Relationship of Family History of Type 2 Diabetes, Hypoglycemia, and Autoantibodies to Weight Gain and Lipids With Intensive and Conventional Therapy in the Diabetes Control and Complications Trial

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Intensive therapy for type 1 diabetes results in greater weight gain than conventional therapy. Many factors may predispose to this greater weight gain, including improved glycemic control, genetic susceptibility to obesity, and hypoglycemia. To study this, relationships among family history of type 2 diabetes, frequency of severe hypoglycemia, β-cell autoantibodies, and weight gain were examined in 1,168 subjects aged ≥18 years at baseline randomized to intensive and conventional therapy groups in the Diabetes Control and Complications Trial. With intensive therapy, subjects with a family history of type 2 diabetes had greater central weight gain and dyslipidemia characterized by higher triglyceride levels and greater cholesterol in VLDLs and intermediate-density lipoproteins compared with subjects with no family history. Neither the frequency of severe hypoglycemia nor positivity to GAD65 and insulinoma-associated protein 2 antibodies was associated with increased weight gain with either intensive or conventional therapy. These data support the hypothesis that increased weight gain with intensive therapy might be explained, in part, by genetic traits.

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Weight gain frequently accompanies improved glycemic control achieved through intensive diabetes therapy (1–3). In the Diabetes Control and Complications Trial (DCCT), a subset of subjects with type 1 diabetes (~25%) gained an excess amount of weight while treated with intensive therapy and became, on average, obese (4). When compared with those whose weight remained stable throughout intensive therapy, this group also developed changes in lipids and blood pressure similar to those found in the central obesity–insulin resistance syndrome (4). This metabolic syndrome consists of the clustering of intra-abdominal obesity, insulin resistance, dyslipidemia, hyper-coagulability, and elevated blood pressure in various combinations within individuals (5–8) and is characteristically found in subjects with type 2 diabetes (9–11).

Components of the central obesity syndrome have been found to cluster within families (12–19). Furthermore, type 2 diabetes has a strong genetic component, as has been evidenced in twin concordance studies (20,21). Because of the familial nature of both the metabolic syndrome and type 2 diabetes, individuals with a family history of type 2 diabetes would be expected to be more likely to carry obesity traits, whether they are genetic or related to the familial environment (8). These traits might predispose these individuals to greater weight gain than individuals without a family history of type 2 diabetes. Therefore, we hypothesized that with near normalization of glycemic control, individuals with a first-degree relative with type 2 diabetes would be likely to express an otherwise latent obesity component of the central obesity syndrome phenotype and experience greater weight gain during intensive therapy than subjects with no such family history.

Hypoglycemia acutely increases hunger and, if it occurs repeatedly, may also lead to unwanted weight gain. Subjects in the intensive therapy group of the DCCT experienced a threefold increase in severe hypoglycemic events compared with the conventional therapy group (22,23), and this complication is thought to be a major contributor to the weight gain that accompanies intensive therapy. In support of this, we previously showed (4) that subjects who gained an excess amount of weight with intensive therapy had a small, but significant, increase in severe hypoglycemic episodes compared with the group that retained stable weight during intensive therapy. However, no studies have examined the relationship between the frequency of documented hypoglycemic episodes and the amount of weight gain in the entire DCCT cohort or whether increased hypoglycemia interacts with other risk factors for weight gain in this population. This study therefore examines the association of a family history of type 2 diabetes and the frequency of hypoglycemia with the amount of weight gained with the treatment of type 1 diabetes in subjects from the DCCT.

Autoimmune-mediated destruction of β-cells plays an
important role in the pathogenesis of type 1 diabetes, and antibodies against GAD65 and insulinoma-associated protein 2 (IA-2) are useful markers of the autoimmune type 1 diabetes disease process (24). β-Cell autoimmunity, including GAD65 and IA-2 antibodies, also has been detected in subjects with phenotypic type 2 diabetes, albeit at a much lower frequency than in subjects with type 1 diabetes. When detectable, positivity for these antibodies is associated with earlier failure of oral agents and need for insulin treatment compared with antibody-negative subjects with phenotypic type 2 diabetes (25–28). We therefore sought to determine if those in intensive therapy who gained the most weight or those with a family history of type 2 diabetes would have less positivity to GAD65 and IA-2 antibodies, potentially identifying a group of subjects with an immunological resemblance to type 2 diabetes (implying nonimmunological contributions to hyperglycemia) that manifests phenotypically with type 1 diabetes.

RESEARCH DESIGN AND METHODS

The design and methods of the DCCT have been described in detail elsewhere (29). At the present study was reviewed below. The DCCT was a prospective, randomized, controlled multicenter clinical trial designed to study the effect of conventional versus intensive diabetes therapy on microvascular complications in subjects with type 1 diabetes. A total of 1,441 subjects, aged 13–39 years at baseline, were randomized to conventional or intensive therapy and followed for 3.5–9 years (mean 6.5 years). Subjects in the conventional therapy group typically received one or two insulin injections per day and had a quarterly follow-up at their DCCT clinic. Intensive therapy subjects practiced more rigorous diabetes management by taking three or more insulin injections per day or using an insulin infusion pump, self-monitored their blood glucose four or more times per day, and visited their DCCT care providers monthly to achieve blood glucose and HbA1c levels as close to normal as possible.

Intensive therapy subjects received counseling on dietary carbohydrate intake and adjustments of insulin dosage to achieve the pre- and postprandial intensive therapy glycemic goals of 70–120 mg/dl. Otherwise, dietary guidelines were similar for the two groups: subjects were advised to restrict total fat intake to ≤30% of their calories, with the largest portion of calories (45–55%) coming from carbohydrates and the remaining 10–20% from protein. Exercise was encouraged for both conventional and intensive therapy subjects.

All enrolled subjects were in good general health. Specific reasons for exclusion from the study included a body weight of >30% above ideal, defined according to age and sex in the 1983 Metropolitan Life Insurance norms (30). These were a total cholesterol level >3 SDs above the mean for age and sex, as defined by the Lipid Research Clinic Population Studies Data Book (31), calculated LDL cholesterol level >100 mg/dl, major electrocardiographic abnormalities, or clinical history of symptoms of coronary heart disease or peripheral vascular disease. Only subjects aged ≥18 years at baseline for whom a complete set of lipid data were available were included in the current analysis (n = 1,168). Subjects aged <18 years were excluded from our analysis to minimize any confounding effects on the results by adolescent weight gain. Of this total sample, 1,168 subjects were included in this study, 586 in the conventional therapy group (mean follow-up 6.0 years) and 582 in the intensive therapy group (mean follow-up 6.2 years). Conventional and intensive therapy subjects have been previously stratified into quartiles of weight gain (Q1–Q4) defined by change in BMI from baseline to the final follow-up visit in the DCCT (4).

Family history of type 2 diabetes. As part of a specific protocol for the DCCT Family Study in 1991, DCCT subjects completed a family survey, and 372 participants reported having one or more first-degree relatives with any type of diabetes (32). Relatives from these affected families were then contacted and interviewed, and those who agreed to further participate underwent a DCCT-standardized history and physical exam (n = 241). These relatives were then classified into either type 1 or type 2 diabetes by an algorithm based on reported requirements for insulin, age of onset of diabetes, duration of diabetes, and measured C-peptide level (if obtained) (32). Positive family history of type 2 diabetes was found in 61 of 582 intensive therapy subjects and 54 of 586 conventional therapy subjects.

Body mass index, body mass index, and blood pressure. Height (cm) was measured using a stadiometer, and weight (kg) was measured on the same balance-beam scale for the duration of the trial (subjects were in lightweight clothing and stockinged feet) (30). BMI was calculated as weight in kilograms divided by the square of height in meters. Waist-to-hip ratio (WHR) was calculated from measurements obtained at the final follow-up visit. Natural hip and waist circumferences were available at follow-up in 541 intensive therapy subjects and 548 conventional therapy subjects. Measurements were performed twice by study-certified dietitians using inelastic tapes, and if they differed by >0.5 cm, they were repeated. The waist measurement was taken at the level of the natural waist. The hip measurement was taken at the maximum extension of the buttocks with the subject in the relaxed standing posture. Blood pressures were measured using standard techniques in the right arm.

Severe hypoglycemia. Episodes of severe hypoglycemia were defined as symptoms consistent with hypoglycemia requiring the assistance of others for treatment and confirmed with blood glucose levels <2.8 mmol/l (50 mg/dl) or reversal of symptoms by oral or intravenous glucose or subcutaneous glucagon (26,27).

Laboratory methods. Fasting triglyceride, total cholesterol, and HDL cholesterol were measured using enzymatic methods (33). LDL cholesterol was calculated by the Friedewald equation. Hba1c was determined as previously described (34,35).

Additional samples from the final follow-up visit were shipped on dry ice to laboratories in Seattle, Washington, and stored at −80°C. These samples were then assayed for lipoprotein density distribution by nonequilibrium density gradient ultracentrifugation, using a modification of a previously described technique and a vertical rotor (Beckman VTi-65; Beckman Instruments, Fullerton, CA) (36,37). Of the 38 sequential fractions collected for cholesterol analysis, HDL particles were located in fractions 1–6, LDL in fractions 7–18, intermediate-density lipoprotein (IDL) in fractions 19–20, and VLDL in fractions 20–30–38. For each of the 4th and 5th yr subjects, using the algorithm based on reported requirements for insulin, age of onset of diabetes, duration of diabetes, and measured C-peptide level (if obtained) (32). Positive family history of type 2 diabetes was found in 61 of 582 subjects previously assigned to the conventional therapy group and 498 subjects previously assigned to the intensive therapy group, and it was measured for GAD65 and IA-2 antibody titers by radio-binding immunosassays, as previously described (39). Antibody titers were considered positive when they exceeded the 99th percentile based on 200 nondiabetic control subjects (antibody indexes of 0.085 and 0.017 for GAD65 and IA-2, respectively) (39).

Statistical analysis. Comparisons between subject groups were performed by t test of means when results followed normal distributions or a rank-sum test (Mann-Whitney) when results were not normally distributed. Two-way ANOVA was used to test for significant interaction for weight gain in subjects categorized by family history of type 2 diabetes and the frequency of severe hypoglycemic episodes. Differences between groups in the proportions of subjects positive for GAD65 and IA-2 antibodies and subjects with a family history of type 2 diabetes were tested using a 2 test. To test for significant differences in cholesterol distributions in the various lipoprotein subfractions between groups of subjects, a difference plot is generated by subtracting the mean cholesterol value of each fraction in the first group from the mean cholesterol value in the same fraction of the second group and determining the 95% CI for this difference. A difference in fractional cholesterol content between groups becomes significant (P < 0.05) when the 95% CI does not cross the zero line.

RESULTS

Family history of type 2 diabetes. At baseline, the ratio of men to women, BMI, Hba1c, and insulin dose were the same for subjects with and without a family history of type 2 diabetes (Table 1). Subjects with a family history were slightly older and had lower HDL cholesterol levels than subjects without a family history (Table 1).

At follow-up, glycemic control was similar for subjects with and without a family history in the conventional and intensive therapy groups; however, the intensive therapy group with a family history required a greater insulin dose to achieve target glycemic control than the intensive therapy group without a family history (Table 2).

With conventional therapy, the amount of weight gained was the same for all subjects regardless of family history (change in BMI: 1.2 ± 1.9 kg/m2 for both groups [mean ± SD]) (Fig. 1A), and their BMI values at follow-up were not different (Table 2). The proportion of subjects with a family history was the same in each of the weight-gain quartiles (Q1 8%, Q2 8%, Q3 11%, and Q4 11%; P = 0.56).
With intensive therapy, subjects with a family history had a greater increase in BMI from baseline to follow-up compared with subjects with no family history (change in BMI: 3.8 ± 2.8 vs. 2.9 ± 3.2 kg/m² for subjects with and without a family history, respectively; \( P = 0.004 \)) (Fig. 1B) and had a greater final BMI (Table 2). Although the frequency distributions of subjects in the lower BMI range were similar at follow-up for both groups (Fig. 1), subjects with a family history of diabetes showed greater skewing toward higher BMI (suggesting a second mode) than the subjects with no family history (Fig. 1B). The proportion of subjects with a family history increased in successive quartiles of weight gain with intensive therapy (Q1 7%, Q2 8%, Q3 12%, and Q4 14%), but this trend did not reach statistical significance (Q1 vs. Q4, \( P = 0.06 \)).

Subjects with a family history had greater waist circumferences and WHRs than subjects with no family history in both conventional and intensive therapy, although these differences were accentuated in the intensive therapy group (Table 2). Blood pressures at follow-up were not statistically different between the groups with either conventional or intensive therapy, regardless of family history (Table 2).

Lipid levels increased in both groups with conventional therapy, regardless of family history, but at follow-up, total and LDL cholesterol was higher in the group with a family history than the group without (Table 2). The difference plot of the density gradient ultracentrifugation at follow-up, a technique that studies the distribution of cholesterol among specific lipoprotein fractions, shows that higher cholesterol in the group with a family history compared with the group with none was nearly all due to an increase in cholesterol in the LDL subfractions (Fig. 2). With intensive therapy, triglyceride levels were lower and total cholesterol tended lower at follow-up in the group without a family history. However, in the group with a family history, triglycerides did not decrease with intensive therapy and total and LDL cholesterol levels increased compared with baseline, resulting in higher triglyceride and total and LDL cholesterol levels compared with the group with no family history. The difference plot of the density gradient ultracentrifugation (Fig. 3) for these groups shows that the group with a family history of diabetes had significantly higher cholesterol levels in VLDL, IDL, and LDL subfractions compared with the group with no family history. Higher levels of apolipoprotein B paralleled this increase in cholesterol in the groups with a family history in both conventional and intensive therapies compared with the groups with no family history (Table 2).

**Severe hypoglycemia and weight gain.** The total number of severe hypoglycemic episodes was more than threefold greater in the intensive therapy group than in the conventional therapy group (2,148 vs. 633, respectively, \( P < 0.001 \)). In the combined group of intensive and conventional therapy subjects, the change in BMI for the duration of the study had a linear relation to the frequency of hypoglycemic episodes (number of episodes per year), but only 2% of the variance of weight change could be attributed to the number of hypoglycemic episodes (\( r^2 = 0.016, P < 0.001 \)). When each treatment group was studied separately, however, the change in BMI during the study was not significantly related to the frequency of hypoglycemic episodes for either the conventional or intensive therapy groups (Fig. 4). Identical results were obtained when the total number of severe hypoglycemic episodes, instead of hypoglycemia frequency, was used as the dependent variable. In addition, an interactive relationship between hypoglycemia frequency and family history of diabetes could not be demonstrated by two-way ANOVA for either treatment group (data not shown).

**GAD65 and IA-2 positivity.** The frequency of GAD65 and IA-2 positivity was the same for subjects in the conventional (69% positive for GAD65 or IA-2; 44% for GAD65, 45% for IA-2) and intensive therapy groups (70% positive for GAD65 or IA-2; 47% for GAD65, 47% for IA-2). Furthermore, the frequency of GAD65 and IA-2 positivity was not different for subjects with (70% positive for GAD65 or IA-2; 45% for GAD65, 48% for IA-2) or without (69% positive for GAD65 or IA-2; 52% for GAD65, 38% for IA-2) a family history of type 2 diabetes and for intensive therapy–treated subjects stratified by weight-gain quartile (positive for GAD 65 or IA-2: Q1 66%, Q2 70%, Q3 71%, and Q4 73%; \( P = 0.61 \)).

**DISCUSSION**

We have previously shown that a subset of subjects with type 1 diabetes will gain an excess amount of weight with intensive therapy (4). This group represented the highest

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**TABLE 1**

Baseline demographics of subjects with and without a family history of type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>No family history</th>
<th>Family history</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>1,053</td>
<td>115</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29 ± 5.7</td>
<td>30 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>Men/women (%)</td>
<td>55/45</td>
<td>56/44</td>
<td>0.92</td>
</tr>
<tr>
<td>Conventional/intensive therapy (%)</td>
<td>51/49</td>
<td>47/53</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 2.7</td>
<td>24.1 ± 2.8</td>
<td>0.13</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.8 ± 1.5</td>
<td>8.8 ± 1.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Insulin dose (units · kg⁻¹ · day⁻¹)</td>
<td>0.62 ± 0.21</td>
<td>0.60 ± 0.19</td>
<td>0.57</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>0.90 ± 0.53</td>
<td>0.95 ± 0.43</td>
<td>0.06</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.60 ± 0.85</td>
<td>4.65 ± 0.93</td>
<td>0.24</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.84 ± 0.75</td>
<td>2.97 ± 0.80</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.32 ± 0.31</td>
<td>1.27 ± 0.31</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>115 ± 12</td>
<td>115 ± 12</td>
<td>0.90</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73 ± 8.5</td>
<td>73 ± 9.5</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Data are means ± SD. BP, blood pressure.
quartile (or highest 25%) of weight gain with intensive therapy, which had an average BMI of 31 kg/m² at the close of the DCCT. This weight meets the criterion for obesity (≥30 kg/m²), and this 25% prevalence of obesity is close to that reported for the general population (22.5%) at the time the DCCT concluded (40). Although obesity results from a complex interaction of genetics and environment, studies have estimated that 40–70% of obesity-related phenotypes are heritable (41). Therefore, we reasoned that these same genetic traits would be present in subjects with type 1 diabetes and that with near normalization of glucose control and elimination of significant glycosuria, this genetic tendency for overweight would express itself.

The DCCT Family Study contacted family members of DCCT probands identified as having diabetes (32). Information obtained from this contact allowed further classi-
fication of these first-degree relatives as having either type 1 or type 2 diabetes. Body weights of these family members were also obtained, and in a previous study (32), the reported percentage ideal body weight was higher in relatives classified as having type 2 diabetes (134%) than in those classified as having type 1 diabetes (109%). This sampling of first-degree relatives came, however, from a subset of the entire DCCT cohort (372 of the 1,441 DCCT participants). A limitation of the present study, therefore, is that because the DCCT Family Study did not obtain body weights of first-degree relatives from all participants, it was not possible to directly determine whether the DCCT subjects who gained excess weight with intensive therapy came from families that were also obese. Instead, we reasoned that because type 2 diabetes is both highly heritable and strongly associated with obesity, a family history of type 2 diabetes might be a genetic marker for susceptibility to weight gain with intensive therapy.

In the present study, there is a tendency toward a higher proportion of subjects having a family member with type 2 diabetes in each successive quartile of weight gain with intensive therapy (Q1 7% vs. Q4 14%, $P = 0.06$), but the key finding is that a family history of diabetes predicts increased weight gain in subjects with type 1 diabetes practicing intensive but not conventional therapy. Compared with those subjects with no family history of diabetes from the same subfractions in the group without a family history of diabetes from the same subfractions in the group with a family history of diabetes with 95% CIs for the mean difference for each fraction. Mean peak LDL particle density (LDL density or Rf) was the same for each group: 0.30 vs. 0.30, groups with versus without a family history, respectively ($P = 0.65$).

**FIG. 2.** A: Distribution of lipoprotein cholesterol across subfractions (VLDL, IDL, LDL, and HDL) using nonequilibrium density gradient ultracentrifugation comparing the groups with (○) and without (●) family history of diabetes on conventional therapy. B: The difference plot shows subtracted mean cholesterol levels of subfractions in the group without a family history of diabetes from the same subfractions in the group with a family history with 95% CIs for the mean difference for each fraction. Mean peak LDL particle density (LDL density or Rf) was the same for each group: 0.30 vs. 0.30, groups with versus without a family history, respectively ($P = 0.09$).

**FIG. 3.** A: Distribution of lipoprotein cholesterol across subfractions (VLDL, IDL, LDL, and HDL) using nonequilibrium density gradient ultracentrifugation comparing the groups with (○) and without (●) a family history of diabetes on intensive therapy. B: The difference plot shows subtracted mean cholesterol levels of subfractions in the group with a family history of diabetes from the same subfractions in the group with a family history of diabetes with 95% CIs for the mean difference for each fraction. Mean peak LDL particle density (LDL density or Rf) was the same for each group: 0.31 vs. 0.31, groups with versus without a family history, respectively ($P = 0.99$).
Mechanism responsible for producing the bimodal appearance of obesity and diabetes. Furthermore, it is possible that in some individuals these obesity factors are associated with a family history of type 2 diabetes. The frequency of severe hypoglycemia was not linearly related to weight gain with either conventional or intensive therapy groups considered separately. When the two groups were combined, the number of hypoglycemic episodes could only account for 2% of the weight gain that occurred over the duration of the study. While the data here do not support a major role for hypoglycemia in the expression of weight gain with intensive therapy, a significant limitation to this analysis is the lack of information on mild to moderate episodes of hypoglycemia that occurred in these cohorts, which were data collected as part of the smaller initial DCCT cohort study but not in the entire group over the duration of the study. Therefore, it is still possible that less severe hypoglycemia contributed significantly to excess weight gain with intensive therapy.

In summary, a subset of subjects with type 1 diabetes who had a family history of type 2 diabetes gained more weight with intensive therapy than those who had no family history. This increased weight gain was centrally distributed, accompanied by a greater insulin requirement, and associated with dyslipidemia common in the insulin resistance syndrome and type 2 diabetes. The frequency of severe hypoglycemia was not linearly related to weight gain with either conventional or intensive therapy, but such a relationship might be found in other datasets that include measurements of mild and moderate hypoglycemic episodes. Islet cell autoimmunity in the form of GAD65 and IA-2 positivity had no relationship to weight gain with either conventional or intensive therapy. Therefore, type 1 diabetic patients with a family history of type 2 diabetes practicing intensive therapy represent a group that should be monitored for potentially adverse changes in risk factors for macrovascular complications.

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