

DIABETES AND CARDIOVASCULAR DISEASE

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■ **Abstract** This review focuses on several topics related to the epidemiology of diabetes and cardiovascular disease (CVD). These include the CVD risk factors common in the metabolic syndrome, behavioral risk factors and diabetes, gender differences in the association between diabetes and CVD risk, and how the clinical definition of diabetes influences the association of diabetes and CVD. Nontraditional risk factors potentially linking diabetes and CVD are also discussed, including chronic inflammation, advanced glycation endpoints, autonomic neuropathy, sleep-disordered breathing, and genetic susceptibility to diabetes-associated CVD risk.

INTRODUCTION

Diabetes mellitus and cardiovascular disease (CVD) share several important characteristics. The occurrence of both conditions increases with age; both are associated with an adverse lipid profile, obesity, and a sedentary lifestyle; and the risk of both can be reduced by lifestyle modifications of common risk factors (1). Diabetes is a potent, independent risk factor for CVD. Coronary heart disease (CHD) is the most common and costly vascular complication of diabetes (2).

Cross-sectional epidemiologic studies have consistently shown an association between diabetes and prevalence of CVD in the U.S. population and in community-based studies in the United States and abroad (3-8). Diabetes is associated with an unfavorable distribution of CVD risk factors among people with existing diabetes, and unfavorable CVD risk factors are also present prior to diagnosis of diabetes (9-11). Prospective epidemiologic studies of individuals at risk for CVD yield consistent temporal relationships between diabetes and both incident CVD and mortality (12-21). Results from epidemiologic studies linking diabetes to CVD are consistent in the United States and abroad, in younger and older individuals, among both men and women, and across race/ethnicity (3, 22).

This paper reviews the relationship between diabetes and CVD with an emphasis on findings from epidemiologic studies. Rather than providing an exhaustive summary of the existing literature on diabetes and its relationship to cardiovascular complications, this review highlights several key points related to the epidemiology of diabetes and CVD. These include a discussion of the “metabolic syndrome” that often characterizes diabetes, the differential effect of diabetes on CVD risk in men and women, and how the definition of diabetes influences not only population estimates of diabetes but also the association of diabetes with CVD. This report also explores the new focus on measurement of “nontraditional” risk factors, such as markers of inflammation, advanced glycosylation end products (AGEs), cardiac autonomic neuropathy, sleep-disordered breathing, and polymorphic genes, which may provide novel insights into mechanisms linking diabetes and CVD.

THE METABOLIC SYNDROME

People with type 2 diabetes often have distinct physical and metabolic profiles. Diabetic individuals are considerably heavier than their nondiabetic counterparts, and weight differences between the groups persist even into old age (9, 23). In epidemiologic studies, the body mass index (BMI) is the most common measure of body size. Nonwhite women have higher BMIs than nonwhite men or white women, a phenomenon that is directly related to the high prevalence of diabetes in minority women (9, 23). Apart from elevated BMI, diabetic individuals tend to have an android fat distribution pattern, with accumulation of fat in the abdomen. It has been postulated that abdominal visceral fat is involved in glucose dysregulation and plays a much greater role in the development of diabetes than subcutaneous fat (24–26). In epidemiologic studies, however, it is not possible to distinguish these two fat compartments by using conventional abdominal girth measures such as waist circumferences. Despite this limitation, circumference measures have been consistently associated with diabetes in a number of epidemiologic studies (27–30).

In addition to overall and abdominal obesity, people with diabetes exhibit a pattern of dyslipidemia characterized by elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol and small, dense low-density lipoprotein (LDL) particles (9, 23). In contrast, levels of LDL cholesterol do not consistently differ between diabetic and non-diabetic people (i.e., diabetic patients may present with normal or below-normal LDL levels). Appearing prior to frank diabetes, this constellation of physical and metabolic characteristics (sometimes accompanied by hypertension, hyperuricemia, and abnormalities in hemostatic factors) has been termed the metabolic syndrome, although these features persist following diagnosis of diabetes. A recent study showed an association between the metabolic syndrome and ischemic heart disease, further highlighting the importance of this set of metabolic disorders in risk of CVD (31).

BEHAVIORAL RISK FACTORS AND CVD AMONG DIABETIC INDIVIDUALS

Smoking, Exercise, and Diet

Several behavioral risk factors increase the risk of adverse health events among diabetic individuals, although the effects of these risk factors are not limited to people with diabetes. Smoking has repeatedly been associated with development of diabetic complications and with increased mortality risk among people with diabetes (32–36). It is for this reason that the American Diabetes Association (ADA) recommends prevention and cessation of smoking among individuals with diabetes (37). Diabetic individuals are less likely to participate in regular physical activity than nondiabetic individuals (38). Lack of physical activity, in turn, is associated with mortality among people with diabetes (33, 39). Although sustained physical activity is generally beneficial to health, diabetic individuals should be evaluated by a physician before beginning an exercise program (40). Factors such as ischemic changes in the foot, loss of protective sensation, risk of vitreous hemorrhage, resting tachycardia, and orthostasis are associated with specific diabetic vascular complications. These factors must be considered in the design and implementation of exercise programs in order to ensure patient safety.

Studies of the role of diet in development of diabetes have yielded varied results regarding the risk associated with specific nutrients (41). However, it is clear that a diet high in saturated fat is associated with an adverse CVD risk factor profile both in the presence and absence of diabetes. The ADA does not recommend a single “diabetic diet” but rather one that is based on detailed patient assessment and treatment goals (42).

GENDER DIFFERENCES: PREVALENCE OF DIABETES AND DIFFERENTIAL EFFECTS OF DIABETES ON CVD RISK

When evaluating the effect of gender on the occurrence of diabetes and the association of diabetes with CVD, it is critical to consider other CVD risk factors to determine if gender plays an independent role in the development of either condition. When the gender distribution of key diabetes risk factors, such as obesity, is considered, there is no consistent difference in the occurrence of diabetes between men and women, nor does gender appear to influence the progression of glucose disorders (43, 44). The lack of risk-factor-adjusted differences in diabetes between men and women suggests that intrinsic characteristics distinguishing men from women do not play a role in the pathway from normoglycemia to a state of abnormal glucose metabolism leading to diabetes.

Although risk-factor-adjusted rates of diabetes do not consistently differ by gender, it is important to stress that the public health burden of diabetes is quite dissimilar in men and women. This is partly because key diabetes risk factors such

as obesity are more prevalent in women, as are other factors potentially related to maintenance of normal glucose metabolism in the presence of obesity (45). In the United States, black, Hispanic, and American Indian women are considerably more obese than men of the same ethnicity (9), and these women experience higher rates of diabetes than their male counterparts (46, 47).

Women have lower unadjusted risk of CHD than men. In many studies, rates of CVD in women with diabetes equal or exceed those in men (5, 10, 14, 48–53), although not all studies have demonstrated this relationship (16, 54). A number of mechanisms have been proposed to explain the excess CVD risk among diabetic women.

Estrogen is generally associated with an antiatherogenic CVD risk factor profile, including higher HDL, lower LDL, and lower blood pressure, as well as a peripheral rather than central distribution of fat. The favorable effect of estrogen on these factors may therefore protect premenopausal women from CVD in comparison to men of similar age. At menopause, cessation of ovarian function leads to a reduction in estrogen levels and to elevated LDL and blood pressure, reduced HDL, and changes in body composition that favor deposition of fat in the abdomen. All of these phenomena also accompany chronological aging and are risk factors for CVD. Thus, after menopause and with aging, the favorable CVD risk factor profile commonly observed during women's reproductive years is reduced or eliminated compared to men of similar age, i.e., women's CVD risk may rise more steeply than men's as they age. However, changes in CVD risk factors at menopause do not fully explain the association between diabetes and CVD in women.

What, then, is the link between diabetes and CVD among diabetic women? Insulin resistance may be one answer. A period of insulin resistance often precedes the appearance of frank diabetes, and this period may last for years. During this time, peripheral tissues do not respond normally to the biological effects of insulin. Tissue resistance to insulin results in increased pancreatic beta cell activity, ultimately leading to a state of compensatory hyperinsulinemia that helps maintain euglycemia. At some point, a relative decrease in insulin production results in hyperglycemia because the compensatory hyperinsulinemia common in insulin resistance is no longer sufficient to maintain euglycemia. Paradoxically, diagnosis of diabetes is often accompanied by supranormal levels of insulin despite the high glucose levels.

The hyperinsulinemia of insulin resistance and diabetes is important in understanding the link between female gender and risk of CVD. Insulin resistance is associated with lower estrogen and higher androgen levels. Thus, even premenopausal women who are insulin-resistant or diabetic often have relatively low estrogen and higher androgen levels, characteristics associated with an unfavorable distribution of CVD risk factors. Premenopausal women with insulin resistance or diabetes do not benefit from the protective effects of estrogen experienced by women without these conditions. Although CVD events are relatively rare in the premenopausal years, the adverse effects of unfavorable CVD risk factor levels occurring before menopause may accumulate over time and only become apparent in

the postmenopausal years. Thus, the estrogen deficiency characterizing menopause may be an especially potent CVD risk factor among women who were insulin-resistant earlier in life. Their late-life CVD risk may be a function not only of the unfavorable changes in CVD risk factors that often accompany menopause but also of the cumulative effects of unfavorable CVD risk factors that characterized their reproductive years.

Although estrogen may play a role in reducing CVD risk among diabetic women, secondary trials of postmenopausal women taking exogenous estrogen have not shown a reduction in CVD risk, and hyperestrogenemia has been linked to heart disease in men (55, 56). Studies of the effect of estrogen on CVD risk in both diabetic and nondiabetic women are needed to clarify this relationship.

Other pathways may link diabetes to higher CVD risk in women than in men. For example, although it is known that LDL is a risk factor for CVD, LDL levels are similar in people with and without diabetes (9, 57). However, one study showed not only that the composition of LDL differed between diabetic and nondiabetic individuals, with both diabetic men and women having smaller LDL particle size, but also that after adjustment for other CHD risk factors including lipids, no differences in LDL size remained in diabetic men whereas unfavorable differences persisted in diabetic women (58). Because small, dense LDL may enhance the atherosclerotic process (59), results from this cross-sectional study suggest an additional mechanism by which diabetes may increase CVD risk more in women than in men. This study also highlights the fact that LDL characteristics may play an important role in the vascular disease of diabetes, even at levels similar to those in nondiabetic people.

Another study of diabetic men and women showed that diabetes has a greater adverse effect on multiple CVD risk factors among women than among men (10). This study examined diabetes \times gender interactions and found significant effects for waist-hip ratio, LDL cholesterol, HDL cholesterol, LDL size, apoB, and apoA1, findings that suggest a stronger effect of diabetes on CVD risk in women than in men. Differences in levels of these risk factors may be responsible for the observation of increased CVD risk in diabetic women compared with diabetic men.

EFFECT OF DEFINITION OF DIABETES ON DIABETES PREVALENCE

A key requirement in interpreting epidemiologic research relating diabetes to CVD is the ability to compare results across studies. To achieve this, standardized methods for ascertaining and classifying abnormalities of glucose metabolism are necessary. Similarly, standardized criteria for defining CVD are important. For many years there was no set of standard diagnostic criteria for either type 1 or type 2 diabetes. This resulted in inconsistent practices in both clinical and research settings and in difficulty interpreting research findings across studies (60, 61). In response, the National Diabetes Data group and the World Health Organization

(WHO) proposed criteria for classification and diagnosis of diabetes based on either a fasting glucose of ≥ 140 mg/dL or a two-hour post-challenge glucose of ≥ 200 mg/dL following an oral glucose tolerance test (OGTT) using a standard 75-g carbohydrate challenge (62, 63). These criteria became known as the WHO criteria, and for more than 10 years, epidemiologic studies that collected both fasting and post-challenge glucose often used an “either-or” approach to define prevalence and incidence of diabetes—that is, diabetes was defined as an abnormality of *either* screening test. Diabetic individuals (people with an abnormality of either fasting or post-challenge glucose) were then studied in relation to prevalence and incidence of CHD and other diabetic complications (4–8, 18).

As the dust was settling after publication of the WHO criteria, in 1997 the ADA proposed changing the diagnostic criteria. Two principal features distinguish the ADA criteria from the WHO criteria: (a) a reduction in the fasting glucose threshold that is diagnostic of diabetes from 140 mg/dL to 126 mg/dL; (b) a recommendation against use of the OGTT for diagnosing or classifying diabetes, with a specific recommendation against use of the OGTT in epidemiologic studies (64). Following publication of the ADA criteria, a flurry of papers and editorials addressed not only comparisons in diabetes prevalence and incidence between the 1997 ADA and 1985 WHO criteria but also the relationship between the two definitions of diabetes and outcomes such as CVD and mortality, as well as principles of diabetes screening in general (57, 65–74).

Although one study showed a slight increase in the prevalence of diabetes under the ADA criteria (71), another showed few differences in the prevalence of diabetes under the two sets of criteria but hinted that differences increased with age (65). The latter findings are supported by another report showing that the ADA criteria under-ascertained diabetes by $\sim 50\%$ in older adults (75) and by results from a representative sample of U.S. adults in which an age-associated bias in ADA-defined diabetes diagnosis was demonstrated with increasing age, with proportionally fewer cases of diabetes identified as age increased (57). These results were due to the “missed” cases of diabetes that would have been identified by the OGTT had this test result been included in the ADA definition of diabetes. Consistent with known age-associated decrements in the OGTT with increasing age (76), individuals with post-challenge glucose ≥ 200 mg/dL often do not have a fasting glucose that is diagnostic of diabetes under the ADA criteria (57, 75, 77, 78). This has direct implications for the ADA criteria, which rely on fasting glucose alone to ascertain diabetes.

Whether the prevalence of diabetes was higher, lower, or about the same under the two sets of criteria, most investigators agreed that the lack of concordance of individuals defined as diabetic under the two sets of criteria was a matter of concern. This issue raised questions about which screening tool is appropriate for identifying diabetes in epidemiologic studies, and how these considerations should apply in a clinical setting. The matter of greatest clinical importance, however, is how the choice of tool to identify people with “diabetes” influences the association of abnormal glucose metabolism with adverse health outcomes.

The most obvious question was whether cases of diabetes that were “missed” under the ADA criteria were clinically relevant. Did people with isolated post-challenge hyperglycemia (IPH—those with fasting glucose <126 mg/dL and an OGTT ≥ 200 mg/dL) have worse CVD risk factor profiles than “nondiabetic” people (those with fasting glucose <126 mg/dL and an OGTT <200 mg/dL), and did they experience higher rates of CVD or other adverse health events that clearly distinguished them from people with OGTT <200 mg/dL? These questions were addressed by several studies examining CVD risk factors in groups of individuals in various glucose tolerance categories, as well as the relative strength of fasting versus post-challenge glucose in prediction of CVD and mortality. In most (69, 77–79) but not all (80) studies, the data suggested that after fasting glucose was considered, elevated post-challenge glucose was associated with additional risk of adverse health events, including CVD.

Questions concerning the magnitude of association between diabetes and CVD are complicated by studies in which only one of the two glucose measures was collected and by those in which diabetes is defined by self report, without blood chemistry data. Some investigators hold that diabetes should be defined based on a glycemic threshold that could conclusively be linked with diabetes-associated vascular damage, rather than a cut-point that maximizes concordance between fasting and post-challenge glucose (64). Others propose that diabetes should be diagnosed only when there is clear evidence of glycation, a mechanism by which high blood glucose is thought to be causally linked with vascular damage (81).

Whatever the ultimate conclusion to the controversy over the diagnosis and classification of diabetes, both in clinical and epidemiologic settings, researchers will need to address the belief of some investigators that the OGTT provides information on the risk of CVD that is distinct from that yielded by measuring fasting glucose (82). These considerations must be weighed against the fact that in the United States, the OGTT is not routinely performed in clinical practice, making the clinical application of findings from epidemiologic studies in which OGTTs have been collected and studied somewhat limited. However, use of glycated hemoglobin, in conjunction with fasting glucose, may help identify individuals with normal fasting glucose who show evidence of glycation.

THE FUTURE OF DIABETES-CVD RESEARCH: MEASUREMENT AND EVALUATION OF NONTRADITIONAL RISK FACTORS

Chronic Inflammation

Much attention has been focused recently on how inflammation may contribute to the development of CVD and on the possible role of diabetes in this pathway. It has been proposed that markers of inflammation are part of a complex clustering of pro-CVD risk factors characterizing the insulin resistance syndrome and

that these markers contribute to CVD risk independently of established metabolic abnormalities commonly observed in insulin resistance (83–85).

The inflammatory response involves a complex cascade of events involving many cell types that have interrelated functions. Considerable redundancy is built into this system, a feature that makes specific disease-outcome attributions of inflammatory markers difficult. Studies of diabetes and CVD focusing on inflammation are limited by the nonspecific nature of existing markers, lack of definition of clinically meaningful levels of these markers, and inability of epidemiologic studies to sufficiently distinguish acute inflammation from chronic, low-grade inflammation. Despite these limitations, there is remarkable consistency in findings from a number of studies on the relationship between markers of inflammation, abnormalities of glucose metabolism, and CVD endpoints.

Interleukin 6 (IL-6) regulates the expression of C-reactive protein (CRP). Data from a small, clinic-based study showed that adipose tissue was associated with increased production of IL-6 and CRP, and that these two inflammatory markers were related to insulin resistance (86). These data suggested that low-level, chronic inflammation was associated with endothelial dysfunction, a pathway potentially linking obesity and insulin resistance to CVD. Results from this study are supported by a larger cross-sectional study that found elevated levels of CRP associated with obesity. This report showed elevated CRP in obese individuals as young as 17 years. Compared to their nonobese counterparts, obese men in this study were 2.13 times as likely to have elevated CRP, but women were 6.21 as likely to have elevated CRP (87). If markers of inflammation such as CRP are shown to be causally related to CVD risk, the gender difference in risk of elevated CRP at similar levels of obesity hints at another explanation for differences in CVD risk between men and women with similar CVD risk factor profiles. A study exploring the role of diabetes in relation to obesity and CRP, conducted in the same sample, showed that within levels of BMI, individuals with abnormalities of glucose metabolism had higher levels of CRP than normoglycemic people (88). These findings suggested that the association between diabetes and inflammation does not operate solely through the increased obesity that is common in diabetic individuals. However, it should be noted that data from this sample showed no association between CRP and self-reported angina pectoris but did show an association between CRP and self-reported stroke (89, 90). The inconsistency of these findings may be due to differences in detecting associations between “soft” outcome measures such as angina and “hard” outcomes such as stroke. Findings from these cross-sectional studies have been supported by prospective studies, which can show true CVD risk associated with inflammation.

IL-6 has been shown to predict mortality in women with CVD but not in those without CVD (91), suggesting that the mortality risk associated with this inflammatory marker may be primarily attributable to prevalent CVD. In a prospective study of older adults, markers of inflammation predicted clinically meaningful increases in fasting glucose levels (92). In this study, baseline levels of inflammatory markers predicted changes in ADA-defined categories of glucose regulation from

nondiabetic to impaired fasting glucose, and from impaired fasting glucose to diabetes. Another study of middle-aged adults showed that elevated white-cell count and fibrinogen predicted a new diagnosis of diabetes (93). Although these studies suggest a role for inflammation in the development of glucose abnormalities, others support the temporal relationship between markers of inflammation and occurrence and progression of CVD and CVD mortality (94–97). Two recent studies showed that higher levels of CRP predicted both CVD and long-term mortality in unstable CHD (98, 99) and raised questions about whether a broad recommendation to measure these markers would help reduce CVD-associated morbidity and mortality.

Despite the growing body of evidence linking markers of inflammation to CVD, it is important to stress that these observations may be nonspecific. That is, elevated levels of inflammatory markers are observed in several conditions that are common in old age and may be indicators of the development and/or progression of these conditions (100). Data relating these markers to specific outcomes should therefore be interpreted with caution. The evolving literature on the role of inflammation in risk of CVD seems to indicate that diabetes plays a role, but the complex links between elevated inflammatory markers, impaired glucose regulation, and the occurrence of CVD have not yet been fully described.

Advanced Glycosylation End Products in Vascular Complications of Diabetes

A central pathologic feature of diabetic vascular complications may be the formation of advanced glycosylation end products (AGEs) in the tissues of diabetic individuals, a process that is accelerated in the presence of hyperglycemia (101, 102). Glucose forms early glycosylation products with proteins at a rate proportional to glucose concentrations. Because the amount of these products is reversible depending on the concentration of glucose and does not accumulate in stable tissue proteins, they are not consistently correlated with diabetic complications (103). However, over time, some of the early products undergo further changes and form bonds with other proteins. Levels of AGEs do not return to normal when hyperglycemia is eliminated; they continue to accumulate on wall proteins of both large and small vessels (104). Through several mechanisms, the accumulation of AGEs in tissue is thought to result in increased vascular permeability and thickened, inelastic vessel walls. In contrast to the lack of association between early glycosylation products and diabetic complications, AGEs are related to diabetic vascular disease (105). Numerous AGEs have been characterized (106, 107) but the relative importance of specific AGEs in diabetes-associated vascular damage is still unknown, as are the potentially differential effects of specific AGEs in different tissues.

One way in which AGEs may accelerate the development of macrovascular disease is by linking plasma lipoproteins with matrix proteins, a process that slows the efflux of lipoproteins from the tissues. This process has been demonstrated *in vitro* (108). Another mechanism potentially linking diabetes with CVD via AGEs

is the induction of endothelial cell surface adhesion molecules resulting from the interaction of AGEs with their receptors (RAGE) (109, 110), a phenomenon that may be a marker for amount and progression of vascular disease in diabetes (111). One study suggested that blocking the activity of RAGE inhibits the accelerated atherosclerosis characterizing the diabetic state and may be a future target for new therapies (112).

Yet another mechanism potentially linking AGEs with vessel disease involves the inflammatory processes described above. Several studies have suggested that binding of AGEs induces release of inflammatory cytokines (113, 114). It is possible that sustained interaction between the stable AGEs and RAGE in tissues of diabetic individuals may result in a long-term proinflammatory environment that increases risk of CVD. The potential role of AGEs as a “fuel” for a pro-CVD inflammatory process may therefore be an important piece of the diabetes-CVD puzzle.

Despite promising data linking AGEs and diabetes-associated vascular damage, measurement and reporting of AGEs in epidemiologic studies have been limited. Although methods for standardization have been proposed (115), use of AGEs in epidemiologic studies has been sparse owing to lack of standardized measurements and the continuing evolution of knowledge about which AGEs are involved in the vascular damage observed in diabetes. In addition, although several studies have shown accumulation of AGEs in tissues of diabetic individuals, it will be important to validate serum measures of AGEs against tissue AGEs, because it is postulated that AGE-associated damage to vessels is more closely related to CVD than circulating AGEs are. However, because tissue samples are rarely available in epidemiologic studies, this type of validation may be difficult.

Chemical characterization of AGEs shows the existence of multiple products, each of which may be differentially related to diabetes and specific vascular complications. However, existing assays for polyclonal anti-AGE antibodies do not distinguish between individual AGEs, a key weakness in efforts to link specific products with vascular damage. Despite these limitations in the application of AGEs in epidemiologic studies, small clinic-based reports have shown that serum levels of AGEs are elevated in children with type I diabetes even before vascular complications appear (116). Such findings suggest important future opportunities for epidemiologic studies of AGEs and CVD.

Cigarette smoke is also a source of AGEs (117, 118), which may be one mechanism linking smoking with increased occurrence of CVD in both the presence and absence of diabetes. This is important because it is known that smoking increases the risk of peripheral arterial disease (PAD) among diabetic individuals, who are already at increased PAD risk, and that smoking can influence relationships between risk factors and the development of PAD.

Diabetes, Sleep-Disordered Breathing, and Cardiovascular Disease

Snoring is the most common symptom of sleep-disordered breathing (SDB) and has been suggested as a risk factor for CVD (119–121). Adverse CVD events

attributable to snoring may be related to the occurrence of sleep apnea among people who snore. SDB is common in people with hypertension, overweight individuals, and older adults (121–123).

Hypertension, obesity, and older age are also well-established characteristics of people with diabetes. The substantial overlap between risk factors for SDB and those for diabetes raises questions about the potential relationship between diabetes and SDB, and how this relationship may be associated with the development of CVD. It is not clear if a potential SDB-CVD association is modified by diabetes or if this relationship is partly or entirely attributable to diabetic complications or metabolic abnormalities characterizing diabetes.

Severity of diabetes is associated with sleep disruption (124), which may result from the activation of metabolic processes involving insulin action or glucose regulation, although these potential pathways are not well-described (125). One mechanism through which diabetes may be involved in the SDB-CVD relationship is through the effects of diabetic cardiovascular autonomic neuropathy (CAN) on CVD risk.

A growing body of literature describes the contribution of CAN to increased CVD risk among diabetic individuals (126, 127). Although impairment of CAN-associated CVD reflexes, such as heart rate variability, may be associated with increased risk of CVD, other mechanisms may link diabetes to CVD via CAN. A recent study showed that one in four diabetic individuals with CAN had obstructive sleep apnea, a proportion significantly greater than in diabetic individuals without CAN (128). The relatively high prevalence of sleep disturbance in the presence of diabetic neuropathy raises the possibility that impairments in CAN-associated central control of respiration may link diabetes and SDB by enhancing the occurrence or consequences of sleep disorders on CVD (129). Reports of increased prevalence of sleep apnea and nocturnal oxygen desaturation in diabetic patients with CAN support a diabetes-SDB link (130–132). However, diabetes and SDB may also be related in the opposite direction, with SDB leading to decrements in glucose metabolism. A recent study showed a reduction in glucose tolerance following sleep deprivation and raised the possibility that disrupted sleep has deleterious effects on endocrine function (133). However, in such small cross-sectional studies, statistical power is often limited, and it is difficult to determine the direction of diabetes and SDB factors and to infer their independent effects because of confounding by obesity. Additionally, clinic-based studies of severe sleep deprivation do not mirror the experience of most people in the community. In cross-sectional studies, individuals with a history of CVD may adopt lifestyle modifications that further hinder interpretation of data related to diabetes and SDB.

Existing prospective studies of SDB and CVD are limited and do not provide the full complement of CVD risk factor data, including diabetes status. However, a large community-based prospective study of SDB and CVD is ongoing (134). Data from this study will begin to address deficiencies in previous studies by allowing improved examination not only of SDB's contribution to CVD but also the role of diabetes in this relationship.

Genetic Susceptibility to Diabetes-Associated Vascular Damage

Genetics may play a key role in determining the severity of vascular complications a diabetic individual is likely to experience. In the future, identification of “susceptibility genes” among diabetic individuals may become an important tool for clinicians as they tailor treatment plans for “susceptible” or “protected” patients. Although no clinical practice guidelines currently exist for genetic screening of diabetic patients for susceptibility to complications, intriguing new data suggest the existence of genes that confer differential susceptibility.

One such gene encodes haptoglobin (Hp), a hemoglobin-binding protein that protects against oxidative stress. Oxidative stress has been implicated as an important mediator of numerous pathophysiological processes, including diabetic vascular complications. The two common Hp alleles yield three phenotypes that appear to differ in their ability to function as antioxidants because of their different biochemical and biophysical properties. Three recent studies examining the Hp gene in relation to diabetic retinopathy, diabetic nephropathy, and coronary restenosis showed that individuals who are homozygous for the Hp 1 allele (1-1) appear to be protected against the development of these diabetic complications (135–137). As the field of genetics continues to develop, new strategies for risk stratification of diabetic patients may be tailored to their genetic profiles.

Risk Factors for Cardiovascular Disease in Diabetes: Possible Interventions

LIPIDS Individuals with type 2 (non-insulin-dependent) diabetes have dyslipidemia characterized by high triglyceride levels, low levels of HDL, and small, dense LDL particles. This pattern results from both hyperglycemia per se and the insulin resistance syndrome that accompanies diabetes (138). Subgroup analyses of several major trials provide evidence that aggressive lipid lowering can be highly effective in reducing CVD risk in diabetic individuals. For primary prevention, the Helsinki Heart Study showed a 60% reduction (NS) in CVD events in a subgroup of 155 diabetic patients treated with gemfibrozil (139), and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) showed a 30% (NS) reduction in CVD events in a subgroup of 264 diabetic patients treated with Lovastatin (140). For secondary prevention, the Cholesterol And Recurrent Events (CARE) Study showed a 25% reduction ($p < 0.02$) of CVD in a subgroup analysis of 586 diabetic individuals (141), and the Scandinavian Simvastatin Survival Study (4S) showed a 50% reduction of CVD in 202 diabetic individuals treated with simvastatin (142). The DAIS Study, the first lipid-lowering study to be completed solely in diabetic patients, showed reduced progression of atherosclerosis with fenofibrate therapy (143).

There is considerable debate concerning appropriate targets for LDL lowering among diabetic (and also nondiabetic) patients. Except for the CARE Study, all intervention studies show consistent risk reduction across the range of LDL levels; i.e., there is little evidence for a threshold below which LDL reduction does

not mitigate CVD risk. Currently, the National Cholesterol Education Program (NCEP) ATP III guidelines indicate a goal of 100 mg/dL for individuals with diabetes (144). The American Diabetes Association (ADA) recommends a target of 100 mg/dL for all such individuals because of their known high risk for CVD and tendency to have multiple risk factors. High LDL levels in diabetic patients are thought to be particularly atherogenic because of altered composition, glycation, and susceptibility to oxidation.

In the above trials, LDL goals were between 100 and 130 mg/dL. However, it has often been suggested that therapeutic goals could be lower. In the Post Coronary Artery Bypass Graft (Post CABG) Trial, the role of aggressive (goal LDL 85 mg/dL) versus moderate (goal LDL 130–140 mg/dL) cholesterol reduction was evaluated in 1351 patients with prior saphenous vein CABG and baseline LDL levels of 130–175 mg/dL using lovastatin (40–80 mg) \pm cholestyramine (2.5–5 mg/d). The aggressive therapy arm produced a 31% relative reduction in the progression of atherosclerosis in the grafts and 29% relative reduction in revascularization procedures compared with moderate therapy (145). In a more recent evaluation of aggressive lipid management in asymptomatic to moderately symptomatic individuals with known CVD, the AVERT Trial revealed that aggressive lipid lowering to 77 mg/dL utilizing 80 mg of atorvastatin daily (with baseline LDL levels \geq 115 mg/dL) reduced the 18-month ischemic event rate by an absolute 8% (NS, a relative reduction of 36%) compared with those treated with angioplasty, and significantly increased the time to the first ischemic event (146). Because the risk of initial CVD events in diabetic patients appears at least as great as the risk for recurrent events in those with proven CVD (147), it appears that the benefits of the aggressive interventions evidenced in secondary prevention would be applicable to those with diabetes.

BLOOD PRESSURE Hypertension in the setting of type 2 diabetes is frequently associated with both CVD and progressive renal insufficiency. Intensive blood pressure (BP) control in patients with type 2 diabetes is associated with a substantial reduction in CVD risk. This has been well described in a number of pivotal trials, including a subgroup analysis of 1501 patients in the Hypertension Optimal Treatment (HOT) Trial ($N = 1501$) (148) and the Israeli Multicenter Study ($N = 94$) (149). Two studies, however, have clearly defined the importance of more rigorous BP control in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) (150) and the Heart Outcomes Prevention Evaluation (HOPE) Trial (151). In the UKPDS study, more than 1000 hypertensive diabetic subjects were randomized to either tight (144/82 mmHg) or less tight BP control (154/87 mmHg). The 10/5 mmHg difference in BP was associated with a 15% decrease in CVD, a 32% decrease in death due to diabetes, and a 44% reduction in the incidence of CVA. The HOPE Trial extended these observations in 3577 hypertensive diabetic individuals by demonstrating that the addition of 10 mg ramipril for patients who already had “well-controlled” BP (139/79 mmHg) further reduced CVD death by 37% and all forms of microvascular complications. Other clinical

trials, such as the ABCD Study (152), the CAPPP Trial (153), and the FACET Trial (154), have similarly demonstrated the survival advantage of more rigorous BP control with ACE inhibitors plus other drugs.

Although the optimum target BP for hypertensives with diabetes has not yet been determined with certainty, completed trials indicate that reducing systolic BP to at least 130 mmHg provides substantial reduction in both macro- and microvascular disease progression. Moreover, these benefits can be demonstrated without increasing the risk for adverse events or myocardial infarction, as some have previously suggested (J-curve effect) (33). Adler et al. carefully assessed the risk of diabetic complications associated with systolic BP in the UKPDS and demonstrated that, with increasing systolic BP, there was a continuous and linear risk of progressive development of both macrovascular and microvascular events (155). Clinical trials have also demonstrated that treatment of BP even in the so-called normotensive range of type 2 diabetes is associated with prevention of BP elevation and increasing urinary protein excretion, and would likely reduce the risk of CVD and the progression of renal disease (156–158). Viberti et al. randomized both type 1 and type 2 diabetic subjects with microalbuminuria to treatment with either an ACE inhibitor or a placebo even though their BP prior to therapy was 124/77 mmHg. This study demonstrated that this intervention, despite minimal BP reduction (4/2 mmHg), was associated with a significant reduction in the risk for progression from microalbuminuria to macroalbuminuria (156). Likewise, Ravid et al. demonstrated in a five-year prospective randomized controlled trial that an ACE inhibitor was capable of preventing BP elevation and increasing proteinuria in type 2 diabetics with a BP of 130/80 mmHg and only 130 mg protein in the urine per 24 h (157, 158). Moreover, within five years, differences in the rate of loss of renal function over time, favoring therapy with the ACE inhibitor, were demonstrated.

These studies in diabetics indicate that early treatment of BP even in the normotensive range may forestall the development of progressive nephropathy. A recent pooled analysis of 11 large randomized controlled trials demonstrated that the optimal systolic BP for preventing progression of nondiabetic renal disease is approximately 110 mmHg (159). Thus, these data show that earlier and more rigorous BP control, particularly with ACE inhibitors, prevents progression of renal disease, and strongly suggest that CVD will also be reduced.

SUMMARY

Diabetes remains a growing public health problem. The aging of the population, along with increasing obesity and decreasing physical activity, will ensure that the number of diabetic individuals will continue to grow. The most effective strategy for preventing diabetes-associated CVD is prevention of diabetes. Among people with diabetes, aggressive modification of conventional CVD risk factors remains a cornerstone of risk reduction. As clinical applications of modern genetics and molecular biology continue to develop, new therapies will likely focus on novel targets in the multiple pathways between hyperglycemia and CVD.

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