

Epidemiology of the Metabolic Syndrome, 2002

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Abstract

Background: The close association of type 2 diabetes and atherosclerotic cardiovascular disease (CVD) suggests that they share a common physiologic antecedent, postulated to be tissue resistance to insulin. Insulin resistance is associated with a cluster of risk factors recognized as the metabolic syndrome.

Objective: To describe the epidemiology of the insulin resistance syndrome, also known as the metabolic syndrome.

Methods: Overall obesity, central obesity, dyslipidemia characterized by elevated levels of triglycerides and low levels of high-density lipoprotein cholesterol, hyperglycemia, and hypertension are common traits that, when they occur together, constitute the metabolic syndrome. The World Health Organization and the National Cholesterol Education Program Adult Treatment Panel III have proposed working definitions for the syndrome based on these traits. Cross-sectional and longitudinal epidemiologic studies provide an emerging picture of the prevalence and outcomes of the syndrome.

Results: National survey data suggest the metabolic syndrome is very common, affecting about 24% of US adults who are 20 to 70 years of age and older. The syndrome is more common in older people and in Mexican Americans. People with the syndrome are about twice as likely to develop CVD and over 4 times as likely to develop type 2 diabetes compared with subjects who do not have metabolic syndrome. While this syndrome may have a genetic basis, environmental factors are important modifiable risk factors for the condition.

Conclusions: The metabolic syndrome is very common and will become even more common as populations age and become more obese. Treatment for component traits is known to reduce the risk for type 2 diabetes and CVD; whether risk is reduced by treatment of the syndrome, specifically, remains uncertain. Primary care physicians must recognize that the co-occurrence of risk factors for type 2 diabetes and CVD represents an extremely adverse metabolic state warranting aggressive risk factor intervention.

(*Am J Manag Care* 2002;8:S283-S292)

Diabetes mellitus is extremely common, affecting more than 8% of the US population between the ages of 20 and 74 years of age.¹ Type 2 diabetes accounts for more than 90% of these cases. Alarming, the incidence of type 2 diabetes is rapidly accelerating worldwide, with prevalence rates in the US alone expected to increase by more than 165% by 2050.¹ This epidemic of type 2 diabetes is largely fueled by obesity and sedentary behaviors.² Although patients with type 2 diabetes are affected by microvascular complications, cardiovascular disease (CVD) complications exert the greatest toll. CVD, including coronary heart disease, peripheral vascular disease, and cerebrovascular disease, is more than twice as common among patients with diabetes than those who do not have diabetes^{3,4} and is the major cause of morbidity and death in type 2 diabetes.⁵⁻⁸ CVD events occur more than twice as frequently as the microvascular events specific to diabetes, and fatal CVD events may be as much as 70 times as common as fatal microvascular events.⁷ Diabetes and its complications cause substantial loss in quality of life; as the fourth most frequent reason for ambulatory physician visits, this disease incurs more than \$100 billion annually in US healthcare expenditures.⁹⁻¹¹ No other common condition is likely to have a more pernicious effect on patient health and healthcare budgets than diabetes. Fortunately, our understanding of the precursors of type 2 diabetes and CVD is improving at the same time better evidence of methods to prevent these conditions are becoming available.

Over the last 25 years, type 2 diabetes and CVD have been shown to develop over time in the setting of adverse levels of

diverse metabolic risk factors. More recently, information has become available that type 2 diabetes and CVD share many risk factors, especially obesity, hyperlipidemia, hypertension, and hyperglycemia. These associations gained broader recognition in the late 1980s with the postulation of syndrome X.¹² Reaven's physiologic research documented that resistance to tissue effects of insulin was a feature of obesity and a fundamental pathophysiologic precursor of type 2 diabetes as well as a possible precursor of hypertension and dyslipidemia, particularly for patients with low levels of high-density lipoprotein cholesterol (HDL-C) and elevated levels of triglycerides. Based on these observations, Reaven proposed that obesity, hyperglycemia, hypertension, and dyslipidemia are at least partially caused by insulin resistance and are recognizable as a syndromic precursor to type 2 diabetes and CVD. The existence of a discrete syndrome has been the subject of controversy, although the emerging body of evidence lends substantial support for a discrete metabolic syndrome.¹³

Evidence for a Metabolic Syndrome

Early population-based evidence supporting existence of an identifiable pathogenic syndrome included prospective associations of individual CVD risk factors with incident development of type 2 diabetes. For instance, data from the San Antonio Heart Study documented a greater prevalence of obesity, hypertension, low levels of HDL-C, hyperglycemia, and hyperinsulinemia among subjects who initially did not have diabetes but developed type 2 diabetes over 8 years of follow-up compared with subjects who did not develop diabetes.¹⁴ Related data suggested that central adiposity in particular was responsible for the role of obesity conferring elevated metabolic risk.¹⁵ Subsequent data from San Antonio demonstrated that prediabetic subjects with insulin resistance had more CVD risk factors than insulin-sensitive prediabetic subjects, supporting a role for insulin resistance in the joint pathogenesis of type 2 diabetes and CVD.¹⁶ Data from

Finland also shows that hyperinsulinemia precedes development of hypertension and dyslipidemia.¹⁷

Critics of the metabolic syndrome hypothesis point out that the constituent traits are themselves quite common and may reasonably be expected to co-occur in some subjects independent of any underlying unifying physiology.¹⁸ However, population studies document that these metabolic risk factors co-occur to a far greater degree than would be predicted by chance alone. For instance, in the Framingham Offspring Study, groupings of 3 or more risk factors, which include low HDL-C levels and elevated values for body mass index (BMI), systolic blood pressure, triglycerides, glucose, and total cholesterol, occurred at twice the rate predicted by chance.¹⁹ Similar risk factor clustering was found in the Atherosclerosis Risk in Communities Study.²⁰ Results of factor analyses provide additional statistical evidence for a physiologic syndrome. Factor analysis is a multivariate correlation method that seeks to identify the unifying correlation patterns underlying a large set of intercorrelated variables such as metabolic traits related to insulin resistance. More than a dozen factor analyses of metabolic risk factor data from a wide array of populations has shown that all of the individual traits of the syndrome stem from 2 to 4 underlying physiologic processes; in many cases, a central role for insulin resistance or hyperinsulinemia is suggested.^{13, 21}

Prospective outcomes data lends further support for the validity of the metabolic syndrome hypothesis. Insulin resistance is well recognized as a major precursor of type 2 diabetes,²² and hyperinsulinemia associated with insulin resistance appears to be an independent risk factor for CVD.^{23, 24} Recently, several studies have shown that the central insulin resistance cluster identified by factor analysis is associated with incident development of both type 2 diabetes and CVD. Several studies from Scandinavia show that among subjects who initially did not have diabetes, the insulin resistance cluster increased relative risk for type 2 diabetes by over 4-fold,²⁵ risk for CVD by about

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

WHO	NCEP ATP III
(IFG or IGT or diabetes) and/or insulin resistance plus 2 or more of:	Three or more of:
Waist-hip ratio >0.85 (women) or >0.9 (men) and/or body mass index >30 km ²	Abdominal obesity: waist circumference >88 cm (women) or 102 cm (men)
Triglycerides ≥1.7 mM and/or HDL-C <0.9 mM (women) or <1.0 mM (men)	Triglycerides ≥1.7 mM
Blood pressure ≥140/90 mm Hg	HDL-C <1.16 mM (women) or <0.91 mM (men)
Microalbuminuria: urinary albumin excretion rate ≥20 mcg/min or albumin/creatinine ratio ≥ 30 mg/g	Blood pressure ≥130/85 mm Hg FPG ≥6.1 mM

HDL-C indicates high-density lipoprotein cholesterol; IFG, impaired fasting glucose: fasting plasma glucose (FPG) 6.1–6.9 mM and 2-hour post-oral glucose challenge plasma glucose (2hPG) < 7.8 mM; IGT, impaired glucose tolerance: FPG < 6.1mM and 2hPG 7.8-11.0 mM; diabetes, treatment for hyperglycemia or FPG ≥7.0 mM and/or 2hPG ≥11.1 mM; insulin resistance, insulin clamp-assessed glucose uptake below the 25th percentile, or homeostasis-model assessed (HOMA; fasting insulin/fasting glucose × 22.5) insulin resistance above the 75th percentile, as measured among subjects with no metabolic abnormalities.

Source: References 33-35.

30%,²⁶⁻²⁸ and in subjects with type 2 diabetes, increased risk for CVD by 40% to 70%.²⁹⁻³¹ Preliminary evidence from the Framingham Offspring Study also shows that subjects with the metabolic syndrome are at a greater than 11-fold increased risk for incident type 2 diabetes and about a 2.4-fold increased risk for incident CVD events.³² Thus, current population based-evidence demonstrates greater-than-chance co-occurrence of metabolic risk factors linked to insulin resistance, giving rise over time to the joint occurrence of type 2 diabetes and CVD.

Definitions of the Metabolic Syndrome

Despite the accumulated evidence cited above, until recently, no uniform definition for the insulin resistance or metabolic syndrome has been available. Each research group has tended to use its own idiosyncratic case definition, effectively prohibiting uniform analysis of the epidemiology of the syndrome. Even the name of the syndrome has been the subject of wide variation.^{13,33} Recently, 2 expert groups, the World Health Organi-

zation (WHO)³⁴ and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)³⁵ have proposed criteria defining the metabolic syndrome. These criteria are listed in **Table 1**, and suggestions for clinical assessment of the component traits are given in **Table 2**. These definitions are similar in their focus on obesity, dyslipidemia, hyperglycemia, and hypertension as constituent traits.

However, substantial differences in these definitions still remain. The WHO includes, as a component trait, the presence of postchallenge hyperglycemia as well as insulin resistance, while the NCEP ATP III considers only fasting hyperglycemia to be a component trait. Some concern has been expressed that relying on fasting glucose only to assess glycemic status overlooks a large proportion of subjects with isolated postchallenge hyperglycemia who may be classified as unaffected according to NCEP ATP III criteria.³⁶ Both criteria explicitly (WHO) or implicitly (NCEP ATP III) include type 2 diabetes as a component trait. Substantial controversy over this issue continues, as

Table 2. Clinical Assessment of Metabolic Syndrome Traits

Glucose tolerance status	
Impaired fasting glucose	Requires an overnight fast of at least 8 hours
Impaired glucose tolerance	Requires an oral glucose tolerance test
Insulin resistance	Not yet recommended in clinical practice; requires (at least) measurement of the fasting insulin level
Body Mass Index	Weight and height measured with the patient in light clothing
Waist circumference	Abdomen measured at the level of the umbilicus
Waist-hip ratio	Hip circumference measured at the level of the iliac crest
Triglycerides	Requires an overnight fast of at least 8 hours
HDL-C	Can be performed on nonfasting blood samples
Blood pressure	Most studies use the average of 2 measurements after the subject has been sitting for 5 minutes
Microalbuminuria	Measured with a timed overnight urine collection or a spot morning urine collection

HDL-C indicates high-density lipoprotein cholesterol.

many experts feel that type 2 diabetes is a consequence, rather than a component, of the syndrome. In addition, assessment of insulin resistance or hyperinsulinemia is not part of usual clinical practice. Therefore, this element of the WHO criteria is quite controversial.³³

Another difference in the definitions involves the WHO criteria that consider either overall obesity (assessed by BMI) or central obesity (assessed by waist-hip ratio) as candidate traits; the NCEP ATP III considers only central obesity. A third difference is that the WHO criteria, which assign points for each component, allow only 1 point for dyslipidemia; the NCEP ATP III criteria assign up to 2 points for low HDL-C and high triglyceride levels, potentially overweighting the contribution of these factors to the metabolic syndrome phenotype. Indeed, an accurate measurement of how each trait contributes to risk for adverse outcomes is uncertain. Regression models predicting development of type 2 diabetes demonstrate, for instance, that fasting hyperglycemia confers a 4-fold greater risk per unit increase

over that of systolic blood pressure.³⁷ Thus, weighting each trait equally may distort risk associated with the metabolic syndrome, especially when comparisons are made across populations with substantial differences in underlying trait prevalence.

Another difference involves blood pressure thresholds, which are higher in the WHO criteria compared with the NCEP ATP III criteria, leaving a lower prevalence, but greater severity, of hypertension among those with the metabolic syndrome according to WHO criteria. Finally, the WHO specify microalbuminuria as a component trait, while NCEP ATP III does not.

The presence of these differences and other problems with proposed criteria for the metabolic syndrome point out the substantial ongoing uncertainty remaining in the field. Whether proposed criteria identify substantially different subjects or confer differential risk for type 2 diabetes or CVD remains to be determined.

Prevalence of the Metabolic Syndrome

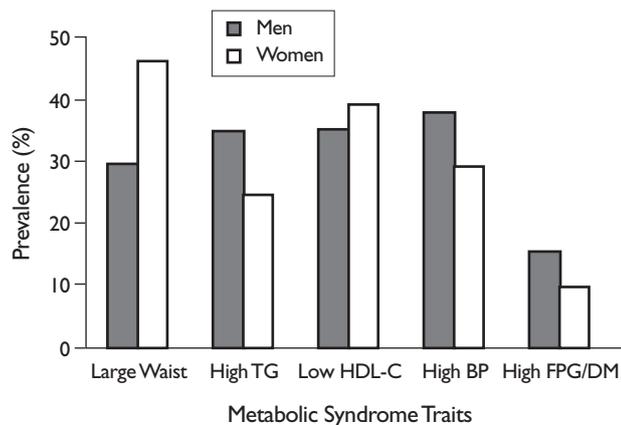
The WHO criteria were proposed in

1998, and the NCEP ATP III criteria were proposed in 2001. To date, very little published data is available on the prevalence of the metabolic syndrome in the US population. The best current data was published in early 2002 by Ford et al based on an analysis of 8814 men and women 20 years of age and older from the Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994), a cross-sectional health survey of a nationally representative sample of the non-institutionalized US civilian population.³⁸ Ford et al used NCEP ATP III criteria to assess prevalence of the syndrome. Currently, no published population-based data are available on the prevalence of the syndrome by WHO criteria.

The prevalence of component traits according to NCEP ATP III criteria in the NHANES III sample stratified by sex are shown in **Figure 1** and by race/ethnicity in **Figure 2**. The prevalence of the metabolic syndrome stratified by age is shown in **Figure 3** and by sex and race/ethnicity in **Figure 4**. These figures show a substantial heterogeneity in the distribution of metabolic syndrome traits. For instance, large waist circumference is more common in women, while elevated triglyceride levels are more common in men. Hypertension is relatively common in African Americans, while high triglyceride levels are relatively uncommon. Four of the traits are roughly equally prevalent in whites, while hyperglycemia is relatively uncommon in all groups.

Overall, the prevalence of the syndrome is similar among men and women, about 24%, but increases dramatically with age, from about 7% among people in their 20s to over 40% among people older than 60 years of age. Racial/ethnic trait heterogeneity gives rise to substantial racial/ethnic variation in the prevalence of the syndrome itself. About 36% of Mexican American women have the syndrome, while only about 16% of African American men are affected. White women (23%) and white men (25%) are equally affected. Overall, 24% of whites, 22% of African Americans, 32% of Mexican Americans, and 20% of other racial/ethnic groups

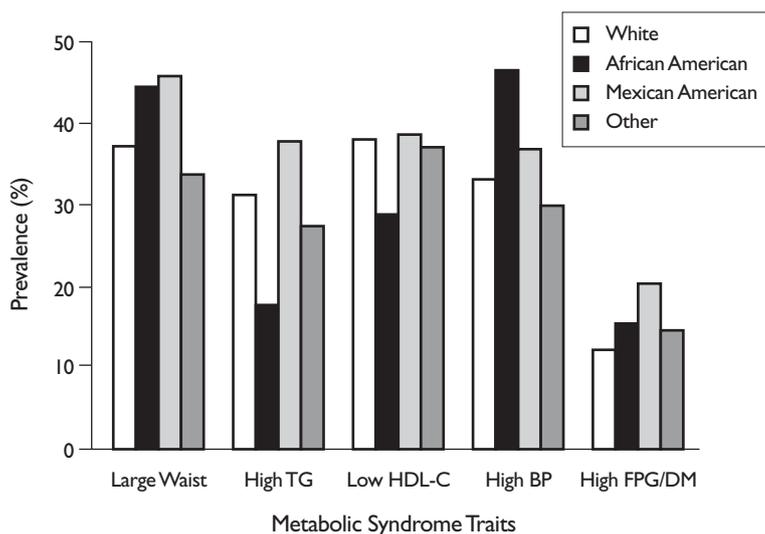
Figure 1. Age-Adjusted Prevalence of Metabolic Syndrome Traits According to NCEP ATP III Criteria Among US Adults Aged 20 Years of Age and Older, Stratified by Sex



TG indicates triglyceride level; HDL-C, high-density lipoprotein cholesterol level; BP, blood pressure; FPG/DM, fasting plasma glucose/diabetes mellitus.

Source: Reference 38.

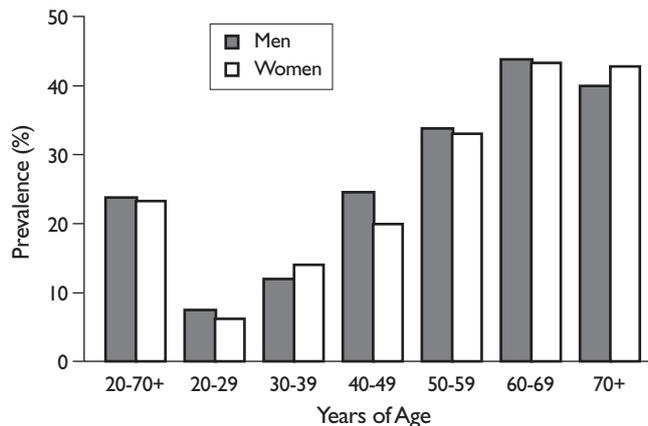
Figure 2. Age-Adjusted Prevalence of Metabolic Syndrome Traits According to NCEP ATP III Criteria Among US Adults 20 Years of Age and Older, Stratified by Race/Ethnicity



TG indicates triglyceride level; HDL-C, high-density lipoprotein cholesterol level; BP, blood pressure; FPG/DM, fasting plasma glucose/diabetes mellitus.

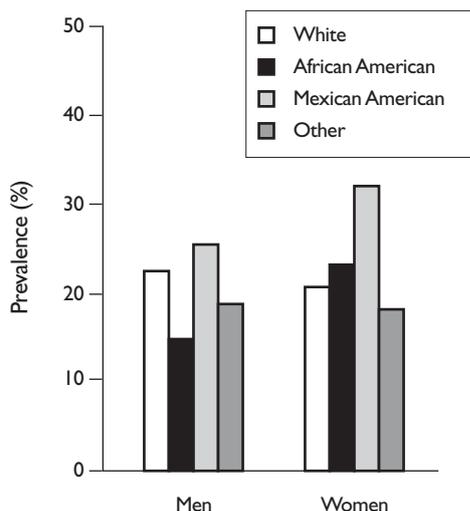
Source: Reference 38.

Figure 3. Prevalence of the Metabolic Syndrome According to NCEP ATP III Criteria Among US Adults 20 Years of Age and Older, Stratified by Age



Source: Adapted from Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356-359.

Figure 4. Age-Adjusted Prevalence of the Metabolic Syndrome According to NCEP ATP III Criteria Among US Adults 20 years of Age and Older, Stratified by Sex and Race/Ethnicity



Source: Reprinted from Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356-359.

combined may be classified with the syndrome. However, these numbers likely underestimate the current prevalence of the syndrome given the accelerating prevalence of obesity and its adverse metabolic effects in the US population over the last decade.³⁹

Genetics of the Metabolic Syndrome

Like most common chronic diseases, the metabolic syndrome is partly determined by modifiable environmental factors, especially obesity and a sedentary lifestyle.⁴⁰ However, emerging evidence also suggests a genetic basis for the syndrome. Family studies demonstrate that clusters of metabolic risk factors are transmitted from parents to offspring.⁴¹⁻⁴² Twin studies demonstrate a higher concordance of components of the metabolic syndrome among monozygotic twins compared with dizygotic twins as well as heritabilities of insulin resistance-related traits or insulin resistance factors, derived from factor analyses, of 40% to 50%.⁴³⁻⁴⁷ Family studies also demonstrate that a common set of genes may determine not only fasting insulin levels but also lipid and obesity traits of the syndrome.⁴⁸ Recent linkage analyses identify loci linked to traits of the syndrome on chromosomes 3, 6, 7, and 17.⁴⁹⁻⁵¹ The significance of these loci remains to be determined, as translation of linkage information into specific gene discovery has proven enormously difficult.⁵² However, identification of specific genes for insulin resistance holds promise for prevention of outcomes of the metabolic syndrome, especially type 2 diabetes. For instance, increased risk for diabetes associated with a common polymorphism in the peroxisome proliferator-activated receptor-gamma gene raises the testable hypothesis that people with this variant and the metabolic syndrome could be targeted for pharmacoprevention of diabetes using thiazolidinediones, as discussed in the next section.

Prevention and Treatment of the Metabolic Syndrome

If insulin resistance is the underlying cause of the metabolic syndrome, then

interventions to improve insulin sensitivity constitute an important treatment for the syndrome, and consequently, for prevention of type 2 diabetes and CVD. Obesity and a sedentary lifestyle are the 2 major modifiable risk factors for insulin resistance and obesity, and probably also for the metabolic syndrome.⁴⁰ Lifestyle changes leading to weight loss and increased physical activity are the foundation of therapy to reduce risk factor levels diagnostic of the metabolic syndrome. Use of insulin sensitizing drugs may also play a role in therapy of the syndrome.

While no experimental data are available that directly address prevention or treatment of the metabolic syndrome, new data supporting the hypothesis that type 2 diabetes can be prevented provide important evidence for the benefits of treatment of adverse metabolic risk factors. Recently, the Diabetes Prevention Program (DPP) demonstrated that an intensive lifestyle modification program with the goals of at least a 7% weight loss and at least 150 minutes of physical activity per week reduced the incidence of type 2 diabetes to 4.8 cases per 100 person-years compared with 11 cases per 100 person-years in a standard lifestyle recommendation control group.⁵³ This effect translated into an absolute risk reduction of 6.2 cases per 100 person-years, with about 7 patients needing treatment for 3 years to prevent 1 case of type 2 diabetes, and a relative risk reduction of 58% (95% confidence interval [CI], 48% to 66%). The results of the DPP confirm findings of several other trials of lifestyle modification, including the Finnish Diabetes Prevention Study and the Da Qing (China) IGT and Diabetes Study.⁵⁴⁻⁵⁵ The American Diabetes Association advocates counseling patients at risk for type 2 diabetes to lose weight and increase physical activity.⁵⁶

Eligibility criteria for the DPP included age ≥ 25 , a BMI of ≥ 24 kg/m², a fasting plasma glucose level of 5.3 to 6.9 Mm and 7.8 to 11.0 Mm 2 hours after a 75-g oral glucose tolerance test. Other features of the metabolic syndrome were not included in eligibility criteria, although many DPP

participants are likely to be classified as having the syndrome. The prevalence of the metabolic syndrome among people otherwise meeting DPP eligibility criteria is the subject of ongoing research.

The DPP also demonstrated that treatment with the insulin-sensitizing drug metformin, at a dose of 850 mg twice daily, reduced the incidence of diabetes to 7.8 cases per 100 person-years compared with placebo. This effect translated into an absolute risk reduction of 3.2 cases per 100 person-years, with about 14 patients needing treatment for 3 years to prevent 1 case of type 2 diabetes, and a relative risk reduction of 31% (95% CI, 17% to 43%). However, metformin therapy was relatively ineffective in subjects older than 60 years of age and in subjects with a BMI less than 30 kg/m². Metformin may also reduce CVD events in patients with type 2 diabetes.⁵⁷ The other major class of insulin-sensitizing drugs is the thiazolidinediones, of which rosiglitazone and pioglitazone are currently available in the United States; these also improve metabolic risk factor levels.⁵⁸ One clinical trial under way is testing whether troglitazone prevents development of diabetes in women with gestational diabetes,⁵⁹ but currently no direct evidence is available indicating that the thiazolidinediones are useful for diabetes or CVD prevention. Recently, 2 other completely different drug classes, hydroxymethyl coenzyme A reductase inhibitors, known as statins, and angiotensin-converting enzyme (ACE) inhibitors, have been suggested to have some effect in preventing development of diabetes. In *post hoc* analyses of randomized controlled trials to prevent CVD, the statin pravastatin⁶⁰ and the ACE inhibitor ramipril⁶¹ were found to reduce the relative risk of diabetes by about 30%. Both of these drugs have beneficial effects on vascular endothelial function; their antidiabetic effect is consistent with the hypothesis that insulin resistance, type 2 diabetes, and CVD share endothelial dysfunction as their ultimate common antecedent.⁶² While direct evidence to support the preventive benefit of statins or ACE inhibitors is currently unavailable, clinical trials are being planned or are

under way to test the hypothesis. On the basis of relatively weak effects, scant experimental data, and the potential for adverse drug effects, the American Diabetes Association currently does not advocate routine use of any drug therapy to prevent type 2 diabetes. By extension, the same argument can be made for prevention of the metabolic syndrome.*

Therapeutic lifestyle changes have broad benefits on health and can be safely recommended for most subjects. However, whether treatment aimed specifically at the metabolic syndrome will reduce risk for adverse outcomes to an equal or greater degree than treatments aimed at individual metabolic traits is not known. Therapies directed specifically at hyperlipidemia, hypertension, and hyperglycemia significantly reduce the risk for major adverse outcomes and should be considered for patients with any of these conditions.^{35,63-64} Perhaps the greatest value in recognizing the metabolic syndrome is not that it suggests specific treatment for insulin resistance, but that it identifies a patient with an extremely adverse metabolic state warranting aggressive intervention for specific risk factors.

Conclusion

Over the last decade, type 2 diabetes and CVD have been shown to have many of the same risk factors. Even mild elevations in blood pressure, plasma lipids, and blood glucose, when they occur in combination, confer substantial excess risk for type 2 diabetes, CVD, and death. The co-occurrence of these risk factors is linked to obesity (especially central obesity) and insulin resistance; this co-occurrence constitutes the insulin resistance, or metabolic, syndrome. Recently proposed case definitions enable epidemiologic analysis of the metabolic syndrome, although specific details of the definition, including which traits (especially diabetes), trait thresholds, and trait weightings are appropriate, remain to be resolved. Emerging

*This paragraph contains discussion of off-label usage of some drugs for the treatment of the metabolic syndrome.

prevalence data suggests that the metabolic syndrome is very common, especially among older people and in Mexican American populations. The syndrome will undoubtedly become even more common over time, paralleling the exploding epidemic of obesity and type 2 diabetes in the United States and worldwide. Weight loss and increased physical activity are important treatments to reduce insulin resistance, but recognition of the syndrome in an individual patient should trigger aggressive intervention to reduce levels of individual traits. The etiology, prevention, and treatment of the metabolic syndrome currently are the focus of intense research activities. Greater understanding of the public health and clinical importance of the syndrome can be expected to have a much stronger evidence base within the next few years.

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