individuals, such as men older than 45 years and women older than 55 years.

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Visceral Fat

The atherogenic metabolic profile of patients with abdominal obesity is likely to contribute to their increased risk of type 2 diabetes and premature coronary heart disease.[26-31] The higher risk of waist circumference associated with diabetes may be explained by the strong relation of insulin levels and insulin resistance to waist circumference.[30,32,33] Elevated waist circumference is a risk factor for the development of diabetes and the metabolic syndrome, both in low-risk patients (normal

Table 6
Potential Advantages of the Metabolic Syndrome Classification

Provides an operational definition for "cardiometabolic" risk
Is much easier to use than global risk measurement or multivariate predicting equations (which are almost never used)
Encourages providers to look for other risk factors
Encourages behavioral therapy rather than treatment of individual risk factors
Is a better predictor of diabetes than of cardiovascular disease

glucose tolerance) and higher-risk patients (impaired glucose tolerance).[34] More definitive measures of abdominal obesity (visceral fat measured by computed tomography scans) show a very strong association with the development of CVD and diabetes in Japanese Americans,[35] a population that is not obese but is at high risk of diabetes.

The Diabetes Prevention Program

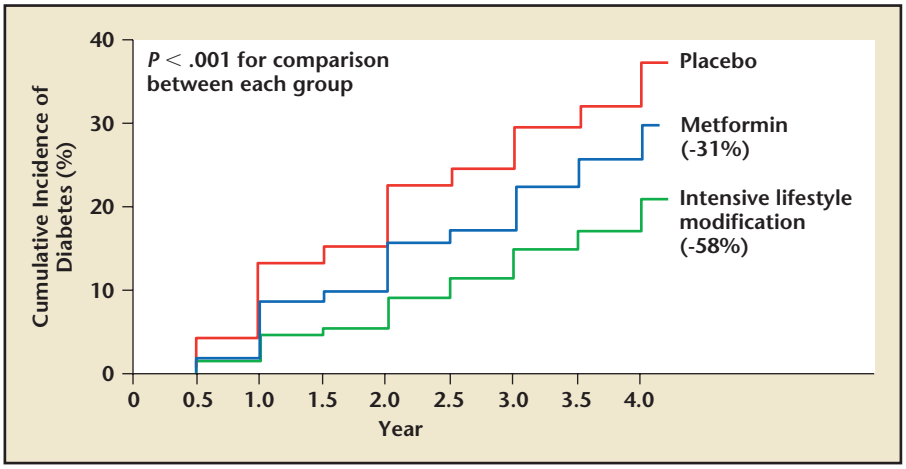
The Diabetes Prevention Program (DPP) was a randomized, controlled trial in subjects with impaired glucose tolerance who were randomized to placebo, metformin 850 mg twice daily, or an intensive lifestyle intervention, including 150 minutes of exercise a week, that was designed to achieve a 7% weight loss. Over the 3.2 years of follow-up, an average 5% weight loss was achieved. Intensive lifestyle interventions reduced the incidence of diabetes by 58%, and metformin reduced the incidence of diabetes by 31% as compared with placebo (Figure 1).[35]

The authors described in a further report[36] the effects of these interventions on the metabolic syndrome as defined by the NCEP.[1] Of the subjects, 53% had the metabolic syndrome. Of the components, an elevated waist circumference was the most common (73%), and high fasting glucose was the least common (33%). The prevalence of the metabolic syndrome between baseline and follow-up increased from 55% to 61% in the placebo group, remained unchanged (54% to 55%) in the metformin group, and decreased from 51% to 43% in the lifestyle modification group. Among subjects without the metabolic syndrome at baseline (approximately 45% of the overall population), the lifestyle intervention reduced the development of the metabolic syndrome by 41% (95% confidence interval [CI], 28%-52%) compared with placebo, and by 29% (95% CI, 13%-42%) relative to metformin. Metformin significantly reduced the metabolic syndrome relative to placebo (17%, 95% CI, 0%-31%; $P = .03$). The lifestyle intervention reduced the incidence of all components except for low HDL-C, whereas metformin was effective only in reducing the incidence of high waist circumference and fasting glucose. Among subjects who had the metabolic syndrome at baseline (approximately 55% of the population), only the lifestyle intervention showed a significant effect compared with placebo ($P = .002$).

This study shows that intensive lifestyle interventions are more effective than metformin in reducing the incidence of diabetes and of other components of the metabolic syndrome. This finding might suggest that in the long-term, intensive lifestyle interventions may be more effective in reducing the incidence of cardiovascular disease. The current study did not analyze which aspect of the DPP lifestyle regimen (weight loss or increased physical activity) was more effective in reducing the prevalence of the metabolic syndrome. Preliminary data from the DPP suggest that weight loss was most responsible for the reduction of the incidence of type 2 diabetes. Unfortunately, in the DPP study, the second pharmacological treatment (troglitazone) was withdrawn early for safety reasons and therefore was not evaluated.

In other studies, pharmacological therapies often reduced obesity by similar or slightly lower amounts than those observed in the DPP study. The independent use of pharmacological agents might be expected to be less effective than the DPP intervention, which included an exercise component. Moreover, the various pharmacological agents are likely to have unequal effects on the prevalence of the metabolic syndrome because they have different effects on blood pressure, glucose, and lipid levels.[37-39] Nevertheless, it is possible that weight loss intervention might be relatively more effective in reducing the incidence of the metabolic syndrome than metformin or acarbose, which have been previously tested for the prevention of diabetes. More work clearly needs to be done in this area.

Figure 1. *Incidence of type 2 diabetes: Diabetes Prevention Program. Adapted with permission from the Diabetes Prevention Program Research Group.*[35]



Summary

Multifactorial risk interventions targeting diabetes, blood pressure, and lipids have reduced cardiovascular events by little more than 50%.[7] One promising type of therapy might be weight reduction (by behavioral and/or pharmacological interventions) and increased physical activity. Such an approach was found in the DPP to be successful in reducing the incidence of diabetes and the metabolic syndrome.[35,36] More studies of these types of interventions using "hard" endpoints for CVD are urgently needed. ■

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Main Points

- The metabolic syndrome has been shown to be a risk factor for cardiovascular disease and diabetes.
- There is a stepwise increase in the risk of both cardiovascular disease and diabetes as one goes from no metabolic syndrome factors to 1 or 2 factors to 3 or more factors.
- About 85% of diabetic subjects in the National Health and Nutrition Examination Survey have the metabolic syndrome.
- Newer, improved criteria for the metabolic syndrome decreased the waist circumference cutpoint for Asian populations and added the use of pharmacological therapy for hypertension or lipids.
- The atherogenic metabolic profile of patients with abdominal obesity is likely to contribute to their increased risk of type 2 diabetes and premature coronary heart disease.
- Intensive lifestyle interventions are more effective than metformin in reducing the incidence of diabetes and of other components of the metabolic syndrome.

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