Diabetes and Cardiovascular Events in Hypertensive Patients

Michael H. Alderman, Hillel Cohen, Shantha Madhavan

Abstract—To determine the relation of self-reported history of diabetes as well as baseline and in-treatment blood sugar to subsequent cardiovascular disease (CVD) in treated hypertensive patients, we assessed the experience of 6886 participants in a systematic treatment program. The presence or absence of a history of diabetes was known for all patients, who were then stratified into 3 groups according to blood sugar at baseline and in treatment (≤6.11, 6.11 to 7.74, and ≥7.75 mmol/L). Some 7.4% of all patients reported history of diabetes, and the overall prevalence of blood sugar ≥7.75 mmol/L was 7.7% and 10.4% at baseline and in treatment, respectively. Patients with a history of diabetes were 10 or 8 times as likely to have blood sugar ≥7.75 mmol/L at baseline (47.2% versus 4.5%) or in treatment (55.0% versus 6.8%), as were patients without history. During an average 6.3 years of follow-up, patients with history of diabetes had a cardiovascular event incidence 2-fold higher than those without history (20.8 versus 8.6/1000 person-years). Age-gender–adjusted CVD incidence rate but not non-CVD was twice as high in the highest compared with the lowest blood sugar stratum (baseline 16.6 versus 8.4/1000 person-years; in treatment 15.2 versus 8.2). Three separate models of Cox multivariate analysis revealed that history of diabetes (with no history as reference) had a greater association with CVD events (hazard ratio 2.37, 95% confidence interval 1.80 to 3.11) than did baseline (1.75, 1.31 to 2.33) or in-treatment blood sugar (1.55, 1.19 to 2.92), neither baseline nor in-treatment blood sugar was independently associated with CVD risk. In the elevated (≥7.75 mmol/L) in-treatment blood sugar group, the age-gender–adjusted rate of CVD events in frequent diuretic users (30.79/1000 person-years) was significantly higher than in moderate (13.34, P<0.004) and rare users (13.25, P<0.008).

These data affirm that the coincidence of diabetes and hypertension is common, that evidence of diabetes substantially increases CVD risk, that self-reported history is a more powerful predictor of CVD events than any measure of blood sugar, and that CVD increases in hypertensive diuretic users who develop hyperglycemia even when blood pressure is well controlled. (Hypertension. 1999;33:1130-1134.)

Key Words: diabetes mellitus ■ hypertension, mild ■ blood glucose ■ cardiovascular diseases ■ hypertension detection and control

Hypertension and diabetes commonly coexist,1-3 and patients with both these diseases are particularly vulnerable to cardiovascular disease (CVD).4-8 Each condition, and its treatment, may affect the other. For example, diabetes, through its nephrotic consequences, can produce hypertension, and diuretic treatment can alter glucose and insulin metabolism.9,10 That these changes may adversely affect the cardiovascular system is well recognized, but few long-term studies11,12 have either quantified these effects or assessed the importance of coincident diabetes in well-controlled hypertensive patients. We now report the association of self-reported history of diabetes as well as baseline blood sugar and its treatment-induced alteration to morbidity and mortality rates over 20 years among 8690 participants in a systematic hypertension treatment program.

Methods

Selection of Study Subjects

Study subjects were mild-to-moderate hypertensive patients identified in 1973 to 1993 who entered a previously described protocol-directed, union-sponsored work site treatment program in New York City.13-15 Of 8690 hypertensive patients enrolled between 1973 to 1993 who had at least 6 months of follow-up, 7974 (91.8%) had information on history of diabetes and baseline blood sugar available. Of these, 6886 (86.4%) remained in care through at least 1 subsequent in-treatment blood sugar measurement and were included in the present study.

History of Diabetes and Blood Sugar

During the initial examination by a nurse, patients were asked if they had or ever had been told of diabetes. A “yes” response was not further documented.
Initial and annual blood sugar levels of patients were, after 1980, invariably fasting levels; before 1980, some were nonfasting. Comparison of values before and after 1980 revealed no significant differences.

**Antihypertensive Drug Therapy**

Until 1988, treatment generally began with either hydrochlorothiazide or propranolol, or, less commonly, α- and/or β-adrenergic blockers. After the 1988 report of the Joint National Committee IV, calcium channel blockers and angiotensin-converting enzyme inhibitors were added as first-line drugs. In 1993, after Joint National Committee V, preference for first drug reverted to diuretics or β-blockers.

**Morbidity and Mortality Rates**

End point evaluation, previously described, included classification of events according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Among all CVD events (codes 390 to 459) included, of interest in this study were myocardial infarction (MI), including angioplasty or coronary bypass surgery, cerebrovascular disease (henceforth referred to as strokes), unstable angina, congestive heart failure, and other cardiovascular deaths. For patients with more than 1 event during follow-up, the first incident CVD event was the end point. Non-CVD events considered here were morbid and mortal cancers and non-CVD deaths.

During an average 6.3 years of follow-up, there were 411 CVD and 117 non-CVD first events. Of the CVD events, 231 were MI (202) or coronary revascularizations (29), 75 strokes, 28 unstable angina, 25 congestive heart failure, and 52 other CVD deaths. Hospital records, death certificates, or both confirmed 86.2% of the CVD events according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Among all CVD events according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Among all CVD events, 80.3% of the non-CVD events.

**Statistical Analysis**

Baseline characteristics were assessed according to gender, and differences between gender were tested for significance by the χ² statistic for categorical variables and ANOVA for continuous variables.

Elevated blood sugar was defined as ≥7.75 mmol/L. In-treatment blood sugar for each patient was the mean of all available annual measures. Patients were stratified according to baseline and in-treatment blood sugar with the use of cut-points of <6.11, 6.11 to 7.74, and ≥7.75 mmol/L. Characteristics of patients in the 3 groups by baseline and in-treatment blood sugar were compared and differences tested for statistical significance by use of the χ² statistic and ANOVA.

Age-gender–adjusted CVD and non-CVD event rates expressed as per 1000 person-years were computed for baseline and in-treatment blood sugar strata. Age-gender–adjusted relative risk (RR) and 95% confidence intervals of CVD incidence were calculated to compare blood sugar strata. Age-gender–adjusted relative risk (RR) and 95% confidence intervals of CVD incidence were calculated to compare blood sugar strata. Age-gender–adjusted relative risk (RR) and 95% confidence intervals of CVD incidence were calculated to compare blood sugar strata. Age-gender–adjusted relative risk (RR) and 95% confidence intervals of CVD incidence were calculated to compare blood sugar strata.

Patients were further categorized and CVD events analyzed according to 4 blood sugar elevation ($\geq 7.75$ mmol/L) status groups as follows: group A: never elevated (neither baseline nor in treatment); group B: elevated only at baseline; group C: elevated at least once during follow-up only; group D: elevated at baseline and at least once during follow-up.

The Cox proportional hazards regression model was applied to determine the effect of history of diabetes and blood sugar measures on CVD, controlling for potential confounders and other covariates. Separate regression models were constructed to assess the relative effects of the 3 diabetes variables on CVD incidence by adding to a background model history of diabetes, baseline blood sugar, and in-treatment blood sugar separately, as well as history and blood sugar measures in combination. Age, systolic blood pressure (BP), body mass index (BMI), cholesterol, smoking status, left ventricular hypertrophy (LVH), gender, diuretic use, and history of CVD were included in the background model.

**Results**

**Patient Characteristics**

Aside from indistinguishable blood sugar (5.94 versus 5.88 mmol/L), men differed significantly ($P<0.001$) from women in most of the baseline characteristics such as LVH (13% versus 6%), initial BP (153/97 versus 151/93 mm Hg), and smoking (26% versus 18%). Women were slightly older (54 versus 53 years, $P<0.001$) and heavier (28.4 versus 27.8 kg/m², $P<0.001$) than men. History of diabetes was significantly ($P=0.008$) but modestly greater among women (8.5%) than men (6.8%).

**Distribution of Blood Sugar at Baseline and in Treatment**

Overall, the prevalence of blood sugar elevation ($\geq 7.75$ mmol/L) was 7.7% and 10.4% at baseline and in treatment, respectively (Table 1); 3.2% of those <6.11 mmol/L at entry exceeded $\geq 7.75$ mmol/L at least once during therapy. By contrast, nearly 40% of those whose single pretreatment value was $\geq 7.75$ mmol/L subsequently fell below 7.75 mmol/L, of which 16% fell to <6.11 mmol/L during therapy.

The 2 blood sugar measures were significantly correlated ($r=0.536$, $P<0.001$). The percentage of patients with elevated blood sugar among those with history of diabetes was 10 times greater than that of patients without history at baseline (47.2% versus 4.5%, $P<0.001$), or 8 times for those with in-treatment elevation (55.0% versus 6.8%, $P<0.001$).

Most of the patient characteristics were significantly ($P<0.05$) different between the 3 baseline blood sugar categories, with patients in the highest category far more likely to have history of diabetes, higher BMI, and more LVH (Table 2) than those in the 2 lower blood sugar groups. Of note, 54% of those with elevated baseline blood sugar reported no history of diabetes. The highest blood sugar group also had significantly ($P<0.05$) higher in-treatment systolic BP and widest pulse pressure. Similar differences were observed between in-treatment blood sugar groups, except that cholesterol did not differ, and the highest blood sugar group contained more smokers.

**Blood Sugar and Incidence of Events**

Age-gender–adjusted overall incidence rate of CVD per 1000 person-years was positively associated with both initial and
TABLE 2. Characteristics of Study Patients by Baseline Blood Sugar

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Blood Sugar, mmol/L</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.11</td>
<td>6.11–7.74</td>
<td>≥7.75</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>(n=4912)</td>
<td>(n=1446)</td>
<td>(n=528)</td>
<td></td>
</tr>
<tr>
<td>Race%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>30.6</td>
<td>31.1</td>
<td>29.8</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42.5</td>
<td>44.3</td>
<td>45.6</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>25.3</td>
<td>22.7</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Male%</td>
<td>60.8</td>
<td>64.9</td>
<td>63.4†</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.8±4.3</td>
<td>28.3±4.6</td>
<td>29.1±4.9*</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.90±1.16</td>
<td>6.00±1.22</td>
<td>6.10±1.24*</td>
<td></td>
</tr>
<tr>
<td>LVH by ECG, %</td>
<td>10.2</td>
<td>9.3</td>
<td>12.3†</td>
<td></td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>2.7</td>
<td>9.5</td>
<td>45.8†</td>
<td></td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22.8</td>
<td>23.8</td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial systolic</td>
<td>151.2±20.9</td>
<td>154.3±21.9</td>
<td>158.0±22.9*</td>
<td></td>
</tr>
<tr>
<td>Initial diastolic</td>
<td>95.7±11.6</td>
<td>95.3±11.4</td>
<td>94.7±11.8</td>
<td></td>
</tr>
<tr>
<td>Final systolic</td>
<td>138.7±16.5</td>
<td>141.4±17.1</td>
<td>143.2±17.5*</td>
<td></td>
</tr>
<tr>
<td>Final diastolic</td>
<td>86.1±9.1</td>
<td>85.2±9.5</td>
<td>84.6±9.9*</td>
<td></td>
</tr>
</tbody>
</table>

*Continuous variables: P<0.05 (significant) between groups by ANOVA.
†Categorical variables: P<0.05 (significant) between groups by χ² statistic.

in-treatment blood sugar (Figure 1). Although the increase was modest from <6.11 mmol/L to 6.11 to 7.74 mmol/L, there was a significant (P<0.001) 2-fold increase from the lowest (<6.11 mmol/L) to the highest stratum (≥7.75 mmol/L). In contrast, no such association was observed for non-CVD rates. For coronary heart disease (CHD) events, which were 81.8% (336/411) of all CVD events, a similar direct relation with event rate and blood sugar at baseline (7.03, 7.74, and 81.8% (336/411) of all CVD events, a similar direct relation rates. For coronary heart disease (CHD) events, which were

For CVD rate, *B vs A: P=0.041; **D vs A: P<0.001.

History of Diabetes and CVD Incidence
The age−gender−adjusted CVD rate for those with a history of diabetes (20.76 per 1000 person-years) was more than double (P<0.0001) that of those without a history (8.62). Those without a history of diabetes showed a 50% increase in CVD rate from the lowest (<6.11 mmol/L) to the highest blood sugar (≥7.75 mmol/L) at baseline (8.1 versus 12.3 per 1000 person-years) and a 30% increase in treatment (8.0 versus 10.8), though the trends were not significant. In contrast, among the 513 patients with a history of diabetes, there was no relation between blood sugar level and CVD event rate.

And in treatment (6.74, 8.67, and 12.40, P<0.001) and in treatment (6.74, 8.67, and 12.40, P<0.001) was observed.

Any blood sugar elevation was associated with increased CVD incidence (Figure 2). Indeed, a single elevation, either before therapy (group B) or in treatment (group C), raised CVD incidence by nearly 50% (not significant) from that of the never-elevated (group A). Those with repeated elevation (group D) had a significant (P<0.0001) doubling of CVD event rate (17.57/1000 person-years) compared with the never-elevated group (8.42/1000 person-years).

Figure 1. Age−gender−adjusted CVD and non−CVD incidence rates by blood sugar at baseline and in treatment in treated hypertensive patients. *CVD rate for blood sugar ≥7.75 mmol/L vs <6.11 mmol/L: P<0.001 at baseline and in treatment.

Figure 2. Age−gender−adjusted CVD and non−CVD incidence rates by blood sugar elevation in treated hypertensive patients. For CVD rate, *B vs A: P=0.041; **D vs A: P<0.001.

Multivariate Analyses
To determine the relative contribution of blood sugar measures in the context of the simple patient report of diabetes, based on a background model of age, gender, systolic BP, BMI, cholesterol, smoking status, diuretic use, LVH, and history of CVD, 3 separate Cox regression models were constructed, adding history of diabetes, baseline blood sugar, and in-treatment blood sugar, respectively, as independent variables. The background model had a −2 log likelihood (−2LL) of 6254.88. The reduction in −2LL produced by adding history of diabetes was greatest (31.83), followed by baseline (12.84) and in-treatment blood sugar (9.74). The hazard ratio for each of these 3 factors in their respective models was highly significant. History of diabetes with no history of diabetes as reference carried the most robust and highest risk ratio (2.37) for CVD. Indeed, this even exceeded the risk ratio (2.22) for history of CVD. In another model, the RR (1.75) for baseline elevated blood sugar (≥7.75 mmol/L) with <7.75 mmol/L as reference was lower than that for history of diabetes but higher than the RR (1.55) in a third model using in-treatment elevated blood sugar. When baseline blood sugar was added to the first model, the hazard ratio for history of diabetes remained high, but the effect of blood sugar on CVD was not significant, as shown in the full model.
TABLE 3. Proportional Hazards Cox Regression Model (Full): Association of History of Diabetes and Blood Sugar With Incidence of CVD in Treated Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>0.7647</td>
<td>&lt;0.001</td>
<td>2.15 (1.58–2.92)</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.0512</td>
<td>&lt;0.001</td>
<td>1.05 (1.04–1.06)</td>
</tr>
<tr>
<td>Male</td>
<td>0.7049</td>
<td>&lt;0.001</td>
<td>2.02 (1.61–2.55)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>0.7995</td>
<td>&lt;0.001</td>
<td>2.22 (1.62–3.05)</td>
</tr>
<tr>
<td>Diuretic use, ≥90%</td>
<td>0.2069</td>
<td>0.1144</td>
<td>1.23 (0.95–1.59)</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.4211</td>
<td>0.0001</td>
<td>1.52 (1.23–1.89)</td>
</tr>
<tr>
<td>L.V.H</td>
<td>0.3982</td>
<td>0.0050</td>
<td>1.49 (1.13–1.97)</td>
</tr>
<tr>
<td>Blood sugar, ≥7.75 mmol/L*</td>
<td>0.2483</td>
<td>0.1337</td>
<td>1.28 (0.93–1.77)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>0.1596</td>
<td>0.0001</td>
<td>1.17 (1.08–1.27)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.0314</td>
<td>0.0090</td>
<td>1.03 (1.01–1.06)</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>0.0045</td>
<td>0.0498</td>
<td>1.00 (1.00–1.01)</td>
</tr>
</tbody>
</table>

*Baseline blood sugar.

In the presence of history of diabetes, baseline and in-treatment blood sugar (model not shown) were not associated with cardiovascular events.

(Table 3). Thus in the presence of history of diabetes, neither baseline nor in-treatment blood sugar achieved an independent association with CVD. These findings were independent of diuretic use (frequent versus else), which was also independently associated with events in the above models.

Diuretic Use and Blood Sugar

Patients were categorized according to frequency of diuretic prescription as rare (0% to 10%), moderate (11% to 89%), and frequent users (≥90%). The percentages of patients in these groups were 35.3%, 48.4%, and 16.4%, respectively. Mean blood sugar levels at baseline (6.09 mmol/L) and in treatment (6.09 mmol/L) did not differ for rare users. Mean in-treatment values were higher than baseline for both moderate users (6.13 versus 5.87 mmol/L, P<0.001) and frequent users (5.87 versus 5.75 mmol/L, P<0.01).

Overall, age-gender–adjusted CVD incidence rates did not differ for the rare, moderate, and frequent diuretic users (9.38, 9.14, and 11.42 per 1000 person-years, respectively). By contrast, in all blood sugar strata, both at baseline and in treatment, CVD incidence had a direct dose-response relation with diuretic use, with frequent users having the highest rate (Table 4). However, this positive association was significant only among those with elevated in-treatment blood sugar (≥7.75 mmol/L). In this stratum, the age-adjusted CVD incidence rate of frequent diuretic users (30.79/1000 person-years) was significantly higher than those of rare (13.25, P=0.008) and moderate users (13.34, P=0.004). Among patients in this stratum, in a Cox regression model with CVD as independent variable, addition of diuretic use as an independent variable to a model without it reduced −2LL from 743.8 to 735.5. This difference of 8.3 was significant as a χ² with 1 degree of freedom.

Discussion

These findings reaffirm the additional cardiovascular disease burden borne by hypertensive patients who also have diabetes and the persistence of this adverse association despite sustained BP control. Moreover, a positive response to the simple question “have you ever been told that you have diabetes?” proved to be a more robust predictor of CVD events than any measure of blood sugar. In fact, although an elevated blood sugar at baseline or in-treatment was associated with increased CVD incidence, that relation did not endure in the presence of history of diabetes in a multivariate analysis. The value of an unsubstantiated self-report of a history of diabetes has been previously reported.

Blood sugar is known to be higher in hypertensive than normotensive subjects, and the prevalence (7.4%) of history of coincident diabetes in these hypertensive subjects was similar to that previously observed. Here, the prevalence of elevated blood sugar rose from 7.7% at baseline to 10.4% in treatment. This reflects, in large part, the impact of diuretic therapy. Of the 3.2% of patients, normal at baseline, who developed elevated blood sugar (≥7.75 mmol/L) during treatment, 76% were moderate or frequent diuretic users. Among patients with a history of diabetes, the prevalence of elevated blood sugar at baseline and in treatment was 10 or 8 times that for those without that history. Of note, most (54%) of those with elevated blood sugar at baseline (528) reported no history of diabetes. This supports earlier reports of widespread underestimation of type II diabetes to patients with coexistent hypertension.

Although this study was not designed to evaluate drug effects, the association of frequent diuretic use and increased blood sugar was striking. Since diuretic therapy has generated

TABLE 4. Age-Gender-Adjusted CVD Incidence Rates According to Blood Sugar Measures and Diuretic Use (per 1000 Person-Years)

<table>
<thead>
<tr>
<th>Diuretic Use</th>
<th>Baseline Blood Sugar, mmol/L</th>
<th>In-Treatment Blood Sugar, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare (n=2428)</td>
<td>&lt;6.11 (61)*</td>
<td>&gt;6.11 (63)</td>
</tr>
<tr>
<td>Moderate (n=3330)</td>
<td>8.09 (140)</td>
<td>10.20 (72)</td>
</tr>
<tr>
<td>Frequent (n=1128)</td>
<td>9.69 (44)</td>
<td>12.69 (22)</td>
</tr>
</tbody>
</table>

*Figures in parentheses indicate number of CVD events.

†CVD rate for frequent diuretic users was significantly higher than those for rare (P=0.008) and moderate (P=0.004) users for in-treatment blood sugar ≥7.75 mmol/L.
less CHD protection in clinical trials than predicted by epidemiological experience, it is reasonable to entertain the possibility that treatment-induced hyperglycemia may contribute to those disappointing results. Although the low-dose diuretic regimens commonly used today are less likely to disturb glucose metabolism than the larger doses used previously, the occurrence of hyperglycemia might still both identify those at greater CVD risk and be an indication to consider alteration of drug therapy.

Most striking here was the 2- to 3-fold difference in CVD event rates between those who did and those who did not have a history of diabetes. Moreover, among those with a diabetic history, CVD incidence was similar regardless of blood sugar status. In the presence of a history of diabetes, knowledge of baseline or in-treatment blood sugar failed to improve the ability to predict CVD. A similar finding has been previously reported.

That diabetic hypertensive patients without a history of CVD had a CVD incidence as high as that of nondiabetic hypertensive patients with prior CVD has also been seen elsewhere. Among diabetics, CVD incidence rates did not differ between those with and those without prior CVD. These striking findings suggest that perhaps hypertensive patients with diabetes should be treated with the tools routinely applied to those with established CHD.

A major strength of this study is rigorous determination of known relevant factors in all subjects at entry, careful regular follow-up, and repeated clinical measures, including blood sugar, throughout the study. Patients received systematic treatment, and there was virtually complete end point ascertainment. The existence of in-treatment blood sugar measures made it possible to investigate the effect of treatment-associated blood sugar changes on CVD events. Regrettably, systematic information on possible treatment for diabetes was unavailable. However, this is probably of minor concern because available data suggest that few patients if any were taking medication.

In summary, these findings demonstrate that the coincidence of a history of diabetes and hypertension is not only common but markedly increases cardiovascular risk for hypertensive patients, even for those whose BP had been normalized. In nearly half of those who ever had it, hyperglycemia developed only during treatment, and this was usually associated with diuretic use. This is important because an elevated blood sugar at any time is associated with increased CVD risk. Finally, and perhaps of greatest practical importance, is the finding that a self-report of “history of diabetes” was a more powerful predictor of CVD risk than any measure of blood sugar or any other CVD risk factor. Indeed, prior knowledge of diabetes is as powerful a prognostic tool among controlled hypertensive patients as is history of stroke or heart attack.

References