Diabetes Mellitus and Macrovacular Complications

An epidemiological perspective

RICHARD P. DONAHUE, PHD
TREVOR J. ORCHARD, MB BCH, M MED SCI

It is clearly recognized that patients with NIDDM have an increased risk for CHD. Recent data indicate that persons with glucose concentrations in the nondiabetic range also may be at higher risk for CHD. These associations may not represent cause and effect, however. Emerging data suggest that hyperglycemia and CHD may both arise from hyperinsulinemia/insulin resistance. In support of this hypothesis are studies showing that NIDDM and CHD have many risk factors in common, including age, elevated blood pressure, dyslipidemia, adiposity, and a central pattern of fat distribution. Moreover, these risk factors are frequent concomitants of hyperinsulinemia, itself a risk factor for CHD and perhaps for NIDDM. Although the duration of NIDDM has been infrequently related to risk of CHD, the authors hypothesize that duration of hyperinsulinemia/insulin resistance would be a more sensitive marker for risk of CHD. The relation of IDDM to CHD is a different situation. The etiological process leading to IDDM, namely the destruction of β-cells in genetically predisposed persons, is not related to cardiovascular risk. However, IDDM patients still have an excess of CVD, the risk factors for which may vary according to the location of the diseases (e.g., LEAD vs. CHD). There is a strong relationship between proteinuria and CVD, which has led to a general theory of vascular complications in IDDM based on defective heparan sulfate metabolism (Steno hypothesis). Recent evidence challenges parts of this hypothesis, and the possibility is raised that a higher case-fatality rate in a subgroup of patients with both renal and CVD explains part of the renal connection, as does the general worsening of CVD risk factors.

DEFINITION — A review of the literature relating glucose intolerance to CHD is complicated by varying definitions of terms. Only recently have criteria been established by which epidemiological studies may define NIDDM and IGT (4). In the past, investigators have used a variety of different definitions to classify a diabetic person, including self-report, use of insulin or oral hypoglycemic
agents, and measures of blood glucose levels. Oral glucose challenges, when used, often have varied in concentration. Currently, both WHO and NDDG recommend a 75-g OGTT in the fasted state as the gold standard for epidemiological studies of diabetes in adults. Comparative analyses indicate that nearly identical results are obtained when classifying diabetic persons using either WHO or NDDG criteria (5). Such is not the case, however, when categorizing subjects with IGT. The NDDG criteria identify only ~50% the subjects with IGT compared with the WHO criteria. It has been suggested that the IGT category itself contains a heterogenous mix of subjects, most of whom will revert to normoglycemia or remain unchanged, whereas ~25–50% eventually will develop diabetes (6). Thus, the relation among hyperglycemia, IGT, NIDDM, and CHD is not straightforward, and the results of such studies are difficult to compare directly.

These considerations are particularly problematic in populations with a relatively low prevalence of diabetes, unlike the Pima Indians (7), Mexican Americans (8), and some Pacific Island groups (9) all of whom demonstrate bimodality of the glucose distribution. Moreover, considerable within-person variability has been noted in the response to an OGTT (10), making it even more difficult to quantify accurately the exposure in observational investigations.

**NIDDM and CHD: A Sex-Related Effect?** — Many population-based studies conducted in the United States (11–16) have shown that NIDDM increases the risk of CHD two- to fourfold. Although diabetic persons have an increased atherogenic risk factor profile (including older age, elevated blood pressure, hypertriglyceridemia, lower concentrations of HDL cholesterol and increased body mass index), statistical adjustment for these differences often fails to remove an independent effect for diabetes per se. Some studies have found that diabetes imparts a stronger risk of CHD to women than men, thus reducing or eliminating the female advantage in CHD mortality (Fig. 1). For example, the Framingham Heart study reported an RR for CHD mortality of 1.7 in diabetic men relative to nondiabetic men (not statistically different from 1.0) and 3.3 in diabetic women compared with their nondiabetic counterparts (11). These RR estimates were adjusted for differences in age, systolic blood pressure, total cholesterol, HDL cholesterol, cigarette smoking, and left ventricular hypertrophy. The Evans County study reported 4.5-yr follow-up results and also found that diabetes was a stronger risk factor in women (RR = 2.8) than in men (RR = 1.0) (12). These results, however, were based on very few deaths. Differing somewhat from these reports are findings of the Chicago Heart Association Detection Project in Industry (13) and the Rancho Bernardo study (14) in which diabetes made an independent contribution to CHD death in both sexes, although the RR estimates were still higher among diabetic women. The Tecumseh study (15) found that the RR of CHD varied with age; from ~7.8 in men and women aged 40–54 yr to 5.3 in women >70 yr, and 1.9 in similarly aged men. The NHANES I Epidemiologic Follow-up study reported fairly similar RR estimates for CHD death in both diabetic men and diabetic women compared with their nondiabetic counterparts (16).

These studies confirm the excess risk of fatal CHD in diabetic women. They differ somewhat in regard to the nature of the effect of diabetes on CHD in men, although the majority of results support an increased risk of CHD caused by diabetes in men and women. It should be emphasized that in these studies a diabetic subject was defined in different ways; from a self-reported history of physician-diagnosed diabetes or treatment for diabetes, to a definition based on results from a casual or fasting OGTT. Quite obviously, the definition of nondiabetic persons also differed, potentially biasing the denominator of the RR estimate. Whether there could also be a sex-related bias in this misclassification is uncertain, but not unlikely. The numbers of diabetic subjects were generally quite limited, thus contributing to the divergent results concerning a sex-specific effect of diabetes.

**Severity of Glucose Intolerance and CHD** — If diabetes were a cause of CHD, one would expect to see an increased risk of CHD with increased duration of diabetes. Most studies, but not all (17), have failed to find such a relation. The lack of an obvious association between duration of diabetes and risk of CHD supports the notion that diabetes itself does not cause CHD. In most studies, it has been difficult to obtain valid incidence data or to accurately assess duration of NIDDM. Because many years of asymptomatic hyperglycemia may precede the clinical diagnosis of NIDDM, the ascertainment of duration of NIDDM may be biased. One may, however, compare rates of CHD across different categories of severity of glucose intolerance in order to shed some light on this question. Several studies have compared the risk of CHD among newly discovered diabetic patients, previously diagnosed diabetic patients, and those with IGT, in an effort to ascertain whether the risk of
Table 1—Summary of prospective studies of glucose intolerance and risk of CHD

<table>
<thead>
<tr>
<th>STUDY REF. NO.</th>
<th>LENGTH OF FOLLOW-UP (YR)</th>
<th>NUMBERS AT RISK</th>
<th>CHD DEATHS</th>
<th>LINEAR EFFECTS</th>
<th>ADJUSTED RELATIVE RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>WHITEHALL (22)</td>
<td>7.5</td>
<td>970</td>
<td>52</td>
<td>X</td>
<td>2.0*</td>
</tr>
<tr>
<td>PARIS (23)</td>
<td>10</td>
<td>7164</td>
<td>126</td>
<td>X</td>
<td>1.9</td>
</tr>
<tr>
<td>FINLAND (24)</td>
<td>9.5</td>
<td>982</td>
<td>26</td>
<td>X</td>
<td>2.0</td>
</tr>
<tr>
<td>BEDFORD (25)</td>
<td>10</td>
<td>249</td>
<td>26</td>
<td>X</td>
<td>5.16* 1.42</td>
</tr>
<tr>
<td>HOLONULU (26)</td>
<td>12</td>
<td>6394</td>
<td>303</td>
<td>X</td>
<td>(MEN)</td>
</tr>
<tr>
<td>RANCHO BERNARDO (27)</td>
<td>14</td>
<td>3458</td>
<td>217</td>
<td>X</td>
<td>(WOMEN)</td>
</tr>
<tr>
<td>CHICAGO HEART ASSN. (11)</td>
<td>9</td>
<td>1871</td>
<td>59</td>
<td>X</td>
<td>2.6* 1.2</td>
</tr>
<tr>
<td>BUSSELTON (28)</td>
<td>12</td>
<td>3331</td>
<td>163</td>
<td></td>
<td>1.1* 1.0</td>
</tr>
<tr>
<td>FRAMINGHAM (29)</td>
<td>10</td>
<td>5532</td>
<td>309</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significantly different from 1.0.

CHD increases with severity of glucose intolerance. In the report on the 15-y follow-up of the Whitehall study (18), RRs for CHD were 1.2 among glucose-intolerant subjects, 2.6 in newly diagnosed patients, and ~2.2 in previously known diabetic persons compared with normoglycemic subjects. These latter two RRs are based on 17 and 21 CHD deaths, respectively. No significant association was noted between duration of diabetes expressed as a continuous variable and risk of CHD. The Paris Prospective study (19) performed similar comparisons after 10 yr of follow-up. RRs for CHD mortality were 3.0 in men with previously diagnosed diabetes, 2.1 in men with newly discovered diabetes, and 1.9 in those with IGT. The Israel Ischemic Heart study observed that 5-yr mortality from MI was 3.4 times higher in both previously diagnosed diabetic men and in newly diagnosed diabetic men compared with their nondiabetic counterparts (20). The finding of similar or higher RR estimates among subjects whose diabetes is newly discovered compared with those with diabetes of long-standing does not support a role for duration or severity of glucose intolerance in relation to increased CHD risk. Because of the difficulties of accurate diagnosis and ascertainment of true NIDDM incidence rates noted previously, further insight into the causal sequence may be obtained by examining glucose concentration itself as a precursor of CHD (Table 1).

Presumably those subjects with high glucose levels are at increased risk to become diabetic and may be at increased risk for CHD. Whether glucose concentrations in the nondiabetic range are independently related to CHD is a matter of substantial interest. In 1979 the International Collaborative Group reviewed 11 studies that investigated whether glucose and CHD mortality were related in nondiabetic populations (21). Overall, they found no clear association of glucose concentration with CHD. These studies, however, were limited in terms of the number of CHD deaths that occurred and had no common protocol. Many more recent reports have reexamined this issue. A reanalysis of data from the Whitehall study indicated a threshold effect for glucose concentration, with an increased risk of CHD mortality among men in the top 5% of the postload glucose distribution (22). Studies in Paris (23) and Finland (24) failed to find a significant linear relation between postload glucose and CHD incidence, but suggested an increase in risk above the 80th percentile of postchallenge glucose level. The 10-y follow-up of the Bedford study (25) found that elevated postchallenge hyperglycemia (120–199 mg/dl) predicted coronary mortality, but only in women. In contrast, the Honolulu Heart study reported a linear relation between glucose level (1-hr after a 50-g challenge) and risk of CHD in men without known diabetes (26). The Rancho Bernardo study (27) also has noted that risk of CHD increased in a linear fashion with increasing fasting plasma glucose among men. These discrepancies are likely caused by different study protocols, varying lengths of follow-up, and inadequate statistical power in some studies attributable to a small number of CHD events (Table 2).

Five studies have examined the role of glucose in CHD mortality among nondiabetic women. The Rancho Bernardo study (27) found a threshold effect for fasting blood glucose and CHD, although the Tecumseh study (16) found no significant relation between glycemia and risk of CHD. In contrast, the Chicago Heart Association Detection Project in Industry (11) reported that hyperglycemia imparted a greater risk of CHD to women than men. The Bedford study (25) observed that borderline diabetic women (impaired glucose tolerance) had a fivefold excess of coronary deaths compared with nondiabetic women. An excess risk of CHD among women with
Diabetes and macrovascular disease

Table 2—Diagnostic criteria for hyperglycemia or IGT*

<table>
<thead>
<tr>
<th>Location</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehall</td>
<td>&gt;95th percentile (96–199 mg/dl) of the 2-hr glucose distribution after a 50-g OGTT.</td>
</tr>
<tr>
<td>Paris</td>
<td>Blood glucose was determined after fasting and 1 and 2 hr after a 70- or 90-g OGTT.</td>
</tr>
<tr>
<td>Finland</td>
<td>Glucose was examined both as a continuous variable and by quintiles.</td>
</tr>
<tr>
<td>Bedford</td>
<td>Borderline diabetic (IGT) defined by 2-hr blood glucose between 120–199 mg/dl after a 50-g OGTT.</td>
</tr>
<tr>
<td>Honolulu</td>
<td>Examined entire glucose distribution 1-hr after a 50-g OGTT. Considered glucose as both a continuous and categorical variable.</td>
</tr>
<tr>
<td>Rancho Bernardo</td>
<td>Fasting plasma glucose &lt;140 mg/dl was examined as a continuous variable and by quintile analysis.</td>
</tr>
<tr>
<td>Chicago Heart Association</td>
<td>Blood glucose was determined 1-hr after a 50-g challenge was obtained. Glucose was examined as a continuous variable. Hyperglycemia was defined as &gt;200 mg/dl in nondiabetic patients.</td>
</tr>
<tr>
<td>Busseleton</td>
<td>Casual blood glucose was determined 1-hr after a 50-g OGTT. Glucose was analyzed both as a continuous variable and by quintile analyses.</td>
</tr>
<tr>
<td>Framingham</td>
<td>Casual blood glucose serially determined over 10 yr. If glucose exceeded 200 mg/dl, the patient was considered diabetic and dropped from further analyses. The glucose distribution under 200 mg/dl was examined as a continuous variable.</td>
</tr>
</tbody>
</table>

*All studies excluded known diabetic patients.

Elevated glucose concentrations was also noted in the Busselton study (28) and the Framingham study (29). In this latter study, the effect of glucose on CHD risk was similar in impact to that of systolic blood pressure. It should be noted, however, the degree to which truly diabetic women were excluded in these studies is uncertain and remains a possible source of bias.

Taken together, these studies suggest that there is evidence that elevated glucose levels in nondiabetic persons significantly increase their risk for CHD, although the shape of this relation (linear or threshold) is unclear. More limited data indicate that the magnitude of this increase may be greater in women than men. Although there appears to be an association between glucose and CHD, this by itself does not prove cause and effect. Indeed, Jarrett has argued that neither diabetes nor hyperglycemia per se are causes of CHD, but that all three conditions share common, but as yet unidentified, antecedent risk factors (30).

**Common antecedents of NIDDM and CHD**—In support of Jarrett's hypothesis are the results of several studies suggesting that CHD risk factors are more common among diabetic persons. Compared with nondiabetic subjects, NIDDM patients tend to be older, heavier, and have higher systolic blood pressures and triglyceride concentrations, and lower HDL cholesterol levels (31,32). Diabetic women have a more disturbed lipoprotein profile than nondiabetic women (33), including lower concentrations of HDL cholesterol consistent with their higher RR of CHD. The results from the Framingham study cited earlier (11) were adjusted for differences in HDL cholesterol, making it unlikely that alterations in the concentration of this lipoprotein fraction were culpable for the female excess in CHD mortality. It is still possible, however, that changes in the composition of the HDL-cholesterol particle or its subfractions could alter its atherogenic potential. Limited evidence (34) suggests that exogenous insulin therapy in patients with IDDM results in a preferential increase in the HDL3 subfraction, which is the subfraction less strongly related to CHD. Thus, statistical adjustment for total HDL cholesterol would not be completely effective in removing the effect of the various HDL subfractions. Although diabetic persons are more likely to have a combination of CHD risk factors than nondiabetic subjects (35), this clustering still does not explain the excess frequency of CHD cases among the former group.

The hypothesis that NIDDM and CHD are the result of common antecedents derives further support from investigations that indicate that several risk factors for CHD also predict the development of NIDDM. In a community-based study of nondiabetic, older adults from Rancho Bernardo, McPhillips et al. (36) found that persons who later developed NIDDM were older, heavier, and had higher systolic blood pressure and triglyceride levels at baseline than those who remained normoglycemic. Similar findings have been reported from the San Antonio Heart study (37). These investigators prospectively showed that subjects who developed NIDDM were earlier found to have a more atherogenic risk factor profile than those who remained normoglycemic. Furthermore, most of the risk factor differences were reduced or eliminated after adjusting for baseline differences in insulin concentration. Another commonality between NIDDM and...
A COMMON THREAD: HYPERINSULINEMIA/INSULIN RESISTANCE — Intriguing data exist suggesting that insulin resistance may be a common thread running through atherosclerosis, CHD, and diabetes (Fig. 2). As recently reviewed by Stout (48), insulin may directly promote atherosclerosis. Additionally, insulin is related to a number of cardiovascular risk factors, including body mass index, fat distribution, blood pressure, triglycerides, and HDL cholesterol (49–51). As previously cited, three prospective epidemiological studies have found that elevated insulin concentration predicted the development of CHD in men (19,24,28). In the only study of women (28), no relation was noted, although the number of CHD events was limited. The findings among men were independent of the effects of blood pressure, blood glucose, body mass index, and total cholesterol. HDL cholesterol was not measured in any of these investigations. HDL cholesterol may, in any event, be an intermediary in the causal chain and not a confounder in the true sense of the term. Elevated insulin also has been shown to be associated with CHD in men with NIDDM (52). Because insulin levels in patients with NIDDM are difficult to measure accurately, C-peptide concentration often is used to assess insulin secretion. The Schwabing study has shown that C-peptide levels were elevated in cases with NIDDM compared with healthy controls and that C-peptide level was positively associated with the prevalence of macrovascular disease (i.e., CHD, peripheral vascular disease, or carotid artery disease) (53). These results may be contrasted with the Bedford study, which reported that patients with IGT who later developed CHD had lower 2-hr insulin values (25). Consistent with the Pima Indian data cited previously (47), these patients may have had a duration of hyperglycemia sufficient to have exhausted the capacity of the β-cells to secrete insulin. This conundrum is complicated, however, because some of the Bedford participants were randomized into a clinical trial to lower blood glucose.

SUMMARY — Hyperinsulinemia/insulin resistance is a strong candidate for an antecedent factor linking hyperglycemia, IGT, and NIDDM with CHD. Hyperinsulinemia is associated with atherogenic risk factors in prediabetic patients and also places them at increased risk for CHD. Interventions noted to increase insulin sensitivity (e.g., weight loss and physical activity) have also been shown to reduce the risk of NIDDM and CHD (54,55). If hyperinsulinemia/insulin resistance predate NIDDM and CHD, this hypothesis would also explain why few studies have found an association between duration of diabetes and risk of CHD. In addition to the confounding influences of age, disease severity, and type of therapy with duration of diabetes, diabetic persons have probably suffered from asymptomatic hyperglycemia and hyperinsulinemia for many years. Thus, the duration most likely to be related to CHD among hyperglycemic and diabetic persons is the (unknown) duration of hyperinsulinemia/insulin resistance, not duration of diabetes per se.

With regard to the apparent stronger effect of diabetes on CHD in women than men, we have previously hypothesized that, in the nondiabetic population, insulin-mediated glucose homeostasis (insulin sensitivity) is higher in women than men, resulting in their better CHD risk factor profile (50) (e.g., the inverse association between insulin and HDL cholesterol is stronger in young men than women). Once women develop diabetes, their greater insulin sen-
sitivity is reduced or lost, resulting in an equalization in CHD risk to that of non-diabetic men. The studies that show a similar or higher RR for CHD in diabetic women than diabetic men are consistent with this view. Further, recent evidence from Modan et al. (56) indicated that hyperinsulinemia may account for much of the sex difference in CHD rates in the nondiabetic population as well.

Thus, fairly convincing observational evidence suggests that persons with hyperinsulinemia/insulin resistance have an increased risk of both NIDDM and CHD. Risk factors for CHD are elevated long in advance of conversion to the diabetic state. Insulin resistance may lead to increased risk of both NIDDM and CHD through alterations in these risk factors, or perhaps as a direct influence on the atherosclerotic process (57). These relationships could be further explored through prospective studies of populations with IGT using standardized measurements of insulin concentration, insulin secretion, and insulin resistance.

Screening of patients with IGT or NIDDM to identify those with elevated CHD risk factors appears warranted. Although lowering blood pressure and lipid concentrations in the glucose-intolerant or diabetic patient is clearly desirable, methods to increase insulin sensitivity (such as weight loss and increased physical activity) should be considered as part of the effort to reduce morbidity and mortality caused by NIDDM and CHD. The effectiveness of such efforts could best be demonstrated in randomized clinical trials of NIDDM patients.

INSULIN-DEPENDENT DIABETES MELLITUS — Although it has long been recognized—and previously discussed—that diabetes generally causes an excess risk of atherosclerotic disease, the magnitude and characteristics of any specific risk for those with IDDM have not been extensively studied. Indeed, very few detailed studies of CHD in IDDM, and virtually no data concerning cerebrovascular disease, are available. This deficiency reflects the relatively poor recognition of IDDM as a separate etiological entity until the development of epidemiological, genetic, and immunological data in the 1960s and 1970s made this clear (58). Even recent studies have not always been able to clearly separate NIDDM from IDDM and have largely used age of diagnosis, rather than proven insulin dependency or immunogenetic markers, for classification purposes. This is important to recognize, for the clear separation of these two potentially different pathophysiological processes may help understand the nature of the increased cardiovascular (CVD) risk seen in diabetes. In NIDDM, the development of CVD and diabetes share in some regards, as has been described, the same risk factors and characteristics: increasing incidence with age, insulin resistance and hyperinsulinemia, obesity and central adiposity, and blood pressure and lipoprotein abnormalities. In IDDM, on the other hand, the process leading to the disease is completely separate, an immunological destruction of B-cells in genetically predisposed persons, usually, but not always, children or young adults (58,59). Thus, to the extent that pure diabetes-related factors (e.g., hyperglycemia, disease duration, and glycosylation of lipoproteins) cause the enhanced CVD risk of diabetes, similar rates and characteristics should be seen in both types of diabetes after accounting for age effects. A study by Knuiman et al. (60) suggested that this was the case for macrovascular disease, after considering time-related variables. More studies of CVD in diabetes comparing IDDM with NIDDM would help in sorting out what is truly related to the consequences of insulin resistance (and its effects) as opposed to hyperglycemia (and its ramifications).

In the following sections, we will review mainly epidemiological data and how this may help explain the excess risk of CVD in IDDM, particularly with regarding the role of renal disease. Although recognized as a real entity, diabetic cardiomyopathy in terms of possible microvascular disease, will not be discussed (61).

PREVALENCE AND INCIDENCE —

The few early studies that clearly followed IDDM subjects (i.e., juvenile-onset in the old terminology), showed a surprisingly low incidence of CVD. For example, Kerr et al. (62) in the first such study found that, after 15 yr, only 4% reported experiencing an MI (62), whereas Knowles et al. (63), after 16 yr of follow-up, found no cases of MI. Data from the Joslin Clinic showed a prevalence of 16% after over 40 yr of follow-up (64), whereas a report from the Steno Clinic showed a cumulative incidence of 21% over a 40-yr follow-up (65). This latter report included subjects with a diagnosis of diabetes ≤31 yr of age. Our own early survey data (66), based on a registry of cases of childhood onset diabetes, showed only a 4% prevalence of MI in 671 cases followed for a mean of 16 yr. These early studies underscore the fact that clinical CVD is largely a disease of adults, as evidenced by the low incidence of MI in the studies where the oldest subjects were generally aged <35–40 yr and, as in the general population, is likely to be a slowly progressive process of arterial occlusion (67). It would thus seem that IDDM does not cause CVD in a short period of time (i.e., within a few years after onset), although it is clear that IDDM brings the onset of clinical disease forward in time considerably (68). Our data suggest that cardiovascular mortality is more than 11-fold higher in childhood onset IDDM subjects with an average age of 21 yr compared with the general population (69). Although this largely reflects the low event rate in the general population, it does suggest, nonetheless, that IDDM has a sufficiently strong effect to bring about early CVD death in 15 subjects (~1%) by age 40 yr. The nature of IDDM’s role in causing excess CVD could therefore be to: 1) initiate the ath-
erosclerotic process earlier, 2) accelerate the process once it has started, 3) cause a greater clinical severity to result from the same underlying degree of atherosclerosis (e.g., causing greater thrombus formation or more frequent complications of an atherosclerotic plaques), or 4) a combination of these factors.

THE JOSLIN DATA — Krowlewski et al. (70), in a more recent article from the Joslin Clinic based on 292 IDDM subjects followed for 20–40 yr, reported that the earliest deaths caused by CAD did not occur until the subjects were in their late 20s and increased rapidly thereafter. This suggests that IDDM accelerates, but does not initiate, the atherosclerotic process. It should be noted that the classification procedure used would tend to favor CAD being counted as the cause of death, thus possibly reducing the proportion caused by renal disease, by far the leading cause of death in IDDM (with 15–30 yr duration) (69). In addition, it seems the Joslin Clinic population is unlikely to be representative of the general IDDM population (71), although the authors did exclude subjects first seen >1 yr after diagnosis to help reduce referral bias. Their conclusion that it is unlikely that IDDM causes (i.e., initiates) CVD is based on the absence of a significant effect of duration or age of onset, independent of age. However, could their data not be just as well explained by IDDM initiating the process at an earlier age (e.g., childhood or early teens as opposed to late teens/early adulthood)? Velican and Velican (72) have reported that the prevalence of coronary artery lesions increases from 1:25 in the age group 11–15 yr to 1:3.6 in those aged 21–25 yr. A small change in the frequency and/or time of onset during the critical adolescent period could thus result in the early CVD seen in IDDM. A similar effect is clearly seen in familial hypercholesterolemia (73). The age effect would still be expected to be present, as seen in familial hypercholesterolemia. If the concept that the prepubertal years of IDDM are relatively harmless (74), one would not expect to see a greatly increased risk for those with an earlier onset, which Krowlewski et al. observed. A small increased cumulative mortality is seen in their data for those diagnosed <10 yr compared with those diagnosed at a later age that is presumed to be nonsignificant, although significance levels were not reported. Other studies do show a duration effect in IDDM (75,76), which is not generally seen in NIDDM. Krolewski et al.’s study, apart from further developing the etiological implications of a relative lack of CVD in young IDDM patients also stressed the loss of a sex difference in CVD experience in IDDM (70), confirming our earlier mortality study (69).

THE PITTSBURGH PERSPECTIVE — These issues of prevalence, sex, and duration have been further addressed in the EDC study (77–80). Like much of our previous work, this study is based on the Children’s Hospital of Pittsburgh registry of IDDM subjects. Although this is a hospital-based registry, we have excluded cases seen after 1 yr of diagnosis to reduce referral bias and have previously shown that this registry is comparable in its epidemiological findings to the community-based Allegheny County registry (78). Of 979 surviving, locally resident Children’s Hospital of Pittsburgh registry cases diagnosed (or seen within 1 yr of diagnosis) between January 1, 1950 and May 31, 1980, 80% participated at baseline (1986–1988), including 657 (67%) who agreed to a 4-hr exam. These subjects had a variety of complication risk
factor measures made and are being followed for 10 yr to determine which factors predict prospectively the development of complications (75–77).

The baseline EDC population (mean age 28 yr; duration 19 yr) gives an opportunity to study cross-sectional relationships. In this study, CHD (physician-diagnosed angina, documented MI, or coronary artery bypass graft/angioplasty), LEAD (amputation or ankle/arm blood pressure ratio less than 0.8 at rest or postexercise), and PAC (ankle pressure 100 mmHg or more greater than arm pressure) were documented separately and their interrelationships also studied. Only four cases of stroke (three of whom also had CHD) were noted at baseline; thus, no separate analyses were possible for this end point. Overall in EDC, 3.4% had CHD, 9% LEAD, and 4.6% had PAC. As expected, these rates increased with age and duration; by 30 yr duration, 23% had CHD, 17% LEAD, and 15% PAC. These figures are similar to those of Krowlewski et al. For example, 10% of EDC subjects have symptomatic CHD in the 30–44-yr-old range, compared with 8.3% of the Joslin population aged 35–44, based on similar evidence of CHD (70).

**AGE VS. DURATION AS RISK FACTORS FOR CHD** — Even though the EDC population is twice the size of that reported by Krowlewski et al., the numbers are still too small to separate fully the effects of age, as opposed to duration, which are correlated with each other with a coefficient of 0.86. By definition, it is virtually impossible to differentiate in a childhood-onset population the effects of age from those of postpuberty duration as the correlation between age and postpuberty duration is virtually 1.00. Both, therefore, are likely to be important and reflect in this situation much the same duration of exposure to life and diabetes.

Two other studies, with a wider range of age of onset of IDDM, have suggested a duration effect in IDDM: the Schwabing study (75) and the follow-up of the WHO London cohort (76). In the former, the incidence of a major cardiovascular event was correlated with duration in cases, overall, but not in those diagnosed >40 yr (i.e., in NIDDM), independent of age. In the latter study, a significant duration effect independent of age and sex, was seen for duration on the development of new ischemic electrocardiographic abnormality and a borderline effect on all new ischemic heart disease events (76). In multivariate analyses in IDDM patients, diabetes duration was a significant predictor of CHD with hypertension and smoking. It thus seems that duration may be of some importance beyond age, with the inference that something about the diabetic process truly adds to CHD risk, although these two studies did not specifically examine postpuberty duration.

**SEX DIFFERENCES** — The EDC data in common with Joslin (70), the Schwabing study (75), and others (68) demonstrated little sex difference in CHD morbidity in IDDM. This therefore is consistent with our study (69), Joslin's (70), and the WHO London cohort (81) data, failing to show a male excess of CHD morbidity. As discussed earlier, in NIDDM the evidence is split and this may represent a difference in CHD between IDDM and NIDDM. Where we did see a marked sex difference in EDC, however, was concerning peripheral arterial disease (78,79).

**PERIPHERAL ARTERIAL DISEASE** — Relatively little is known about the prevalence and incidence of either cerebrovascular disease or LEAD in representative IDDM populations. In terms of the former, both clinical and pathology studies would suggest, if anything, a relative decrease of hemorrhagic stroke (both intracerebral and subarachnoid) in IDDM (82–84). EDC provides little new information, only four cases occurring so far in this study. However, for LEAD, many new findings emerge. It appears that LEAD is fairly rare in both sexes until 25 yr or so duration. These values are similar to those seen in a study reported by Beach et al. (85). However, after 25 yr of diabetes, a threefold greater prevalence in LEAD (mainly ankle/arm blood pressure ratio less than 0.80) is seen in women whose rates are as high as 30%. This greater female excess is likely to reflect, in part, a measurement artifact, resulting from a male excess of arterial wall calcification (79). This is likely to cause males to have spuriously high ankle pressures potentially obscuring occlusive disease. Thus, the measurement of LEAD in IDDM is difficult, and improved methodologies are needed to accurately document the extent of vascular disease.

In the Schwabing study (86), Janka et al. have reported, using a different methodology, a prevalence rate of peripheral vascular disease of 3.2% in diabetes (both NIDDM and IDDM aged 10–49 yr). Duration-specific values were not reported. The WHO Multinational Study's London cohort (baseline age and duration range 35–55 and 6–14 yr, respectively) reported a prevalence of peripheral vascular disease of 4.2% (after a further follow-up of 8.3 yr). This low overall prevalence (again, no duration-specific IDDM rates are reported) in part reflects the relative lack of sensitivity of the methods used (amputation or positive Rose questionnaire). In our study, none of those with an ankle/arm blood pressure ratio less than 0.8 (itself a very conservative cut point) reported intermittent claudication on the Rose Questionnaire, whereas only 5% had undergone amputation of any part of their lower limbs.

**INTERRELATIONSHIP BETWEEN CORONARY AND PERIPHERAL ARTERIAL DISEASE** — The likely excess of all forms of vascular disease in IDDM raises the interesting question of the interrelations between disease in various parts of the arterial tree. One would suspect that if macrovascular disease was...
purely the result of the diabetic process, all locations would be likely to be affected in susceptible individuals and that presence of disease in one location would be highly predictive of disease in another. We have examined the cross-sectional interrelationships in the EDC and, while some overlap is seen, it is not as strong as one might predict. Of 22 cases of CHD, 27% also had LEAD. In contrast, of 59 cases of LEAD, only 10% had CHD. Thus, despite the limitations of these clinical measures, it would seem that CAD is a stronger correlate of LEAD than vice-versa; the situation seen, albeit with lower prevalence rates, in the general population.

These findings therefore suggest that, despite some commonality between the various manifestations of macrovascular disease in IDDM, different pathogenic factors may be responsible for the excess disease in different locations. To examine this, we have examined the relationship between various risk factors in the EDC population and each manifestation of macrovascular disease. Although these data are limited by a cross-sectional nature and a potential survivor bias (26 subjects died from CHD before the study), interesting patterns emerge.

**RISK FACTORS FOR ATHEROSCLEROTIC DISEASE IN IDDM** — First, no relationship is seen with GHb our measure of long-term glycemic control. This is generally consistent with other reports, wherein blood sugar level is not a strong marker of risk in diabetes (68,75). This puts the emphasis, therefore, on searching for other risk factors, which are altered by the development of IDDM. Altered lipoprotein concentrations and/or composition are a leading contender. Interestingly, whereas triglycerides were significantly higher in those in EDC with each of the manifestations of atherosclerosis in multivariate analyses, only LDL cholesterol and HDL cholesterol (and HDL-chol/apolipoprotein A1 ratio) were predictors for LEAD. LDL cholesterol and triglyceride/apo-

lipoprotein A1 ratios were additional multivariate predictors for PAC. No lipid parameter predicted CHD in multivariate analyses. These results are consistent with a role for lipoprotein composition (and possible alterations of reverse cholesterol transport) above and beyond lipoprotein concentration (79,87). Duration (or age) was predictive of all three types of macrovascular disease, whereas blood pressure predicted PAC and CHD, but not LEAD, which showed a further association with fibrinogen concentration. Thus, a variety of risk factor disturbances are likely to be responsible for the excess atherosclerosis seen in IDDM, and these may relate differently to the various manifestations. This variation is further illustrated when the presence of nephropathy is considered. This becomes a strong independent predictor of PAC (replacing the lipoprotein variables) and CHD (replacing hypertension), whereas duration (or age) remains a strong predictor. Nephropathy, however, did not relate to LEAD.

**THE RENAL CONNECTION** — The link between renal disease and CVD in IDDM is a fascinating and important concern. Dramatic data from the Steno Clinic in 1987 showed that virtually all of the excess CVD mortality seen in IDDM was related to the presence of proteinuria (88). Because CVD and renal disease are the two leading causes of death, these findings indicate that renal disease accounts, thereby, for most of the excess mortality seen in IDDM. These striking findings have led Deckert et al. (89) to propose that a subgroup of IDDM subjects have a genetically determined predisposition to renal disease and that this predisposition also causes the enhanced risk of CVD and, possibly, other complications. This general process leads to widespread vascular damage reflected by microalbuminuria. The central core of this hypothesis is that some individuals have different polymorphisms of an enzyme system (e.g., N-deacetylase) involved in heparan sulfate metabolism and that it is this minority of subjects (i.e., <40%) with altered connective tissue leading to renal and vascular damage that will develop nephropathy. Furthermore, by altering lipoprotein lipase activity (this enzyme being anchored to the vascular endothelium by heparan sulfate strands), the characteristic disturbances of lipoprotein metabolism in IDDM (increased VLDL) will also lead to CVD.

Our EDC data does not fully support this hypothesis. First, the premise, long-held, that renal disease will affect only a minority of IDDM subjects (figures of 30–40% are often quoted) that appears central to the Steno hypothesis is, sadly, not seen. In EDC, rates of 50% of ON by >35 yr duration are seen, whereas the combined rate of ON (albumin excretion rate >200 µg/min) and MA (albumin excretion rate 20–200 µg/min) reached 80% in males. Because MA is believed to be a strong predictor of ON (90), it seems that some degree of renal damage is likely to occur in most subjects; albeit some have, probably for a variety of reasons, developed an accelerated course. These observations argue against a single unifying theory of diabetes complications being related to a subgroup destined for renal disease.

The overriding influence of renal disease on other complications (or in terms of the Steno hypothesis, the use of MA as the marker of widespread vascular damage) is further challenged by the data
in Fig. 3. In this figure, we show the proportion of subjects developing each complication by their renal status.

Thus, 44% of CVD occurs in the absence of ON, as does 61% of LEAD. Indeed 24% of CVD and 33% of LEAD occur in the absence of even MA. Two factors, however, complicate these data. One is the varying sensitivity of our measures of each complication. For example, our ability to detect renal damage by measuring albuminuria is likely to be more sensitive than the documentation of angina or MI/CHD death as a measure of coronary disease. There is no easy solution to this problem. The other factor is the dominant effect of duration (and/or age as already discussed) on the development of complications. To examine the interrelationships of complications independent of duration (while still giving sufficient duration for the truly susceptible persons to develop complications), we examined the complication status of those EDC subjects with ≥23 yr duration. In these 174 subjects, ~50% with each of the major complications did not have ON (i.e., 46% of those with proliferative retinopathy), 47% of those with neuropathy, 40% of those with CHD, and 58% of those with LEAD. The absence of either ON or MA in these subjects was 24% for proliferative retinopathy, 22% for neuropathy, 13% for CHD, and 26% for LEAD. Even though renal disease is frequent in other complications, it clearly is not a sine qua non, and a higher occurrence of CHD and LEAD is still seen in IDDM subjects with neither ON nor MA than would be expected in the general population. Krowlewski’s data from the Joslin Clinic also supports this finding, because he found a higher CAD mortality rate in those with IDDM but without renal disease.

How can these data be reconciled with the Steno data referred to previously that relates all excess CAD mortality to the presence of proteinuria? One possible, partial, explanation is a higher case fatality rate in those with CAD and spontaneous whole-blood platelet aggregation (99). Although this may just reflect the relative efficiency of renal disease as a statistical variable in multivariate analyses, it does raise further questions and the possibility that other factors not so far measured are important. Other aspects of the clotting system (rheology and platelet function) may be relevant. This is suggested by two recent, small, case control studies. In one study, O’Donnell et al. (100) found raised thromboglobulin and platelet factor 4 concentrations (reflecting increased platelet activation) in patients with raised urinary albumin excretion (including those with only MA). Surprisingly, however, normal fibrinogen levels were found in both MA and macroalbuminuric subjects in contrast to previous reports (94). Similarly, most tests of platelet aggregation were normal in contrast to many earlier studies (98). In the other study, Jay and colleagues (101) studied blood rheology and CVD risk factors in type 1 patients with MA and concluded that glycosylated hemoglobin, total cholesterol, apolipoprotein B, and lipoprotein (a) are increased, but that blood rheology (including viscosity, erythrocyte aggregation, and fibrinogen) is normal, suggesting that these abnormalities develop later in renal disease.

**RISK FACTORS BEYOND RENAL DISEASE** — In addition to lipoprotein concentration disturbances, compositional changes occur in IDDM that both reflect, and may cause, altered lipoprotein metabolism (87). In the EDC (79) population, not only did LDL cholesterol and HDL cholesterol relate to CVD end points, but also did the HDL cholesterol/apo A ratio and triglyceride/apo A ratio, suggesting that altered reversed cholesterol transport may also be important. Further changes also include glycosylation and oxidation of lipoproteins that may further alter lipoprotein metabolism (e.g., decreasing LDL clearance) (102). This is an exciting and important area of current
research. Oxidized lipoproteins are thought to be more atherogenic and, whereas glycosylation may not directly cause oxidation, it may enhance the process. Data from other studies relating lipoproteins to CVD end points in IDDM is limited. The London Cohort of the WHO study shows cholesterol to be related in NIDDM but not IDDM (76). Janka has shown triglycerides to be related to the incidence of CVD in both IDDM and NIDDM (75).

Apart from the standard lipoproteins and apoproteins, great interest has arisen recently in the role of lipoprotein (a) in diabetes. Overall, it does appear to be increased in diabetes (103–105) and may partly be related to glycemic control in IDDM (106). We found, in a small case-control study in IDDM, no relationship with CVD (107), an issue that needs urgent resolution in NIDDM as well. Furthermore, no correlation was seen with glycosylated hemoglobin consistent with a recent report among blacks (108). It does appear, however, in our data and that of others that lipoprotein (a) is increased in diabetic renal disease, giving another reason for the high CVD rates in this subgroup.

Blood pressure is another risk factor increased in IDDM, particularly, as noted, in the presence of renal disease. As in our EDC study population, Krowlewski et al. (70), Janka (75), and Morrish et al. (76) report hypertension to be a major risk factor for CVD in IDDM. Other risk factor disturbances that occur generally in IDDM, but particularly in renal disease (as discussed earlier), are alterations of clotting factors like increased fibrinogen and platelet behavior (94,96).

CONCLUSIONS — On the basis of the few epidemiological studies described, it seems the risk of macrovascular disease in all locations is increased in IDDM, although our knowledge of stroke in IDDM is too limited to draw conclusions. The risk factor profiles and degree of comorbidity, however, suggest that LEAD and CVD may differ significantly in their pathogenesis. The reasons for these increased risks are as yet poorly understood. Very little prospective data are available to determine the true predictors of CVD disease in IDDM. These data would suggest that the traditional risk factors (blood pressure, lipids, and smoking) are still operative, and additional defects (e.g., glycosylation and oxidation of lipoproteins, lipoprotein compositional changes, platelet aggregation, and clotting factors) also contribute to varying degrees. A striking, but far from absolute, relationship between proteinuria (renal disease) and CVD mortality has been shown by the Steno Clinic, which has led to a unifying theory of vascular complications in IDDM based on defective heparin sulfate metabolism in a subgroup of subjects (89). Certain epidemiological features, however, challenge parts of this theory, and it seems more likely that much of the renal connection may be mediated by a higher case mortality and alterations of other CVD risk factors, although some special independent effect also appears to be possible (79). It is likely that the etiology of CVD in IDDM is multifactorial and may differ in key aspects from NIDDM that further needs closer study. Further research is also clearly needed to establish prospectively the main risk factors for CVD/LEAD, the incidence of cerebrovascular disease in IDDM, better ways to measure LEAD in IDDM (overcoming the problems posed by the presence of arterial calcification), and above all else the careful evaluation of preventive strategies (e.g., close blood pressure control and cholesterol lowering) to reduce CVD risk. Sadly, subjects with diabetes have been excluded from virtually all preventive trials to date. Because pure glycemic control does not seem to be so important for the macrovascular complications, and because the study design and length of follow-up in the Diabetes Control and Complications Trial (109) are unlikely to allow any conclusions to be made about glycemic control and macrovascular outcome, serious consideration should be given to conducting a primary prevention trial embracing vigorous treatment of lipid and blood pressure disorders, and good glycemic control. The latter is still probably important to help delay renal complications and to improve the lipid profile. Meanwhile, as women have similar CVD risk to men in IDDM, the National Cholesterol Educational Program Guidelines (110) should be revised to give all IDDM patients (male and female) an LDL cholesterol goal of 130 mg/dl or below. Future research will hopefully throw further light onto the genetic background that may predispose certain IDDM subjects to a relatively more accelerated course of CVD complications. However, regrettably, it seems unlikely that many IDDM patients will avoid some degree of accelerated CVD, and that CVD and renal disease are, like the other complications, a more or less inevitable long-term consequence of diabetes given sufficient age or duration. Major research efforts are needed to alter this gloomy picture.

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Diabetes and macrovascular disease


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Diabetes and macrovascular disease


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