Insulin Therapy, Hyperglycemia, and Hypertension in Type 1 Diabetes Mellitus

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Background: Diabetes mellitus and hypertension are closely linked, but the long-term blood pressure effects of glucose-lowering therapy and hyperglycemia are not clear.

Methods: We examined the effects of intensive insulin therapy and hyperglycemia on the development of hypertension in the Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Incident hypertension was defined as 2 consecutive study visits with a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medications to treat high blood pressure.

Results: Participants were enrolled from August 23, 1983, through June 30, 1989. During a 15.8-year median follow-up, 630 of 1441 participants developed hypertension. During the DCCT, the incidence of hypertension was similar comparing participants assigned to intensive vs conventional therapy. However, intensive therapy during the DCCT reduced the risk of incident hypertension by 24% during EDIC study follow-up (hazard ratio, 0.76; 95% confidence interval [CI], 0.64-0.92). A higher hemoglobin A1c level, measured at baseline or throughout follow-up, was associated with increased risk for incident hypertension (adjusted hazard ratios, 1.11 [95% CI, 1.06-1.17] and 1.25 [95% CI, 1.14-1.37], respectively, for each 1% higher hemoglobin A1c level), and glycemic control appeared to mediate the antihypertensive benefit of intensive therapy. Older age, male sex, family history of hypertension, greater baseline body mass index, weight gain, and greater albumin excretion rate were independently associated with increased risk of hypertension.

Conclusions: Hyperglycemia is a risk factor for incident hypertension in type 1 diabetes, and intensive insulin therapy reduces the long-term risk of developing hypertension.

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THE DCCT and EDIC STUDY

The DCCT was a multicenter clinical trial that examined the effects of intensive diabetes therapy aimed at lowering glucose levels to as close to the nondiabetic range as safely possible in participants with type 1 diabetes mellitus. The trial included 2 cohorts: a primary prevention cohort (1 to 5 years’ duration of diabetes, albumin excretion rate [AER] <40 mg/24 h, and no retinopathy by fundus photography) and a secondary intervention cohort (1 to 15 years’ duration, AER ≤200 mg/24 h, at least 1 microaneurysm in either eye, and no more than moderate nonproliferative retinopathy). Potential participants were excluded if they already had hypertension, defined as a systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic blood pressure (DBP) of 90 mm Hg or higher, or treatment with antihypertensive medications. Clinical cardiovascular disease and hyperlipidemia were also exclusion criteria.

From August 23, 1983, through June 30, 1989, 1441 participants between the ages of 13 and 39 years were enrolled and randomly assigned to intensive or conventional insulin therapy. Intensive therapy included 3 or more insulin injections daily and on alternate years during the DCCT, allowing assessment of the effect of glucose lowering on the development of hypertension.

From DCCT baseline and through EDIC study year 12 (2005), participants were offered instruction in intensive therapy, and all participants returned to their own health care professionals for diabetes care. All DCCT participants were invited to join the EDIC study, an observational extension of the DCCT, and 1375 of 1428 (96.3% of the surviving cohort) agreed to participate. During the EDIC study, mean hemoglobin A₁c level achieved during the mean 6.5 years of the DCCT, allowing assessment of the effect of glucose lowering on the development of hypertension.

DEFINITION OF INCIDENT HYPERTENSION

Incident hypertension was defined to occur when any of the following criteria were met on 2 consecutive occasions: SBP of 140 mm Hg or higher, DBP of 90 mm Hg or higher, or use of antihypertensive medications to treat high blood pressure. Blood pressure was measured by trained observers, with participants comfortably seated in a quiet room at a comfortable temperature for at least 3 minutes, the arm slightly flexed, and the forearm supported at heart level. Mercury manometers were used during the DCCT, with digital manometers used during the EDIC study.

During the DCCT, blood pressure was measured every 3 months, and hypertension was a predefined outcome of interest. In the event that an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher was observed, participants were asked to return for reevaluation in 1 month. If the SBP or DBP was again greater than threshold, hypertension was diagnosed. Use of antihypertensive medications, including angiotensin-converting enzyme (ACE) inhibitors, was discouraged before a diagnosis of hypertension, unless for the treatment of cardiovascular disease.

During the EDIC study, blood pressure was measured and a current medication form was completed at each yearly visit. The current medication form included separate questions regarding ACE inhibitor use and antihypertensive medication use. When use of angiotensin II receptor blockers (ARBs) became more common, an additional question regarding ARB use was added. When used, participants were asked to indicate the intended purpose of these medications, with treatment of high blood pressure as one option listed. During the EDIC study, we defined incident hypertension to occur when at least 1 diagnostically criterion was met on 2 consecutive yearly visits.

STATISTICAL ANALYSIS

Participants were considered at risk for incident hypertension from DCCT entry until they were diagnosed as having incident hypertension or until they were censored for loss to follow-up (145 participants [10.1%]) or the EDIC study year 12 visit. Blood pressure data were 95% complete. Unadjusted incidence rates of hypertension were calculated as the number of cases of incident hypertension divided by person-years at risk.

The effect of intensive insulin therapy on incident hypertension was assessed using intent-to-treat analyses. The cumulative incidence of hypertension was displayed graphically using a Kaplan-Meier plot, with difference by treatment group tested using the log-rank test. Cox proportional hazards models were used to estimate risk associated with intensive insulin therapy. Cumulative incidence curves suggested different effects during the first 6 to 7 years of follow-up (approximately the mean duration of the DCCT) compared with subsequent years. For this reason and because differences in therapy between treatment groups changed markedly transitioning from the DCCT to the EDIC study, risk for incident hypertension by DCCT treatment assignment was calculated separately for the DCCT and EDIC study periods using a time-dependent period indicator variable (DCCT vs EDIC study). The proportional hazards model included a treatment × period interaction term and was strati-
Table 1. Baseline Characteristics of DCCT Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional Therapy (n=730)</th>
<th>Intensive Therapy (n=711)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>27 (7)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>395 (54.1)</td>
<td>366 (51.5)</td>
</tr>
<tr>
<td>Race, No. (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>704 (96.4)</td>
<td>687 (96.6)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>17 (2.3)</td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.2)</td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Duration of diabetes, median (IQR), y</td>
<td>4 (2-8)</td>
<td>4 (2-10)</td>
</tr>
<tr>
<td>Retinopathy, No. (%)</td>
<td>352 (48.2)</td>
<td>363 (51.1)</td>
</tr>
<tr>
<td>Active smoking, No. (%)</td>
<td>158 (21.6)</td>
<td>146 (20.5)</td>
</tr>
<tr>
<td>Daily insulin dose, mean (SD), U/kg</td>
<td>0.66 (0.25)</td>
<td>0.67 (0.25)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>23 (3)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>115 (11)</td>
<td>114 (11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 (9)</td>
<td>73 (8)</td>
</tr>
<tr>
<td>Hemoglobin A1c, mean (SD), %</td>
<td>9.1 (1.6)</td>
<td>9.1 (1.6)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>176 (34)</td>
<td>177 (33)</td>
</tr>
<tr>
<td>Triglycerides, mean (SD), mg/dL</td>
<td>82 (51)</td>
<td>81 (43)</td>
</tr>
<tr>
<td>HDL-C, mean (SD), mg/dL</td>
<td>50 (12)</td>
<td>51 (12)</td>
</tr>
<tr>
<td>LDL-C, mean (SD), mg/dL</td>
<td>109 (29)</td>
<td>110 (29)</td>
</tr>
<tr>
<td>Albumin excretion rate, mean (IQR), mg/24 h</td>
<td>12 (7-19)</td>
<td>12 (7-17)</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

*SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; HDL-C, LDL-C, and total cholesterol to micromoles per liter, multiply by 0.0259; hemoglobin A1c to proportion of total hemoglobin, multiply by 0.01; and triglycerides to millimoles per liter, multiply by 0.0113. Because of rounding, percentages may not total 100.

Results

BASELINE CHARACTERISTICS

At DCCT randomization, the mean (SD) age of the participants was 27(7) years, 47.2% were female, and 96.5% were white. Participant characteristics, described further in Table 1, did not differ by treatment assignment.

INCIDENT HYPERTENSION

During a median of 15.8 years of follow-up, 630 participants met the definition of incident hypertension. At hypertension diagnosis, 395 participants (62.7% of incident cases) had elevated blood pressure and 277 (44.0%) reported use of antihypertensive medications to treat high blood pressure, with some participants meeting multiple criteria. Unadjusted incidence rates of hypertension, expressed per 100 person-years, increased with updated age: 1.1 for those aged 13 through 19 years, 1.5 for those aged 20 through 29 years, 2.1 for those aged 30 through 39 years, 4.8 for those aged 40 through 49 years, and 8.3 for those aged 50 through 58 years.

EFFECT OF INTENSIVE THERAPY

During the DCCT itself, intensive therapy did not lead to a statistically significant reduction in the risk of incident hypertension (Figure and Table 2). However, participants assigned to intensive therapy during the DCCT had a 24% reduction in the risk of incident hypertension during EDIC study follow-up (hazard ratio, 0.76; 95% confidence interval [CI], 0.64-0.92). During the complete period of DCCT and EDIC study follow-up combined, intensive diabetes therapy reduced the overall long-term incidence of hypertension by 20% (hazard ratio, 0.80; 95% CI, 0.69-0.94; P = .006 by log-rank test). Age, race, BMI, and blood pressure, each measured at DCCT baseline, did not modify the effect of intensive therapy.

Further analyses were performed to determine whether results may be biased by misclassifying hypertension diagnoses based on use of antihypertensive medications. The proportions of participants diagnosed as having hypertension attributable to elevated blood pressure and use of medication to treat high blood pressure (including ACE
Intensive insulin therapy reduced the long-term risk of incident hypertension in the DCCT and EDIC study. Hyperglycemia, measured as greater hemoglobin A1c level at baseline or throughout follow-up, was a risk factor for the subsequent development of hypertension, and the antihypertensive effect of intensive insulin therapy was explained by improved glycemic control. These results strongly suggest that hyperglycemia plays a role in the pathogenesis of hypertension in type 1 diabetes mellitus. Moreover, this study has identified long-term prevention of hypertension as an additional benefit of intensive insulin therapy.

The salutary effect of intensive insulin therapy occurred in a delayed fashion. During the DCCT itself, there was little or no blood pressure benefit to intensive insulin therapy. In contrast, during EDIC study follow-up, participants who had previously been assigned to intensive insulin therapy were at lower risk for developing hypertension. This benefit was observed despite the fact that glycemic control during the EDIC study was similar, comparing people who had been assigned to intensive therapy with those who had not. That the benefit associated with intensive therapy persisted beyond the period of active treatment is similar to the “metabolic memory” effect previously described in the context of preventing albuminuria and other long-term complications of diabetes.

**RISK ASSOCIATED WITH COVARIATES**

Higher hemoglobin A1c levels, measured at DCCT baseline, were associated with increased risk of incident hypertension, as were male sex, a family history of hypertension, greater baseline BMI, and higher baseline AER (Table 3). Active smoking and unfavorable lipid concentrations were associated with increased risk for incident hypertension in univariate models but not in the multivariate adjusted model. During the study visit before the development of hypertension, the AER was less than 30 mg/24 h in 456 of 630 participants (72.4% of cases), 30 to 299 mg/24 h in 133 participants (20.1%), and 300 mg/24h or higher in 41 participants (6.5%). In time-updated models, time-averaged hemoglobin A1c level, weight gain, and time-averaged AER were each independent predictors of incident hypertension (Table 4).

**MEDIATORS OF INTENSIVE THERAPY**

To explore the mechanisms through which intensive therapy may reduce risk of hypertension, the risk for incident hypertension during EDIC study follow-up associated with intensive therapy during the DCCT was compared without adjustment and with adjustment for time-updated characteristics. Adjustment for time-averaged DCCT hemoglobin A1c level changed the corresponding hazard ratio from 0.76 (95% CI, 0.64-0.92) to 1.03 (95% CI, 0.83-1.28), suggesting that improved glycemic control fully accounted for the protective effect of intensive therapy on the development of hypertension during EDIC study follow-up. Adjustment for time-averaged AER changed this hazard ratio from 0.76 (95% CI, 0.64-0.92) to 0.82 (95% CI, 0.69-0.99), suggesting that albuminuria prevention accounted for a relatively smaller portion of this treatment effect. Finally, adjustment for change in BMI (weight gain) slightly greater had the intensive therapy group not experienced greater weight gain than the conventional therapy group. Adjustment for weight gain changed the hazard ratio for incident hypertension during the DCCT associated with intensive therapy from 0.94 (95% CI, 0.69-1.28) to 0.86 (95% CI, 0.63-1.17).

**Table 2. Incident Hypertension by Period of Observation and Treatment Assignment**

<table>
<thead>
<tr>
<th>Period of Observation and Treatment Assignment</th>
<th>No. of Events</th>
<th>Incidence Rate per 100 Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional therapy</td>
<td>84</td>
<td>2.0</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Intensive therapy</td>
<td>77</td>
<td>1.8</td>
<td>0.94 (0.69-1.28)</td>
</tr>
<tr>
<td>EDIC study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional therapy</td>
<td>255</td>
<td>4.5</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Intensive therapy</td>
<td>214</td>
<td>3.6</td>
<td>0.76 (0.64-0.92)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications.
In addition, the observed delay suggests that the protective effect of intensive therapy on blood pressure occurs over a relatively long period and/or that beneficial effects of glucose lowering are counterbalanced by unmeasured adverse effects of intensive insulin therapy in the short-term.

The DCCT and EDIC study provide a unique opportunity to assess the associations of intensive diabetes therapy and hyperglycemia with incident hypertension. Limited data regarding blood pressure levels were published at the conclusion of the DCCT and at year 8 of the EDIC study, but this is the first study, to our knowledge, to report in detail the effects of intensive therapy.

The effect of glucose-lowering therapies on blood pressure after 6 years of treatment was greater for participants assigned to intensive glucose-lowering treatment (chlorpropamide, 43%; glibenclamide, 36%; and insulin, 38%) than for those assigned to conventional dietary treatment (34%), perhaps owing to greater weight gain with the intensive glucose-lowering therapies. Data for longer-term follow-up, during the period for which intensive therapy reduced risk for hypertension in the current study, have not been published for the United Kingdom Prospective Diabetes Study.

Incidence rates of hypertension were higher in this study of type 1 diabetes than in a cohort of similar age from the general population. Nevertheless, most non-glycemic risk factors for incident hypertension are also associated with increased risk of diabetes complications, including mortality. These factors reflect the need for better management of chronic complications of diabetes in all ages. The current study results suggest that associations of greater fasting glucose level and overt type 2 diabetes with increased risk for hypertension observed in prior studies may have been mediated by hyperglycemia, at least in part.

The effect of glucose-lowering therapies on blood pressure has been examined among people with impaired glucose tolerance and in those with type 2 diabetes. In the STOP–Noninsulin-Dependent Diabetes Mellitus trial, acarbose therapy was associated with a 34% reduction in the risk of incident hypertension among 1368 people with impaired glucose tolerance followed up for a mean of 3.3 years. This reduced risk may have been due to glucose control or weight loss associated with acarbose treatment, whereas in the study reported herein, the long-term incidence of hypertension was reduced with intensive therapy despite weight gain. In the United Kingdom Prospective Diabetes Study of type 2 diabetes, the prevalence of hypertension after 6 years of treatment was greater for participants assigned to intensive glucose-lowering treatment (chlorpropamide, 43%; glibenclamide, 36%; and insulin, 38%) than for those assigned to conventional dietary treatment (34%), perhaps owing to greater weight gain with the intensive glucose-lowering therapies. Data for longer-term follow-up, during the period for which intensive therapy reduced risk for hypertension in the current study, have not been published for the United Kingdom Prospective Diabetes Study.
fied herein are consistent with those described elsewhere, including older age, family history of hypertension, greater BMI, and weight gain.21-24 Both BMI and weight gain merit specific note because their associations with incident hypertension add to growing evidence that obesity is a clinically relevant health problem for people with type 1 diabetes.5,9,25 Male sex has been associated with an increased incidence of hypertension in some studies21,22 but not in all. Baseline and time-averaged AERs were strongly associated with increased risk for hypertension, but these results do not prove that albuminuria necessarily precedes or causes hypertension in type 1 diabetes. The temporal relationship of AER and blood pressure was not evaluated in depth, and elevated blood pressure (below the threshold used to define hypertension) could confound the observed AER-hypertension association. In addition, the AER was less than 30 mg/24 h before the development of hypertension in more than two-thirds of incident hypertension cases.

How might hyperglycemia lead to hypertension during long-term follow-up? Extensive literature6,7 describes effects of hyperglycemia on the vascular wall. Through increased quantities of advanced glycation end products, reactive oxygen species, and sorbitol, hyperglycemia can lead to vasoconstriction (via alterations of endothelin and nitric oxide) and to extracellular matrix deposition. Activation of protein kinase C may play a central role in these pathways. Changes leading to vascular remodeling may progress over long periods, explaining the delayed effect of intensive insulin therapy on the development of hypertension observed in this study. This delay has other possible explanations. Hyperinsulinemia has been described to stimulate renal sodium reabsorption, sympathetic nervous system activity, and the renin-angiotensin-aldosterone system, and such reversible adverse hemodynamic effects may have obscured the benefits of glucose lowering during short-term follow-up.25 Alternatively, the effect of intensive therapy may be delayed if it is mediated via protection from kidney disease. Our results did not suggest that the protective effect of intensive insulin therapy was largely mediated by albuminuria prevention. However, protection from kidney disease cannot be excluded as a viable mechanism because variability in measurement of AER may lead to underestimation of its effect and because no sensitive longitudinal measurement of glomerular filtration rate was available for analyses.26 Finally, greater weight gain among participants assigned to intensive therapy reduced the effect of intensive insulin therapy that may have been seen otherwise but did not fully explain differences in effect during the DCCT compared with the EDIC study.

This study has a number of limitations. First, a blood pressure threshold of 140/90 mm Hg is standard for the definition of hypertension,1 but elevated blood pressure measurements below this threshold are also likely to have clinical relevance. Our analyses assessing blood pressure as a continuous outcome may be biased toward the null by not accounting for use of antihypertensive medications. Second, treatment assignment was not blinded, potentially leading to biased use of antihypertensive medications. However, sensitivity analyses suggested that the effect of treatment was robust. In particular, when the hypertension outcome was restricted to elevated blood pressure alone (not including antihypertensive therapy), the beneficial effect of intensive therapy was slightly greater than that observed with the combined outcome. Finally, the study population consisted of predominantly white clinical trial participants with type 1 diabetes. Results may differ for people of other races, for people with type 2 diabetes, and possibly for people treated outside a monitored trial setting. The strengths of this study include its large size, long duration, minimal loss to follow-up, frequent measurement of relevant covariates, and assessment of a clinically relevant therapeutic intervention.

In conclusion, the results of this study suggest that hyperglycemia contributes to the pathogenesis of hypertension in people with type 1 diabetes mellitus. Prevention of hypertension was identified as an additional long-term benefit of intensive insulin therapy.

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REFERENCES


