Identification of Appropriate Patients for Cardiometabolic Risk Management

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Patients at increased risk for cardiovascular disease have a wide array of clinical features that should alert practitioners to the need for risk reduction. Some, but not all, of these features relate to insulin resistance. Multiple approaches exist for diagnosing and defining this risk, including the traditional Framingham risk assessment, various definitions of the metabolic syndrome, and assessment of risk factors not commonly included in the standard criteria. This article reviews the many clinical findings that should alert healthcare providers to the need for aggressive cardiovascular risk reduction.

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In order to provide adequate treatment to patients at risk of cardiovascular disease (CVD), healthcare providers must be aware of the clinical features that indicate high risk. Current studies reveal that physicians are undertreating at-risk patients. In a study examining control of CVD risk factors in patients with diabetes and hypertension who were treated at an academic medical center, only 27% had achieved a hemoglobin A_{1c} level $< 7\%$, 36% had a low-density lipoprotein cholesterol (LDL-C) level < 100 mg/dL, 27% had

a blood pressure level < 130/85 mm Hg, and 46% were taking aspirin.[1] Only 2% of patients met the target levels for all 4 factors (blood pressure, lipids, A_{1c}, and aspirin use). Therefore, healthcare providers need to be educated on how to identify these high-risk patients with metabolic and cardiovascular risk factors, so they can effectively implement and monitor appropriate therapies.

Is There a Syndrome?

Clinicians often are confused when trying to define who is at increased risk for CVD. The Framingham risk scoring[2,3] has established the standards for CVD risk factors. The factors considered are sex, age, LDL-C and high-density lipoprotein cholesterol (HDL-C), blood pressure, smoking, and diabetes history. However, recently a great deal of attention has been paid to patients with the "metabolic syndrome." The patients identified as at risk for CVD vary, depending on the syndrome definition used (Table 1). A joint statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes raised concerns about defining the metabolic syndrome as a specific entity, because "while there is no question that certain CVD risk factors are prone to cluster . . . the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker . . . clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the 'metabolic syndrome.'"[4]

From a clinical perspective, this approach makes sense. The goal of lowering the risk for CVD and type 2 diabetes mellitus focuses on identifying individuals at the greatest risk. It may or may not mean fitting patients to a definition of the "metabolic syndrome." An individual who is obese and has a strong family history of CVD needs risk factor modification. A study in a US population found that the presence of even 1 or 2 features of the metabolic syndrome caused a 2-fold increase in CVD and coronary heart disease (CHD),[5] indicating that individuals identified for treatment may lack the traditional clustering of features that define a syndrome. Therefore, clinical judgment needs to be used when assessing patients for their risk of a future cardiovascular event, and patients who have insulin resistance or who are at risk for diabetes need to be considered at risk for CVD as well. The ADA risk assessment engine, Personal Health Decisions (PHD),[6] considers the most complete set of factors for these patients and can easily be accessed should a clinician need more specific information on assessing a patient.

Table 1
Comparison of Definitions for Cardiovascular Disease Risk

Risk Factor	Framingham[3]	NCEP/ ATP III[5]	WHO[7]	IDF[6]	AACE[8]	PHD[13]
Age	✓					✓
Sex	✓			✓		✓
Race/ethnicity				✓*		✓
Family history						✓
Physical activity						✓
Body mass index			✓		✓	✓
Waist circumference		✓		✓		
Waist:hip ratio			✓			
Fasting plasma glucose 100 mg/dL to 125 mg/dL		✓	✓		✓	
Fasting plasma glucose ≥ 126 mg/dL	✓	✓	✓			✓
Low-density lipoprotein cholesterol	✓					✓
High-density lipoprotein cholesterol	✓	✓	✓	✓	✓	✓
Triglycerides		✓	✓	✓	✓	
Microalbuminuria			✓			
Smoking	✓					✓
Hypertension	✓	✓	✓	✓	✓	✓
Polycystic ovarian syndrome					✓	
Others					✓	

*Different waist circumferences were used for people of different ethnicities.
NCEP/ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); WHO, World Health Organization; IDF, International Diabetes Federation; AACE, American Association of Clinical Endocrinologists; PHD, Personal Health Decisions.

Diabetes and/or Known CVD

It is accepted that patients with type 1 diabetes[7] or type 2 diabetes[8] have high rates of CVD and need risk factor modification. Additionally, any such patient with known CHD needs aggressive cardiovascular risk modification, with the highest-risk group being patients with type 2 diabetes and a history of CVD.[8,9] The targets for lipid lowering in patients with type 2 diabetes (LDL-C $<$ 100 mg/dL), and, in particular, those with type 2 diabetes and known CVD (LDL-C $<$ 70 mg/dL), reflect the high risk of cardiovascular events in these patients.[10]

Obesity

The easiest finding for physicians (and patients) to recognize is excess weight. The link between obesity and heart disease was noted long before current technologies existed. Specific types of fat distribution have been associated with increased risk for insulin resistance and CVD.[11,12] Straightforward measurement of body mass index (BMI) has been a useful and clinically reproducible parameter for assessing risk in some studies,[13-15] but in other studies, waist circumference is more sensitive for assessing CVD risk.[16] Clearly, with both increasing BMI and increasing waist circumference, there is an increased risk for CVD.[11,17] Current definitions describing weight are as follows: normal weight (BMI of 18.5 to 24.9), overweight (BMI of 25 to 29.9), obese I (BMI of 30 to 34.9), and obese II+ (BMI $\geq$ 35).[18]

There are 2 fundamental problems with measurement of waist circumference. First, it is not routinely done in clinical practice; second, accurate measurement is difficult. Care must be taken to measure precisely and in a standard fashion. A standard tension must be applied to the tape measure, and the tape must remain in the same horizontal plane as it encircles the abdomen. The methodology for measuring abdominal circumference comes from the National Health and Nutrition Examination Survey protocol: "The subject stands and the examiner, positioned at the right of the subject, palpates the upper bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration"[19] (Figure 1). Ideally, this measurement should be done at least twice and the results should be within 1 cm of each other.

Cutoff points for waist circumference are best defined in the National Cholesterol Education Program (NCEP) guidelines. A waist circumference of $\geq$ 88 cm in women and $\geq$ 102 cm in men is considered a risk factor for the metabolic syndrome; these values were initially derived in a white population[20] and later validated for a more racially/ethnically diverse population.[21] However, when adjusted for BMI, waist circumferences tend to be greater in white populations than in other racial/ethnic groups.[16,22] In older adults, waist circumference may be a better indicator of total fat mass than of visceral fat mass.[23] In Asians, the waist circumference associated with an increase in CVD is smaller than for other groups (Table 2).[24-26]

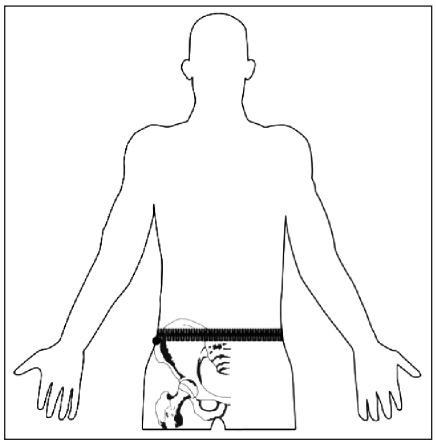

Figure 1. *Position for measurement of waist (abdominal) circumference. Reproduced with permission from the National Health and Nutrition Examination Survey.*[19]

Hypertension

Hypertension is an easily measured physical finding, and it identifies patients at risk for both CVD and

Table 2
Waist Circumference Measurements in Asian and Non-Asian Populations: Cutoff Points for Increased Cardiovascular Disease

Racial/Ethnic Population	Waist Circumference Cutoff, Men (cm)	Waist Circumference Cutoff, Women (cm)
General population (NCEP/ATP III)[46]	$\geq$ 102	$\geq$ 88
Europids (IDF)[74]	$\geq$ 94	$\geq$ 80
South Asians (IDF)[74]	$\geq$ 90	$\geq$ 80
Chinese (IDF)[74]	$\geq$ 90	$\geq$ 80
Japanese (IDF)[74]	$\geq$ 85	$\geq$ 90

NCEP/ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); IDF, International Diabetes Federation.

insulin resistance. In addition, some of the medications used for treating hypertension can contribute to the development of diabetes.[27,28] Many patients diagnosed with hypertension and glucose intolerance or diabetes have additional cardiovascular risk factors.[29] Much of the early work on identifying the cluster of findings was based on the association between insulin resistance and hypertension.[30,31] High blood pressure should be assessed and treated in all adults, but perhaps even more rigorously in patients with insulin resistance and diabetes. The target for treatment is < 130/80 mm Hg, and those with a higher blood pressure should be considered at risk and treated accordingly.

Impaired Fasting Glucose/ Impaired Glucose Tolerance

A late finding in patients with insulin resistance and CVD risk factors is an elevation in fasting blood sugar levels. The presence of CVD risk factors increases the risk of developing diabetes.[32] Unfortunately, many patients are diagnosed with diabetes or prediabetes only after being admitted to the hospital following a cardiovascular event, instead of earlier, when preventive measures could have been implemented.[33] Many of the estimated 41 million people in the United States who have prediabetes could benefit from preventive care measures.[34]

One of the issues for clinicians is that, other than measuring fasting glucose level, there is no easy method for quantifying insulin resistance. In research settings, glucose clamps or frequently sampled impaired glucose tolerance tests can be performed, and modeling techniques have been developed, such as the homeostasis model assessment (HOMA)[35] and the quantitative insulin sensitivity check index (QUICKI),[36] but these methods are better for assessing insulin resistance in populations than in a given individual. In most patients, fasting insulin levels are more accurately measured, and provide a more valid direct measurement, than estimates of insulin resistance. However, it is often an assessment of overall risk—for instance, obesity, family history of diabetes, race/ethnicity (Latino, African American, American Indian, Asian, Pacific Islander), and a personal history of gestational diabetes or delivery of a baby > 9 pounds—that should signal the need for diabetes prevention measures.[37]

When a mild elevation in fasting glucose is noted, its importance is often underappreciated in terms of CVD risk.[38] Cardiovascular risk rises even across the range of increasing but normal blood glucose levels.[39,40] Once patients have abnormal glucose tolerance, their outcomes following cardiovascular events are worse. This finding is true for myocardial infarction[41,42] and for cerebrovascular accidents.[43]

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Although some clinicians have advocated using glucose tolerance testing to detect patients with increased CVD risk,[44] this approach may not be practical in general practice. Oral glucose tolerance tests are unreliable,[45] need to be repeated twice for confirmation, and are often not performed. Even if test results are positive, initial treatment for patients with diabetes risk factors and an A_{1c} of < 6% is lifestyle modification, and treatment of hypertension, dyslipidemia, and use of aspirin remains the same. As fasting blood glucose and/or A_{1c} levels rise, medications to reduce insulin resistance and treat diabetes may be prescribed.

Dyslipidemia

Elevations in LDL-C levels are associated with an increased risk for CVD in patients with or without diabetes, and those with both diabetes and the metabolic syndrome are considered to be at high risk, similar to that of patients without diabetes who have had a cardiovascular event.[46] In addition to elevated LDL-C, however, low HDL-C and/or an elevated triglyceride level are indicative of insulin resistance and are often underappreciated risk factors for CVD and the development of diabetes.[47] Clinicians need to evaluate HDL-C and triglyceride levels in addition to testing for total cholesterol and LDL-C.

Inactivity

Inactivity increases the risk for obesity, insulin resistance, CVD, and diabetes. In one study, men who engaged in 3 or more hours per week of moderate to intense leisure time physical activity were half as likely as sedentary men to have the metabolic syndrome, even after adjusting for BMI and other confounding variables.[48] Also, VO_2max measurements were inversely associated with the risk for developing the metabolic syndrome. Levels of physical activity are incorporated into the PHD risk assessment tool, since physical activity helps reduce insulin resistance and CVD risk. Therefore, people who are inactive in both their work and leisure time environments are at risk for insulin resistance and its sequelae.

Family History

Family history of CHD, diabetes, and insulin resistance is a risk factor

for developing these conditions.[49,50] In a meta-analysis of studies using euglycemic clamp measurements for insulin resistance in more than 2000 subjects, various models were used for predicting insulin resistance. The "clinical predictors" model was able to predict insulin resistance in an individual if any of the following conditions were met: BMI > 28.7 kg/m^2, BMI > 27 kg/m^2 and family history of diabetes, or no family history of diabetes but triglycerides > 2.44 mmol/L. This model had an estimated sensitivity of 81.3% and a specificity of 76.3%. Therefore, knowledge of family history of diabetes can affect a patient's risk assessment.

Age

The risk for diabetes and for CVD increases with age. By age 85, 25% of people will develop diabetes. The metabolic syndrome, measured by the NCEP/Adult Treatment Panel (ATP) III criteria, had a prevalence of 28.1% in older individuals.[51] The "metabolic syndrome" designation was associated with a higher risk of coronary and cerebrovascular events. Age is a factor in most risk assessment tools.[2,13]

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is the leading cause of infertility in the United States and is a form of insulin resistance in women that can easily be identified.[52] Women with PCOS commonly present with irregular menses, hirsutism, acanthosis nigricans, and/or infertility. In the United States, more than half of patients with PCOS are obese,[53] and 20% to 40% have impaired glucose tolerance.[54,55] Women with PCOS also have other CVD risk factors, such as dyslipidemia and hypertension. Using the NCEP/ATP III criteria for the metabolic syndrome, a 46% incidence of the syndrome was found in women with PCOS.[56] In addition to concerns related to CVD and diabetes,[57,58] these women are at increased risk for endometrial cancer because of chronic anovulation.[59] Findings of CVD risk were echoed in a retrospective study in which women with PCOS were found to have a 43% prevalence of the metabolic syndrome, compared with 24% in the general population.[60]

Gestational Diabetes

Women who have had gestational diabetes are at increased risk of developing diabetes in the future: Approximately 50% will develop diabetes in their lifetime.[61] Women with a history of gestational diabetes should be considered at risk for insulin resistance as well as for diabetes and should be routinely monitored.[62]

Psychiatric Illness

Patients with psychiatric illness, particularly those being treated with the newer-generation antipsychotic drugs, are at increased risk for obesity, the metabolic syndrome, and diabetes.[63,64] These patients may be particularly vulnerable to poorer health outcomes and should be identified and treated with risk factor modification as needed.

Liver Function Abnormalities

Liver function abnormalities are commonly detected in automated chemistry panels, and they may be a sign of nonalcoholic fatty liver disease (NAFLD), which is a manifestation of insulin resistance.[65] NAFLD occurs in approximately 20% of adults in the United States[66] and, increasingly, in obese children with insulin resistance.[67] The finding of NAFLD should trigger a search for other features associated with a high risk for CVD and the development of diabetes.[68,69] Risk factors such as obesity and inactivity increase the risk for NAFLD because they increase the development of insulin resistance.

Although liver biopsy is the sine qua non for a diagnosis of NAFLD, the finding of elevated alanine aminotransferase and aspartate aminotransferase, in the absence of alcoholism or the viral forms of hepatitis, should lead to investigation for fatty liver and insulin resistance.[70] A liver ultrasound may be indicated for any patient perceived to be at high risk.

Obesity in Youth

Obesity in children is also associated with insulin resistance and is an increasing problem, as more young people are becoming inactive and overweight.[71] In a study of 103 obese children (ages 2 to 18 years), one third had features of the insulin resistance syndrome. Children from high-risk groups are at particular risk. In a study of African American school children (third to sixth grade) in a low-income urban school, most had one or more features of the metabolic syndrome.[72] Development of standards for overweight and obesity in children is important because, unlike in adults, definitions must include developmental age.[73]

Conclusion

There are numerous clinical characteristics that suggest an individual is at increased risk for CVD and/or insulin resistance. If they are unnoted, the patient may eventually have a cardiovascular event or develop type 2 diabetes, or both. Therefore, it is important during routine patient visits to consider any and all potential risk factors and, if such risk factors are identified, to work on risk reduction

Table 3
Clinical Characteristics Associated With an Increased Risk for CVD and/or Insulin Resistance

History
Older age
Personal history of diabetes, CVD, prediabetes, gestational diabetes, polycystic ovarian syndrome, or use of antipsychotic medications
Member of a high-risk race/ethnicity for diabetes (African American, Latino, Asian, American Indian, Pacific Islander)
Family history of type 2 diabetes or CVD
Smoking
Low level of physical activity
Physical examination
Increased body mass index (> 27 kg/m^2)
Increased waist circumference (adjusted for race/ethnicity)
Increased waist:hip ratio
Blood pressure $> 130/80$ mm Hg
Acanthosis nigricans
Facial hirsutism (in women)
Laboratory tests
Elevated low-density lipoprotein cholesterol
Reduced high-density lipoprotein cholesterol
Increased triglyceride
Fasting blood glucose ≥ 100 mg/dL
Elevated alanine/aspartate aminotransferase due to fatty liver

CVD, cardiovascular disease.

strategies. Table 3 lists many of the clinical findings that suggest an increased risk for CVD and insulin resistance. Many are part of published definitions and risk equations; some are not. Often it takes nothing more than looking at a patient across an examination room and noting central obesity to know that he or she is at risk. For these patients, and for others who for some reason fit into a pattern of increased risk, measurement of height, weight, and blood pressure as well as fasting blood tests (for a lipid profile and a glucose level) will allow ascertainment of risk. Appropriate strategies can then be developed to prevent or treat obesity, hypertension, dyslipidemia, prediabetes, and/or diabetes, as indicated by the findings for each individual patient. ■

References

1. McFarlane SI, Jacober SJ, Winer N, et al. Control of cardiovascular risk factors in patients with diabetes and hypertension at urban academic medical centers. *Diabetes Care*. 2002;25:718-723.
2. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847.
3. National Heart, Lung, and Blood Institute. Framingham Heart Study. Available at: www.nhlbi.nih.gov/about/framingham/index.html. Accessed May 7, 2006.
4. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. *Diabetes Care*. 2005;28:2289-2304.
5. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245-1250.
6. American Diabetes Association. Diabetes PHD: Personal health decisions. Available

Main Points

- Hypertension is associated with both cardiovascular disease (CVD) and insulin resistance. Some medications used for treating hypertension can contribute to the development of diabetes.
- In addition to elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol and/or an elevated triglyceride level are indicative of insulin resistance and are often underappreciated risk factors for CVD and the development of diabetes.
- Polycystic ovarian syndrome (PCOS) is a form of insulin resistance in women. In the United States, more than half of patients with PCOS are obese, and 20% to 40% have impaired glucose tolerance. Women with PCOS also have other CVD risk factors, such as dyslipidemia and hypertension.
- Patients with psychiatric illness, including those treated with the newer-generation antipsychotic drugs, are at increased risk for obesity, the metabolic syndrome, and diabetes.
- Liver function abnormalities may be a sign of nonalcoholic fatty liver disease, a manifestation of insulin resistance; this finding should trigger a search for other features associated with a high risk for CVD and diabetes.

at: www.diabetes.org/diabetesphd/default.jsp?WTLPromo=HOME_PHD. Accessed May 7, 2006.
7. Soedamah-Muthu SS, Fuller JH, Mulnier HE, et al. High risk of cardiovascular disease in patients with type 1 diabetes in the UK. *Diabetes Care*. 2006;29:798-804.
8. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234.
9. Cho E, Rimm EB, Stampfer MJ, et al. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Coll Cardiol*. 2002;40:954-960.
10. American Diabetes Association. Standards of Medical Care in Diabetes—2006. *Diabetes Care*. 2006;29(suppl 1):S4-S42.
11. Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk. *Arch Intern Med*. 2002;162:2074-2079.
12. Seidell JC, Perusse L, Despres JP, Bouchard C. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr*. 2001;74:315-321.
13. Brown CD, Higgins M, Donato KA, et al. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res*. 2000;8:605-619.
14. Maison P, Byrne CD, Hales CN, et al. Do different dimensions of the metabolic syndrome change together over time? *Diabetes Care*. 2001;24:1758-1763.
15. Haffner SM, D'Agostino R, Festa A, et al. Low insulin sensitivity (Si = 0) in diabetic and nondiabetic subjects in the Insulin Resistance Atherosclerosis Study: is it associated with components of the metabolic syndrome and nontraditional risk factors? *Diabetes Care*. 2003;26:2796-2803.
16. Zhu S, Heymsfield SB, Toyoshima H, et al. Race-ethnicity-specific waist circumference cutoffs for identifying cardiovascular disease risk factors. *Am J Clin Nutr*. 2005;81:409-415.
17. Zhu S, Wang Z, Heshka S, et al. Waist circumference and obesity-associated risk factors among whites in the Third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr*. 2002;76:743-749.
18. National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obes Res*. 1998;6(suppl 2):S51-S210.
19. National Health and Nutrition Examination Survey. *Anthropometry Procedures Manual*. Hyattsville, MD: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2000. Available at: www.cdc.gov/nchs/data/nhanes/bm.pdf. Accessed April 29, 2006.
20. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *BMJ*. 1995;311:158-161.
21. Okosun IS, Liao Y, Rotimi CN, et al. Predictive values of waist circumference for dyslipidemia, type 2 diabetes and hypertension in overweight white, black, and Hispanic American adults. *J Clin Epidemiol*. 2000;53:401-408.
22. Ardern CI, Janssen I, Ross R, Katzmarzyk PT. Development of health-related waist circumference thresholds within BMI categories. *Obes Res*. 2004;12:1094-1103.
23. Harris TB, Visser M, Everhart J, et al. Waist circumference and sagittal diameter reflect total body fat better than visceral fat in older men and women. The Health, Aging and Body Composition Study. *Ann NY Acad Sci*. 2000;904:462-473.
24. Tan CE, Ma S, Wai D, et al. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care*. 2004;27:1182-1186.
25. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. *Obes Rev*. 2002;3:141-146.
26. Regional Office for the Western Pacific, World Health Organization, International Association for the Study of Obesity, and the International Obesity Task Force. Asia-Pacific perspective: redefining obesity and its treatment. Available at: www.idi.org.au/home.htm. Accessed May 7, 2006.
27. Messerli FH, Grossman E, Leonetti G. Antihypertensive therapy and new onset diabetes. *J Hypertens*. 2004;22:1845-1847.
28. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2004;27:247-255.
29. Hypertension in Diabetes Study (HDS). I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens*. 1993;1:309-317.
30. García Puig J, Ruilope LM, Luque Otero M, Bobadilla JF. Prevalence of carbohydrate metabolic alterations in hospital based hypertension units in Spain: the AVANT study [abstract]. *J Hypertens*. 2004;22(suppl 1):S97.
31. Zavaroni I, Mazza S, Dall'Aglio E, et al. Prevalence of hyperinsulinemia in patients with high blood pressure. *J Intern Med*. 1992;231:235-240.
32. D'Agostino RB Jr, Hamman RF, Karter AJ, et al. Cardiovascular disease risk factors predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2004;27:2234-2240.
33. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002;359:2140-2144.
34. Benjamin SM, Valdez R, Geiss LS, et al. Estimated number of adults with prediabetes in the US in 2000: opportunities for prevention. *Diabetes Care*. 2003;26:645-649.
35. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.
36. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *J Clin Endocrinol Metab*. 2000;85:2402-2410.
37. American Diabetes Association. Diabetes risk test. Available at: www.diabetes.org/risk-test.jsp. Accessed May 24, 2006.
38. Björnholt J, Erikssen G, Aaser E, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care*. 1999;22:45-49.
39. Meigs JB, Nathan DM, Wilson PW, et al. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med*. 1998;128:524-533.
40. Lim SC, Tai ES, Tan BY, et al. Cardiovascular risk profile in individuals with borderline glycemia: the effect of the 1997 American Diabetes Association diagnostic criteria and the 1998 World Health Organization provisional report. *Diabetes Care*. 2000;23:278-282.
41. Bartnik M, Malmberg K, Norhammar A, et al. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J*. 2004;25:1990-1997.
42. Aguilar D, Solomon SD, Kober L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. *Circulation*. 2004;110:1572-1578.
43. Kernan WN, Viscoli CM, Inzucchi SE, et al. Prevalence of abnormal glucose tolerance following a transient ischemic attack or ischemic stroke. *Arch Intern Med*. 2005;165:227-233.
44. Stern MP, Fatehi P, Williams K, Haffner SM. Predicting future cardiovascular disease: do we need the oral glucose tolerance test? *Diabetes Care*. 2002;25:1851-1856.
45. Davidson MB, Schriger DL, Peters AL, Lorber B. Revisiting the oral glucose tolerance test criterion for the diagnosis of diabetes. *J Gen Intern Med*. 2000;15:551-555.
46. Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
47. Solano MP, Goldberg RB. Management of dyslipidemia in diabetes. *Cardiol Rev*. 2006;14:125-135.
48. Laaksonen DE, Hanna-Maaria L, Jukka TS, et al. Low levels of leisure-time physical activity and cardiorespiratory fitness predict development of the metabolic syndrome. *Diabetes Care*. 2002;25:1612-1618.
49. Stern SE, Williams K, Ferrannini E, et al. Identification of individuals with insulin resistance using routine clinical measurements. *Diabetes*. 2005;54:333-339.
50. Tang W, Hong Y, Province MA, et al. Familial clustering for features of the metabolic syndrome: the National Heart, Lung, and Blood Institute Family Heart Study. *Diabetes Care*. 2006;29:631-636.
51. Scuteri A, Najjar SS, Morrell CH, Lakatta EG. The metabolic syndrome in older individuals:

prevalence and prediction of cardiovascular events. The Cardiovascular Health Study. *Diabetes Care*. 2005;28:882-887.
52. Sartor B, Dickey RP. Polycystic ovarian syndrome and the metabolic syndrome. *Am J Med Sci*. 2005;330:336-342.
53. Carmina E, Legro RS, Stamets K, et al. Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. *Hum Reprod*. 2003;18:2289-2293.
54. Legro RS, Kunselman AR, Dodson WE, et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab*. 1999;84:165-169.
55. Ehrmann DA, Barnes RB, Rosenfield RL, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care*. 1999;22:141-146.
56. Glueck CJ, Papanna R, Wang P, et al. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism*. 2003;52:908-915.
57. Talbott E, Guzick D, Clerici A, et al. Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol*. 1995;15:821-826.
58. Elting MW, Dorsen TJM, Bezemer PD, et al. Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Hum Reprod*. 2001;16:556-560.
69. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol*. 1983;61:403-407.
60. Apridonidze T, Essah P, Luorno M, et al. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005;90:1929-1935.
61. Lobner K, Knopff A, Baumgarten A, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes*. 2006;55:792-797.
62. Noussitou P, Monbaron D, Vial Y, et al. Gestational diabetes mellitus and the risk of metabolic syndrome: a population-based study in Lausanne, Switzerland. *Diabetes Metab*. 2005;31:361-369.
63. Henderson DC, Nguyen DD, Copeland PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry*. 2005;66:1116-1121.
64. Correll CU, Frederickson AM, Kane JM, Manu P. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. *J Clin Psychiatry*. 2006;67:575-583.
65. Neuschwander-Tetri BA. Nonalcoholic steatohepatitis and the metabolic syndrome. *Am J Med Sci*. 2005;330:326-335.
66. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2003;124:71-79.
67. Lavine JE, Schwimmer JB. Nonalcoholic fatty liver disease in the pediatric population. *Clin Liver Dis*. 2004;8:549-558.
68. Luyckx FH, Lefebvre PJ, Scheen AJ. Non-alcoholic steatohepatitis: association with obesity and insulin resistance, and influence of weight loss. *Diabetes Metab*. 2000;26:98-106.
69. Chalasani N, Deeg MA, Persohn S, et al. Metabolic and anthropometric evaluation of insulin resistance in nondiabetic patients with nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2003;98:1849-1855.
70. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol*. 2003;98:960-967.
71. de Ferranti SD, Gauvreau K, Ludwig DS, et al. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;110:2494-2497.
72. Braunschweig CL, Gomez S, Liang H, et al. Obesity and risk factors for the metabolic syndrome among low-income, urban, African American schoolchildren: the rule rather than the exception? *Am J Clin Nutr*. 2005;81:970-975.
73. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000;320:1240-1243.
74. International Diabetes Federation. The IDF Consensus worldwide definition of the metabolic syndrome. Available at: www.idf.org. Accessed June 2, 2005.