

Prevention Conference VI Diabetes and Cardiovascular Disease Writing Group I: Epidemiology

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Individuals with diabetes have increased rates of all forms of cardiovascular (CV) disorders affecting the heart, brain, and peripheral vessels. Epidemiological studies have been powerful tools to study this phenomenon, providing data on prevalence and incidence rates in diverse populations and uncovering risk factors. Studies to date have documented that diabetic CV disease (CVD) is increasing, but there are many unanswered questions concerning the temporal relations between diabetes and CVD, the metabolic and cellular etiologic mechanisms, and the most effective strategies for predicting and reducing CVD risk in patients with diabetes. Epidemiological studies can provide important information concerning all of these issues. This writing group has attempted to describe the scope of the problem based on current data. The group is convinced of the importance of understanding and intervening early in the continuum of events that lead to CVD, starting with the metabolic syndrome as it progresses to impaired fasting glucose (IFG) and ultimately hyperglycemia. The group also addressed the issue of defining CVD risk factors in the patient with diabetes and focused on lifestyle strategies for the prevention and treatment of CVD in individuals with diabetes. This report contains several recommendations for future research, as well as recommendations for American Heart Association (AHA) programs.

The Epidemic of Diabetes in the United States

There are ≈ 17 million people in the United States who have diabetes, of whom $\approx 95\%$ have type 2 diabetes.¹ On the basis of fasting plasma glucose levels, approximately one third of all cases of type 2 diabetes (5 to 6 million people) are undiagnosed and untreated. Although type 1 diabetes occurs primarily in children and adolescents, reports from selected research centers indicate that type 2 diabetes in this population is now as common as type 1 diabetes, particularly in Hispanic and black groups.²

Type 2 diabetes has become a common disease in the United States, conveying substantial morbidity and premature mortality. More than 5% of adults have this disease, with prevalence rising from 1% in those aged 20 to 39 years to 13% in those aged 60 years and older. Undiagnosed diabetes occurs in $\approx 3\%$ of adults, rising from 0.6% at age 20 to 39 years to 6% at age 60 years and older.¹ Impaired glucose tolerance (IGT) and IFG, conditions with increased risk for CVD and premature mortality, are also common in adults. Minority population groups are at high risk for diabetes. Blacks³ and Hispanic Americans⁴ have approximately twice the rate of diabetes as whites, and many American Indian tribes are experiencing epidemic rates of diabetes.⁵

The age-adjusted prevalence of diabetes has risen dramatically in the past 40 years. In the United States, 2.6% of adults aged 45 years and older had been diagnosed with diabetes in 1960; by 1990, this proportion had risen to 7.0%.⁶ These trends may be attributed to marked increases in obesity and physical inactivity, which are major risk factors for type 2 diabetes. Obesity has become epidemic in the United States. In 1960, 13% of US adults were obese (body mass index >30 kg/m²); this rate had risen to 27% in 1999.⁷ Obesity is also becoming widespread among US children and adolescents, and a sedentary lifestyle is increasingly common.

Marked increases in type 2 diabetes are occurring worldwide. Even if age- and sex-specific diabetes rates in international populations do not change, the aging of these populations and their increasing urbanization will be associated with large increases in the prevalence of diabetes. There will be an estimated 35% increase in the number of people with diabetes in developed countries between 1995 and 2025 and a 48% increase in the developing nations.⁸ The increasing frequency of obesity and sedentary lifestyles, major risk factors for type 2 diabetes, in both developed and developing countries portends that diabetes will continue to be a growing clinical and public health problem worldwide.

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In sum, considering diagnosed and undiagnosed diabetes and IGT, almost 35 million Americans—20% of those in the middle-adult years and 35% of the elderly population—have some degree of abnormal glucose tolerance, which conveys increased risk for CVD and premature mortality.

Present and Future Impact of Diabetes on CVD

The prevalence, incidence, and mortality from all forms of CVD (myocardial infarction, cerebrovascular disease, peripheral vascular disease, and congestive heart failure) are strikingly increased in persons with diabetes compared with those without diabetes.^{9–12} Excess risk for CVD extends to both type 1 and type 2 diabetes. Furthermore, excess risk of CVD and subclinical atherosclerosis occurs in states of impaired glucose homeostasis, including IFG, IGT, and insulin resistance.^{13–16}

The relative excess risk for CVD is 2- to 8-fold higher in persons with diabetes than in nondiabetic individuals of similar age, sex, and ethnicity. For people with diabetes, absolute rates of CVD increase with age and are higher in men than in women. Compared with sex-matched nondiabetic individuals, however, the relative risk is higher in women than in men.^{17–21}

The absolute risk of CVD among those with diabetes varies to some extent in different ethnic groups.⁶ The absolute risk appears to be lower in Mexican Americans than in the general US population. Rates in blacks are rather similar to those in non-Hispanic white Americans. However, relative risks of CV events and CV mortality in those with diabetes compared with those without diabetes are at least as high in Mexican Americans, Japanese Americans, and American Indians as in the nonminority population.

The extent to which diabetes accounts for CVD in the United States varies in different ethnic groups, largely because of the differences in the frequency of diabetes among them. The proportion of CVD attributable to diabetes or IGT ranges from ≈14% in the white population to 50% to 80% among the American Indian population.¹ Because of the increasing frequency of diabetes during the past 30 years in Americans of all ethnic groups, the importance of CVD attributable to diabetes will continue to increase, even if the incidence of CVD in the nondiabetic population continues to diminish. The extent of the increasing burden of diabetes on CVD in the United States should be recognized.

The impact of diabetes on the prevalence and incidence of CVD in populations with low rates of CVD is significant. Populations such as American Indians, who have experienced epidemics of diabetes, are now experiencing increasing frequencies of CVD many years later.²² The increased risk for diabetes-associated CVD may begin even before onset of the disease, increases with age and diabetes duration, and persists until death. The increasing diabetes incidence in the United States will be reflected in increased proportions of diabetic populations being afflicted with CV complications as they age. Because diabetes is beginning to manifest in younger individuals, the proportion of persons with diabetes affected by CVD likely will continue to expand for the next 20 to 30 years (Figure 1). Thus, unless effective preventive strategies

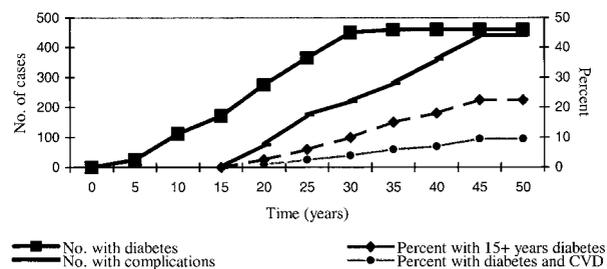


Figure 1. Theoretical projection of effect of epidemic of diabetes on CVD. BP indicates blood pressure.

are implemented, the burden of diabetes-related CVD will rise progressively in the foreseeable future.

Although conventional CVD risk factors are operative in diabetes, attention has recently been focused on defining risk factors specific to individuals with diabetes. The Table summarizes these factors, indicating which are well established and which need more investigation.

Increase in Diabetes in Children

Evidence is rapidly accumulating that both type 1 and type 2 diabetes are increasing in children and adolescents. The prevalence of type 1 (autoimmune) diabetes has risen in most European populations studied and may also be on the rise in US youth. However, more alarming is the increase in type 2 diabetes in American youth. The latter appears to be related to more obesity and physical inactivity among young people. Much of the current data are limited to case reports and

Summary of CVD Risk Factors in Patients With Diabetes

Factor	Longitudinal Evidence	Clinical Trial Evidence
Classic risk factors		
Cholesterol (LDL)	Conclusive; may be stronger than in ND	+ (Subgroup analyses)
Blood pressure	Conclusive	+
Smoking	Conclusive	NA
Sex	Conclusive; weaker than in ND	NA
Additional risk factors		
Glucose	Almost conclusive	+
Insulin	Inconclusive	+ (Insulin Rx—less CVD)
Insulin resistance syndrome	Conclusive	NA
Lipoprotein(a)	Little available	NA
Albuminuria	Conclusive	+ (ACE inhibitors)
Inflammatory markers	None available	NA
Fibrinogen	Suggestive	NA
Subclinical atherosclerosis*	Suggestive	NA
Physical inactivity	Incomplete	NA
Diet	None available	NA

LDL indicates low-density lipoprotein; ND, nondiabetics; NA, not applicable; Rx, treatment; and ACE, angiotensin converting enzyme.

*Some prefer the term “risk predictor” rather than “risk factor” for subclinical atherosclerosis.

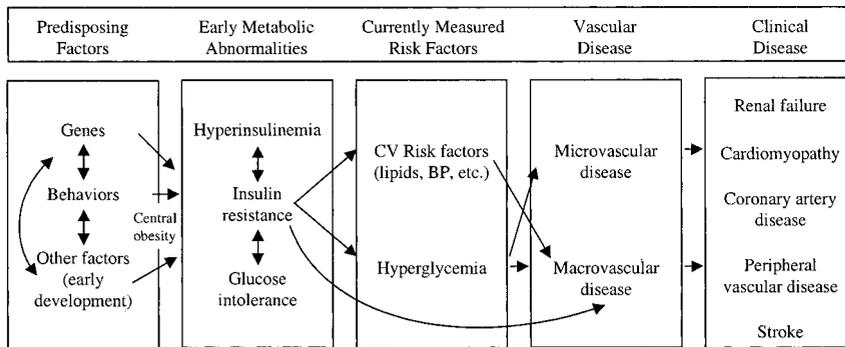


Figure 2. Pathophysiological model of development of diabetes and vascular disease.

clinical series, but population data in American Indians²³ and First Nations youth in Canada²⁴ show rising rates of type 2 diabetes occurring at early ages. This phenomenon also appears in Hispanic and black American youth and is the subject of active investigation.²

In all likelihood, an earlier onset of diabetes will lead to an earlier onset of CV complications. Importantly, recent non-invasive studies in youth with type 1 diabetes show early increases in coronary calcification and elevated CVD risk factors. Pathological patterns of insulin resistance, dyslipidemia, and elevated blood pressure also appear to exist among youth with type 2 diabetes. These patterns suggest that CVD will have an earlier onset in many persons with diabetes.

Intervening Early in the Continuum of Events

Primary prevention of atherosclerosis and vascular disease must be the goal of programs to substantially reduce the incidence of and morbidity and mortality associated with diabetes-related CVD. A fundamental question is, "At what stage in the evolution from elevated blood glucose or insulin resistance to clinical diabetes is it necessary to intervene to effectively reduce the risk for CVD?" (Figure 2). Although various interventions such as lipid lowering or blood pressure reduction will reduce risk, it is doubtful that such therapies applied to patients with established diabetes will reduce the risk of clinical atherosclerotic disease to the levels of age-comparable individuals without diabetes. The determinants of progression of atherosclerosis and other vascular pathology in persons with diabetes must be elucidated. Beyond the major risk factors, such factors as insulin resistance, inflammation, thrombin generation, and decreased fibrinolysis likely play a role and may require intervention.

For persons who are destined to develop type 2 diabetes, one hypothesis states that development of atherosclerosis and vascular pathology accelerates before the onset of clinical diabetes.²⁵ The risk factors responsible for this acceleration are those of the metabolic syndrome. They are common in individuals with insulin resistance and include dyslipidemia, raised blood pressure, and prothrombotic and proinflammatory factors (eg, increased plasminogen activator inhibitor-1, fibrinogen, and inflammatory cytokines). In addition, some investigators hold that hyperinsulinemia and insulin resistance are major determinants of atherosclerotic vascular disease. Other potential pathogenic processes include elevated blood glucose, increased glycosylation of proteins, and oxidative stress. Finally, the possibility exists that there are

shared genetic factors for development of both atherosclerotic vascular disease and diabetes.

Epidemiological studies have demonstrated that increased visceral fat or upper-body obesity is associated with insulin resistance, early vascular "stiffness," and poor endothelial function. Because increased abdominal fat is accompanied by increased plasma free fatty acid levels and increased triglyceride in liver and muscle, it appears to increase or exacerbate insulin resistance.

Possible determinants of increased visceral fat and/or abdominal obesity are higher cortisol levels (possibly modulated by various psychosocial stressors) and altered hypothalamic/pituitary axis. Increased visceral fat is also associated with higher levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor- α , variables that have been related to increased risk of diabetes, myocardial infarction, and stroke in persons both with and without diabetes. Increased intra-abdominal fat or central obesity thus may be a precursor for both atherosclerosis and diabetes.

Relation of Early Metabolic Abnormalities to Diabetes and Atherosclerotic Disease

An important concept implied by the model in Figure 2 is that several CV risk factors commonly are present in persons destined to develop type 2 diabetes. The time of onset of these risk factors that are characteristic of the metabolic syndrome varies and appears to depend in part on racial or ethnic predisposition. With earlier-onset obesity, dyslipidemia (high triglycerides and low high-density lipoprotein) and hypertension are being observed earlier. Elevated plasma glucose and frank diabetes are frequently part of the syndrome in its later stages. This metabolic syndrome, exclusive of categorical hyperglycemia (clinical diabetes), commonly precedes the onset of diabetes by several years. Furthermore, insulin resistance apparently predates these commonly assessed risk factors; thus, detection of insulin resistance relatively early in life offers the opportunity to identify at an early stage those persons likely to develop dyslipidemia, hypertension, and ultimately, diabetes. The metabolic syndrome can lead to clinical CVD whether or not diabetes ensues. Indeed, some people develop coronary or other vascular disease first, only to develop diabetes concurrently or subsequently. It is unclear how many patients have the metabolic syndrome and which will develop vascular disease before diabetes. The fact that the metabolic syndrome per se is a multiplex risk factor for

CVD emphasizes the disadvantage of a strategy that waits for diabetes to develop before intervening aggressively to lower risk factors such as lipid disorders, obesity, and hypertension.

Gene-Environment Interactions

The known risk factors for the metabolic syndrome, CVD, and diabetes overlap substantially.^{26,27} Whether the underlying genetic predispositions for these conditions are the same or whether they differ in number and effect on metabolic pathways is largely unknown at present. It has long been postulated that diabetes and CVD risk represent interactions of behavioral (eg, diet, inactivity, smoking, and alcohol intake) and genetic factors. Such hypotheses are now actively under study, and more genetic markers and genes in multiple relevant pathways are being identified. Interactions of the lipoprotein lipase gene with physical activity and alcohol intake provide examples of the types of studies required to elucidate these complex relationships. It appears likely that interaction of environmental factors with specific combinations of multiple genes (including gene-gene interaction) will ultimately be responsible for the varying onset and co-occurrence (or lack of co-occurrence) of CVD with diabetes, as well as the varying temporal onset of these conditions. Prior studies of CVD have often ignored the careful characterization of diabetes, which restricts their utility in understanding the interrelationships of these conditions. There is an urgent need to establish large, informative population studies with simultaneous measurement of relevant genetic and environmental factors that can be followed for long periods of time for the occurrence of CVD or diabetes.

The Import of Sociocultural Factors

Migration studies have shown that nonwhite populations, with relatively low rates of diabetes in their traditional culture, have significant increases in diabetes and heart disease rates as they adopt a Western lifestyle. Sociocultural factors, such as metabolic indices of the stress response, dietary intake patterns related to food availability and marketing, and physical inactivity associated with increasing use of technology in modern society, must be considered when attempting to identify individuals at risk.

Clinical Implications of the Diagnostic Criteria for Diabetes in Identifying CVD Risk

The American Diabetes Association revised the diagnostic criteria for diabetes in 1997. A plasma glucose level ≥ 126 mg/dL (≥ 7.0 mmol) was recommended as the categorical level because it is the approximate threshold for initiating development of microvascular complications. The World Health Organization has more recently affirmed this threshold. The American Diabetes Association also established a new diagnostic category of IFG to identify individuals in an intermediate metabolic stage between normal fasting glucose and diabetes. Diagnostic criteria for diabetes and IGT (using a 75-g oral glucose challenge) of 2-hour glucose concentrations ≥ 200 mg/dL (11.1 mmol) and 140 to 199 mg/dL, respectively, as described by the World Health Organization, still hold, but an oral glucose tolerance test is not recommended for routine clinical use.

Recent reports nonetheless suggest that in older individuals, the post-glucose-challenge glucose level may be a stronger predictor of CV morbidity and mortality than fasting plasma glucose.^{27,28} The post-glucose-challenge glucose level has the potential to identify individuals who have abnormal glucose tolerance and increased CV risk who would not be detected on the basis of fasting glucose alone. Indeed, epidemiological studies in the elderly suggest that CV outcomes occur more frequently in those with elevated postchallenge glucose levels. Data from the Honolulu Heart Program, Baltimore Aging Study, Rancho Bernardo, and Cardiovascular Health Study show that undiagnosed diabetes and IGT identified from postchallenge values are associated with an adverse CVD risk factor profile,¹³ including hypertension; higher body mass index, central obesity, and triglyceride, insulin, and fibrinogen levels; and lower high-density lipoprotein cholesterol. Identification of diabetes based on post-glucose-challenge levels would result in a higher prevalence of diabetes in the elderly and thus the identification of more persons who would be candidates for rigorous intervention to reduce their CVD risk factors.

New Concepts in Evaluating CVD in Persons With Diabetes

The development of noninvasive methods of measuring atherosclerosis and vascular disease provides the opportunity to test hypotheses related to the development of atherosclerosis in persons with diabetes. These new methods can evaluate the following:

- The extent of atherosclerosis and its progression over time (electron beam computed tomography, spiral computed tomography, carotid ultrasound [intima-media thickness])^{15,16,26}
- Large-vessel vascular function, such as vascular stiffness and compliance (ie, pulse-wave velocity, tonometry)
- Endothelial function (brachial artery flow-mediated vasodilatation plethysmography)
- Cardiac function (echocardiography and magnetic resonance imaging)
- Peripheral vascular disease (ankle-brachial blood pressure)
- Brain imaging (magnetic resonance imaging—detected silent infarct, brain structure, and white matter characteristics)
- Characteristics of atherosclerosis plaque (magnetic resonance imaging of carotid, aortic, and coronary arteries)

Each of these tests has potential specific utility for epidemiological studies to provide surrogate end points for the study of the pathogenesis of atherosclerosis across the spectrum of diabetes and vascular disease. The techniques can be used to test specific intervention hypotheses with much smaller sample sizes and shorter follow-up times. These new noninvasive methods, in combination with measures of thrombogenesis, fibrinogenolysis, and inflammation, will enhance our ability to predict clinical CVD.

Summary and Recommendations for AHA Programs

This group strongly recommends that the AHA increase the volume and scope of its programmatic activities related to

diabetic CVD. Given the magnitude of the current role that diabetes plays in CVD in the United States and the strong likelihood that the impact of diabetes on CVD will increase greatly in the near future, aggressive programs will be needed to further reduce the nation's CVD mortality and morbidity. The magnitude and scope of the problem are so great that it will be imperative to collaborate with other organizations such as the American Diabetes Association, National Institutes of Health, and Centers for Disease Control and Prevention, which are also concerned with this issue. Writing Group I thus makes the following recommendations for future AHA programs:

- Monitor the extent of the increasing burden of CVD attributable to diabetes in the US population and in different ethnic groups to assess its public health and clinical importance for the general US population. This can be achieved by CV event and mortality follow-up on the National Health and Nutrition Examination Survey (NHANES) II, NHANES III, and Hispanic Health and Nutrition Examination Survey populations in a similar way to that performed in the NHANES I study.
- Monitor changes and trends in the population distribution of plasma glucose to determine whether temporal changes in glucose homeostasis are occurring throughout the population or are affecting only a segment of it.
- Establish large cohorts of youth with type 1 and type 2 diabetes to define CVD risk factors and clinical outcomes so that preventive strategies can be tested. Clinical trials of proven therapies in adults should also be initiated in youth to determine their efficacy.
- Identify children who already have type 2 diabetes, IGT, or high risk for developing these (ie, obese with strong family history or exposure to a diabetic in utero environment). Demonstrate the effects of incorporating nutrition education and physical activity into school programs in reducing CVD risk for these children.
- Develop and evaluate healthcare strategies based on clinical trial evidence for individuals with insulin resistance and IFG or IGT. This should include intervention to prevent development of diabetes, as well as aggressive CVD risk management.
- Develop, implement, and evaluate public education programs to increase understanding of the role diabetes plays in CVD and how individuals can recognize and address risk factors for CVD if they have diabetes.
- Develop, implement, and evaluate education programs for both the public and healthcare providers on dietary and physical activity programs appropriate for preventing or reducing CVD and its risk factors in patients with diabetes.
- Develop and evaluate programs to ensure that every person with newly diagnosed diabetes has aggressive control of all CVD risk factors. Develop effective programs to ensure that every patient with diabetes, regardless of ethnicity and economic status, receives adequate preventive therapies aimed at smoking cessation, dyslipidemia correction, blood pressure lowering, and blood glucose level reduction.
- Stimulate research to better understand risk factors for CVD in those with diabetes. This should include research

into both lifestyle and biochemical markers. Research should include appropriate intervention studies.

- More thoroughly define the economic burden of diabetes-related CVD and examine the impact of current healthcare policy on the costs of CVD in persons with diabetes.

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