From Hyperglycemia to the Risk of Cardiovascular Disease

Lawrence A. Leiter, MD, FRCPC, FACP

Division of Endocrinology and Metabolism, St. Michael's Hospital and Departments of Medicine and Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada

Blood glucose is a continuous, progressive risk factor for cardiovascular disease (CVD) throughout the dysglycemic range. There is also evidence that post-prandial hyperglycemia may be a better predictor of CVD risk than fasting plasma glucose or A1C. Targeting normoglycemia appears to reduce CVD events in diabetes mellitus (DM), although definitive studies in type 2 DM, as well as in prediabetes, are ongoing. Prediabetes has some, but not total, overlaps with the metabolic syndrome. Patients with the metabolic syndrome are at a significantly increased risk for both CVD and DM. Although the individual components of the syndrome predict risk for CVD to approximately equal degree, increased blood glucose, perhaps not surprisingly, is the best predictor of diabetes. Finally, there are multiple mechanisms by which hyperglycemia can increase the risk for CVD.
[Rev Cardiovasc Med. *2006;7(suppl 2):S3-S9*]

Key words: Cardiovascular disease • Diabetes mellitus • Dysglycemia • Hyperglycemia • Metabolic syndrome

It has long been established that diabetes mellitus (DM) is associated with a significantly increased risk for chronic complications including cardiovascular disease (CVD). There are now increasing emerging data indicating that even milder states of hyperglycemia, sometimes termed "dysglycemia," can also be associated with increased risk. This article will review the relationship between hyperglycemia and the risk of both micro- and macrovascular disease, as well as the relationship between impaired fasting glucose (IFG)/impaired

glucose tolerance (IGT) (collectively known as prediabetes) and the risk for both DM and CVD. It will also discuss the relationship between the various definitions of the metabolic syndrome and the risk for DM and CVD, as well as the overlap between dysglycemia and the metabolic syndrome. Finally, it will briefly highlight mechanisms by which hyperglycemia can increase the risk of CVD.

What Is Normoglycemia?

The current American Diabetes Association classification of diabetes[1] defines a normal fasting plasma glucose (FPG) as < 100 mg/dL, IFG as a blood glucose of 110 to 125 mg/dL, and diabetes as a fasting glucose ≥ 126 mg/dL. With regard to the 2-hour glucose, "normal" is < 140 mg/dL, IGT is ≥ 140 to < 200 mg/dL, and diabetes is ≥ 200 mg/dL. What is not well appreciated, however, is that even the cut-offs for "impaired" fasting glucose or glucose tolerance are well above what is probably truly normal. For example, data from NHANES III[2] reveal that the mean FPG level in people without DM or IGT is 92 mg/dL (with a 75th centile of 97 mg/dL), and the mean 2-hour PG is 97 mg/dL (and a 75th centile of 122 mg/dL).

What Is the Relationship Between Dysglycemia and Risk for DM and CVD?

The first issue in attempting to assess glycemic risk is to determine which of these parameters of glycemia should be addressed: the basal glucose level represented by the FPG level, the peak glucose level represented by the post-prandial value, or the long-term mean glucose level represented by A1C?

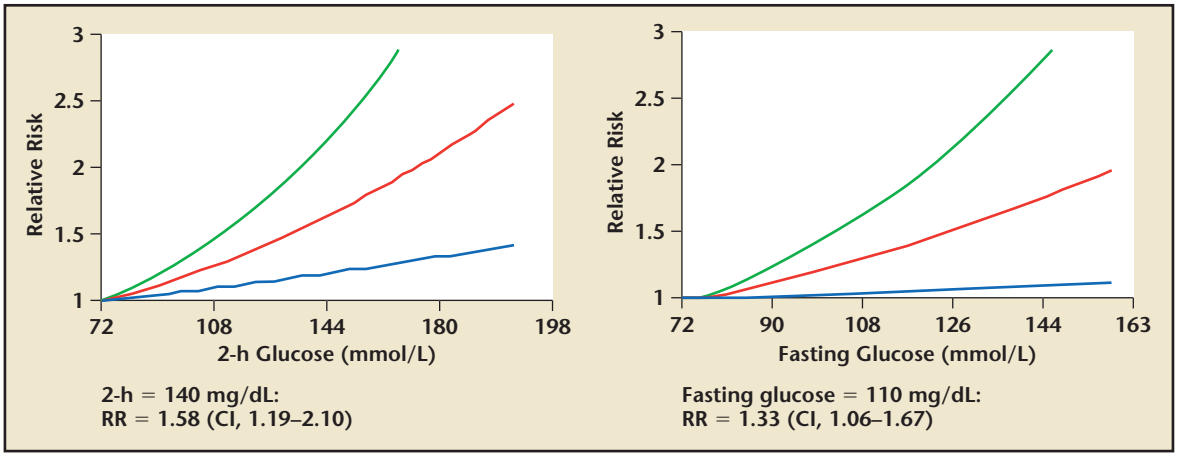
A meta-regression analysis by Coutinho and colleagues[3] (Figure 1) showed a continuous and exponential relationship between both fasting and 2-hour glucose levels and risk of CV events. Even glucose levels in the "normal" range were already associated with increased vascular risk. An FPG of 110 mg/dL was already associated with a 33% increased relative risk, with a 2-hour blood glucose of 140 mg/dL associated with a 58% increased relative risk for CVD.

It has therefore been proposed that whereas the current diagnostic criteria for DM are based on risk for microvascular complications, the risk for CVD may begin to increase at lower glucose levels. Interestingly however, recent evidence from the Diabetes Prevention Program[4] revealed cases of retinopathy in individuals with IGT alone, suggesting that microvascular complications can also occur in individuals with dysglycemia.

With regard to A1C and risk of vascular disease, data from the Epic-Norfolk Study[5] showed an increased risk for both coronary heart disease (CHD) and CV events, as well as all-cause mortality events, even in individuals without significantly elevated A1C levels. An especially increased risk was associated with an A1C $> 7\%$, especially in women. Overall, every absolute 1% increase in A1C was associated with a 20% to 30% increase in CV events or mortality.

Data from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) Study, a collaborative prospective study of 22 European cohorts involving almost 30,000 individuals not known to have DM,[6] revealed a progressive rise in risk for all-cause mortality as fasting glucose levels progressed from normal to IFG, and to

Figure 1. *Glucose levels and risk of cardiovascular events, based on 2-hour glucose and fasting blood glucose levels. Reprinted with permission from Coutinho M et al.[3]*



DM. Similar increases were observed with regard to the 2-hour glucose levels as values progressed from normal to IGT, and to DM. Interestingly, however, if the 2-hour glucose level was corrected for the fasting glucose level, the relationship was maintained, whereas if the fasting glucose level was corrected for the 2-hour glucose level, the relationship disappeared. These findings imply that the excessive CV risk is driven primarily by the post-prandial, rather than by the fasting, glucose levels.

The differing risks associated with IGT versus IFG are perhaps not very surprising if one recognizes that these states of glucose intolerance also differ in terms of their epidemiology and pathophysiology.

The differing risks associated with IGT versus IFG are perhaps not very surprising if one recognizes that these states of glucose intolerance also differ in terms of their epidemiology and pathophysiology. IGT is more common in older individuals, and more common in women than in men. Furthermore, it appears to be primarily related to increases in insulin resistance in peripheral tissues such as muscle. IFG, in contrast, has peak prevalence in middle-aged individuals, occurs more commonly in men, and appears to be related to increased hepatic glucose production, as well as defects in insulin secretion.

The Hoorn Study, a Dutch cohort study, showed that the risk of developing DM is similarly strongly related to the presence of both IFG and IGT.[7] In 1342 non-diabetic individuals aged 50 to 75 years with a mean duration of follow up of 6.4 years, an FPG of 110 to 140 mg/dL was associated with a > 7-fold increased risk of developing type 2 DM relative to an FPG of < 110 mg/dL. IGT was associated with a similar risk. Individuals who had both IFG and IGT, however, had about a 15-fold increased risk of developing DM. Interestingly, data from the Hoorn Study also revealed, perhaps not so surprisingly, that dropping the lower limit for IFG from 110 to 100 mg/dL added a population at lower risk of developing DM relative to those who had an FPG of 110 to 125 mg/dL. Subjects with an FPG between 110 and 125 mg/dL had an approximate 43% risk of developing DM over 6 years compared to an approximate 15% risk for those who had a fasting value between 100 and 110, and an approximate 5% risk for those who had a fasting value < 100 mg/dL.

Although IFG and IGT are associated with similar risks for developing DM, the associated risks are different for CVD. In the Japanese Funagata Study,[8] for example, subjects with IGT, similar to those with DM, had a cumulative survival rate from CVD that was significantly lower than those with normal glucose tolerance over 7 years of follow-up. In contrast, those subjects with IFG had a cumulative survival rate from CVD that was not significantly lower than those with normal glucose tolerance.

What Are the Data on the Benefits of Glucose Lowering and CVD Risk in DM?

With regard to intervention data, the largest study in type 2 DM is the United Kingdom Prospective Diabetes Study (UKPDS). In this large, randomized controlled trial of almost 4600 patients who were followed for a mean of 10 years, the risks for both microvascular disease and myocardial infarction (MI) were related to A1C levels, with no lower threshold to the benefits of glycemic control.[9] Nonetheless, in the primary intention-to-treat analysis, the intensive control policy was not associated with a significant reduction in CV events.[10] There are recent data, however, from long-term follow-up in 1441 subjects with type 1 DM from the Diabetes Control and Complications Trial (DCCT), demonstrating that improved glycemic control is associated with long-term CV benefits.[11] In the main DCCT study,[12] intensive therapy was associated with a non-significant reduction in CV events. More recently, the long-term follow-up of the DCCT cohort revealed that early intensive therapy reduced the risk of non-fatal MI, stroke, or death from CVD by 57% (P = .02).[11] Although the DCCT cohort had type 1 DM, rather than type 2 DM, these data are important as they confirm the glucose hypothesis and are the first convincing intervention data that improved glycemic control reduces CV risk. Furthermore, they highlight the long-term benefits of early improved glycemic control.

The long-term follow-up of the Diabetes Control and Complications Trial cohort revealed that early intensive therapy reduced the risk of non-fatal myocardial infarction, stroke, or death from cardiovascular disease by 57%.

What Are the Data on the Benefits of Glucose Lowering and CVD Risk in Prediabetes?

There are, as yet, no data suggesting that glucose lowering in individuals with prediabetes will lower CV risk. Ongoing studies, such as the Outcome Reduction with Initial Glargine Intervention (ORIGIN)

study using the long-acting insulin analogue glargine in subjects with IFG, IGT and early diabetes, and the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) study, using the short-acting insulin secretagogue nateglinide in subjects with IGT, may provide us with this important information.

What Is the Relationship Between the Metabolic Syndrome and the Risk for Both DM and CVD?

Although dysglycemia is a feature of the metabolic syndrome, it must be recognized that, despite this overlap, many patients with the metabolic syndrome do not have dysglycemia. Much has been written recently about the concept of the metabolic syndrome, whether it is a distinct syndrome, and whether the concept is a useful one.[13,14] A thorough discussion of this topic is beyond the scope of this review. It should, however, be recognized that all the definitions of the metabolic syndrome include the essential components of an atherogenic dyslipidemia, insulin resistance/glucose intolerance (which may evolve into type 2 DM), a pro-inflammatory profile, a prothrombotic profile, and raised blood pressure. Despite this conceptual agreement, the specific criteria used to define the metabolic syndrome vary from definition to definition.[15]

One of the more widely used definitions of the metabolic syndrome is that of the National Cholesterol Education Program (NCEP). In their original 2001 classification,[16] (Table 1) the diagnosis of metabolic syndrome required at least 3 of the following 5 criteria: abdominal obesity, high triglycerides, low HDL, elevated blood pressure, and an FPG > 110 mg/dL. In a 2004 update,[17] the FPG criterion was lowered to 100 mg/dL to be consistent with the new American Diabetes Association criteria for IFG.[18]

Table 1
NCEP Adult Treatment Panel III Definition of Metabolic Syndrome

Risk Factor	Defining Level[16]
Abdominal obesity (waist circumference)	
Men	> 40 inches
Women	> 35 inches
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/ ≥ 85 mm Hg
Fasting plasma Glucose	> 110 mg/dL > 100 mg/dL[18]

Data from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults[16] and American Diabetes Association.[18] NCEP, National Cholesterol Education Program; HDL, high-density lipoprotein.

The International Diabetes Federation (IDF) recently developed its own definition of the metabolic syndrome.[19] It employs the same 5 criteria, but diagnosis requires central obesity as a mandatory criterion plus 2 of the other 4 criteria. In addition, the waist circumference cut-offs for the definition of central obesity are country/ethnicity specific. This recognition of the ethnic differences in body fat distribution is most welcome, but the data supporting the specific cut-offs are not always robust.

The prevalence of the metabolic syndrome and its associated risk depend on the definition being used and the population being studied. Using the NCEP definition in adult Americans from the NHANES III database,[20] an age-adjusted prevalence of 23.7% was found with an approximately equal overall prevalence between men and women. In contrast, the prevalence of abnormal fasting glucose (≥ 110 mg/dL) was 12.6%. This highlights the fact that although dysglycemia is a feature of the metabolic syndrome, only a fraction of patients with the syndrome will also have dysglycemia.

Many studies have shown increased CV risk associated with the presence of the metabolic syndrome. In the Kuopio Heart Study, for example, all-cause mortality was increased by 2.13-fold and CVD mortality by 3.55 fold in subjects with the metabolic syndrome who were followed over a median of 11.6 years.[21] Another study looking at the San Antonio Heart Study population[22] compared the relation between the metabolic syndrome, defined by either the NCEP or World Health Organization (WHO) criteria, and the risk for all-cause and CV mortality. Both definitions predicted increased risk for CV mortality in the general population (but with an adjusted hazard ratio of 2.53 for patients with NCEP-defined versus 1.63 for WHO-defined metabolic syndrome). In lower-risk subjects (those without DM or CVD), only the NCEP definition predicted increased risk. Another interesting study published by Alexander and colleagues[23] studied the prevalence of coronary heart disease (CHD) in adults in the NHANES cohort over the age of 50 and revealed an interesting interaction between the presence or absence of the metabolic syndrome and of type 2 DM. Subjects with the metabolic syndrome and no type 2 DM had a 13.9% prevalence of CHD versus an 8.7% prevalence in those individuals without the metabolic syndrome and without type 2 DM. Not surprisingly, people with type 2 DM plus the metabolic syndrome had a significantly higher prevalence of 19.2%. What was of interest, however, was

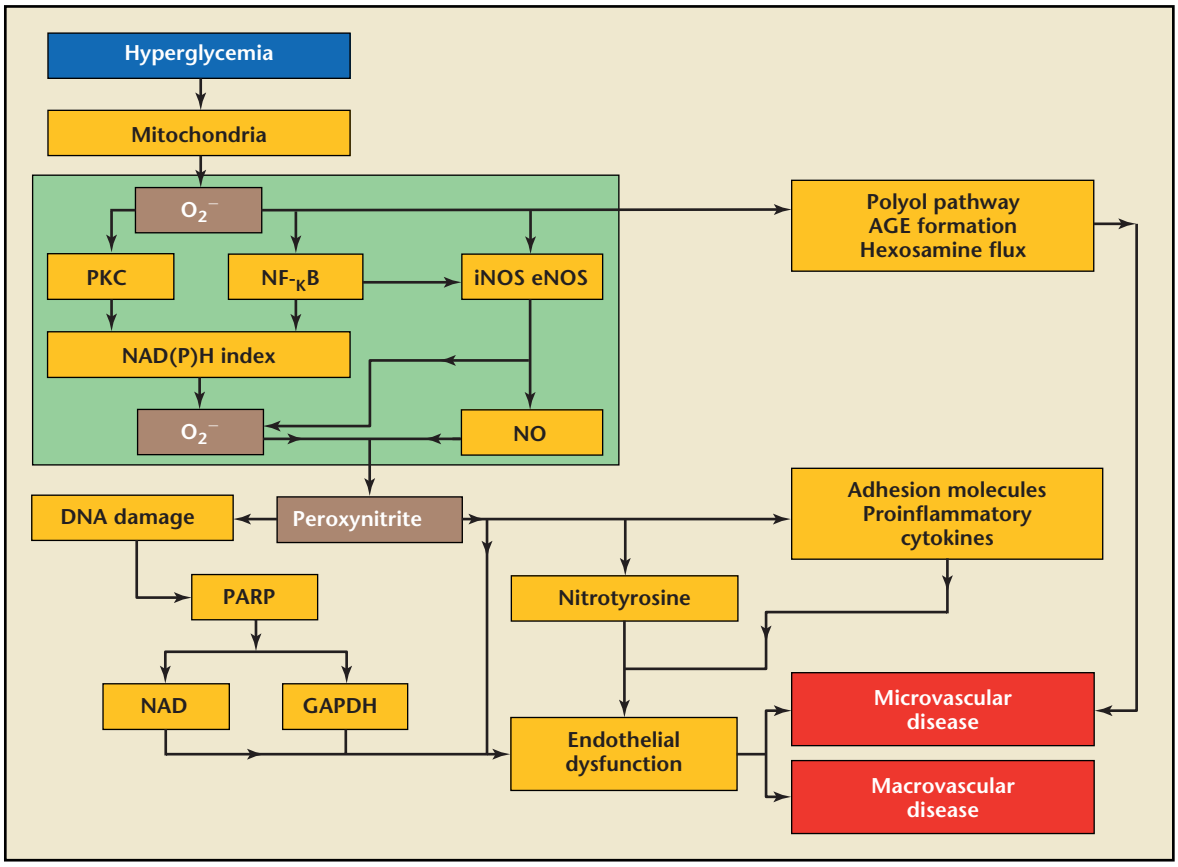
the fact that in people with type 2 DM who did not have the features of the metabolic syndrome (which comprised only about one sixth of the patients with type 2 DM), the prevalence of CHD (7.5%) was no higher than in people without DM and without the metabolic syndrome. This study highlights the heterogeneity of CV risk in individuals with type 2 DM.

Another concern about the concept of the metabolic syndrome is that it is a dichotomous definition. That is, patients either have or do not have the syndrome. A number of studies have shown, not surprisingly, that the number of features of the metabolic syndrome will also predict risk. For example, in the West of Scotland Coronary Prevention Study of 5974 men, those individuals with 4 or 5 features of the metabolic syndrome had a greater risk for coronary death and non-fatal MI, and a much higher risk of new-onset type 2 DM relative to those individuals with just 3 of the features.[24]

Regarding which of the metabolic syndrome features is the best predictor of risk, in another analysis of the NHANES III database, an FPG ≥ 110 mg/dL was associated with a nonsignificant 1.25 odds ratio of MI, whereas the presence of the metabolic syndrome was associated with a 2.01 odds ratio ($P < .0001$).[25] In the San Antonio Heart Study,[26] it was reported that metabolic syndrome traits did not have equal predictive power. In terms of the risk of type 2 DM per unit change in risk trait level, every 1 mg/dL increase in FPG was associated with an 8% increased risk for type 2 DM. The corresponding figures were 7% for every kg/m^2 increase in BMI, 4% per mg/dL decrease in HDL cholesterol, and 2% for every 1 mm Hg increase in systolic blood pressure.

A very useful study was published by Wilson and colleagues[27] looking at 3323 subjects in the Framingham Offspring Study followed for a mean of 8 years. Each of the 5 traits of the NCEP definition of metabolic syndrome was associated with an approximately 1.5- to 2.5-fold increased relative risk for CVD, "hard" CHD, and CHD. In contrast, perhaps not surprisingly, with regard to the predictive value for type 2 DM, hyperglycemia (defined as an FPG ≥ 100 mg/dL) was associated with a

Figure 2. *Pathways of vascular glucotoxicity. AGE, advanced glycation end product; PKC, protein kinase C; NF-$_K$B, nuclear factor-$_K$B; iNOS, inducible NO synthase; eNOS, endothelial NO synthase; NO, nitric oxide; DNA, deoxyribonucleic acid; PARP, poly(ADP-ribose)polymerase; NAD, nicotine adenine dinucleotide; GAPDH, glyseraldehyde-3-phosphate dehydrogenase. Adapted with permission from Ceriello A.*[28]



12.5-fold increased relative risk versus 2.4 to 4.4 for the other individual traits. Similarly, looking at the various combinations of 2 and 3 traits, those combinations that included an elevated blood glucose were associated with an increased risk for DM, although once again the risk for the CV outcomes were similar.

How Does Hyperglycemia Increase the Risk of CVD?

A number of putative pathways have been proposed to explain the mechanism(s) by which hyperglycemia may lead to vascular disease. Ceriello[28] proposed that hyperglycemia may lead to overproduction of superoxide as the first and key event in the activation of other pathways involved in the pathogenesis of diabetes complications, including polyol pathway flux, advanced glycation end product formation, activation of protein kinase-C and nuclear factor-κB, and increased hexosamine pathway flux (Figure 2). These abnormalities result in endothelial dysfunction leading to the development of diabetes-related micro- and macrovascular disease complications. He also suggests that post-prandial hyperglycemia may be particularly atherogenic, as it leads to even greater increases in peroxynitrite and, thus, increased levels of nitrotyrosine and endothelial dysfunction.

Summary

In summary, there is considerable evidence that blood glucose is a continuous, progressive risk factor for CVD outcomes throughout the dysglycemic range. There is also evidence to suggest that post-prandial hyperglycemia may be a better predictor of risk than FPG or A1C. Targeting normoglycemia appears to reduce CV events in DM, although definitive studies in type 2 DM are ongoing. Evidence is also still pending as to whether normoglycemia reduces CV events in dysglycemic individuals without DM. Prediabetes (IFG/IGT) has some, but not total, overlap with the metabolic syndrome. The prevalence and risk of diabetes and CVD depends on the definition of the metabolic syndrome that is employed, but there is increasing emerging evidence that patients with the metabolic syndrome are at significantly increased risk for both of these cardiometabolic outcomes. Finally, there are multiple mechanisms by which hyperglycemia can increase the risk for CVD. ■

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2006;29:S43-S48.
2. National Diabetes Data Group. *Diabetes in America. 2nd Edition*. Bethesda, MD: National Diabetes Data Group; 1995.
3. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233-240.
4. Knowler WE, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;246:393-403.
5. Khaw KT, Wareham N, Bingham S, et al. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141:413-420.
6. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Lancet*. 1999;354:617-621.
7. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. *JAMA*. 2001;285:2109-2113.
8. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care*. 1999;22:920-924.
9. Stratton IM, Adler A, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000:321:405-412.
10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352:837-853.

Main Points

- There is great evidence that blood glucose is a continuous, progressive risk factor for cardiovascular disease (CVD) outcomes throughout the dysglycemic range, and evidence to suggest that post-prandial hyperglycemia is a better predictor of risk than fasting plasma glucose levels or A1C.
- Targeting normoglycemia appears to reduce cardiovascular events in patients with diabetes mellitus (DM), although definitive studies in type 2 DM are ongoing.
- Prediabetes has some overlap with the metabolic syndrome.
- There is increasing emerging evidence that patients with the metabolic syndrome are at significantly increased risk for cardiometabolic outcomes.
- There are many mechanisms by which hyperglycemia can increase the risk for CVD.

11. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
12. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
13. Kahn R. The metabolic syndrome (emperor) wears no clothes. *Diabetes Care*. 2006;29:1693-1696.
14. Grundy SM. Diabetes and coronary risk equivalency. What does it mean? *Diabetes Care*. 2006; 29:457-460.
15. Despres JP. Is visceral obesity the cause of the metabolic syndrome? *Ann Med*. 2006;38:52-63.
16. Expert Panel on 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 Treat Panel III). *JAMA*. 2001;285:2486-2497.
17. Grundy SM, Cleeman JI, Merz CN, et al. National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;13;110:227-239.
18. American Diabetes Association. Diagnosis and classification of diabetes. *Diabetes Care*. 2004; 27(suppl 1):S5-S10.
19. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med*. 2006;23: 469-480.
20. 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; 287:346-359.
21. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*. 2002;288:2709-2716.
22. Hunt KJ, Resendez RG, Williams K, et al; San Antonio Heart Study. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*. 2004;110: 1251-1257.
23. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease amount NHANES III participants age 50 and older. *Diabetes*. 2003;52:1210-1214.
24. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation*. 2003;108:414-419.
25. Ninomiya JK, L'Italien G, Criqui MH, et al. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation*. 2004;109:42-46.
26. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med*. 2002;16;136:575-581.
27. Wilson PW, D'Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112:3066-3072.
28. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes*. 2005;54:1-7.