The Effect of Excess Weight Gain With Intensive Diabetes Mellitus Treatment on Cardiovascular Disease Risk Factors and Atherosclerosis in Type 1 Diabetes Mellitus

Results From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) Study

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Background—Intensive diabetes mellitus therapy of type 1 diabetes mellitus reduces diabetes mellitus complications but can be associated with excess weight gain, central obesity, and dyslipidemia. The purpose of this study was to determine whether excessive weight gain with diabetes mellitus therapy of type 1 diabetes mellitus is prospectively associated with atherosclerotic disease.

Methods and Results—Subjects with type 1 diabetes mellitus (97% white, 45% female, mean age 35 years) randomly assigned to intensive or conventional diabetes mellitus treatment during the Diabetes Control and Complications Trial (DCCT) underwent intima-media thickness (n=1015) and coronary artery calcium score (n=925) measurements during follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Intensive treatment subjects were classified by quartile of body mass index change during the DCCT. Excess gainers (4th quartile, including conventional treatment subjects meeting this threshold) maintained greater body mass index and waist circumference, needed more insulin, had greater intima-media thickness (+5%, P<0.001 DCCT year 1, P=0.003 DCCT year 6), and trended toward greater coronary artery calcium scores (odds ratio, 1.5; confidence interval, 0.97 to 2.49; P=0.07) than minimal gainers. DCCT subjects meeting metabolic syndrome criteria for waist circumference and blood pressure had greater intima-media thickness in both EDIC years (P=0.02 to <0.001); those meeting high-density lipoprotein criteria had greater coronary artery calcium scores (odds ratio, 1.6; confidence interval, 1.1 to 2.4; P=0.01) during follow-up. Increasing frequency of a family history of diabetes mellitus, hypertension, and hyperlipidemia was associated with greater intima-media thickness with intensive but not conventional treatment.

Conclusions—Excess weight gain in DCCT is associated with sustained increases in central obesity, insulin resistance, dyslipidemia and blood pressure, as well as more extensive atherosclerosis during EDIC.


Key Words: calcium ■ carotid intima-media thickness ■ coronary vessels ■ diabetes mellitus, type 1 ■ imaging, diagnostic ■ obesity

Intensive therapy (INT) of type 1 diabetes mellitus (T1DM) reduces the incidence and progression of microvascular complications,1 risk factors for macrovascular complications,2 coronary artery calcium (CAC),3 and intima-media wall thickness (IMT).4 After 17 years of combined follow-up in the randomized, controlled Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC), INT was also shown to reduce the incidence of major cardiovascular disease (CVD) events by 58% compared with conventional therapy (CONV).5

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and who then elected to continue in the EDIC study and underwent
during treatment, meeting criteria for obesity. Compared
observational studies of T1DM.10,11
associated with increased risk of CVD events and mortality in
≥
included in this analysis are a subset of the original 1441 DCCT
until the final closeout visit in 1993, a mean of 6.5 years. Annual
versus CONV diabetes mellitus therapy in the DCCT and were treated
During 1983 to 1989, 1441 subjects were randomly assigned to INT
Subjects
of type 2 diabetes mellitus (T2DM),12 we hypothesized that
excess weight gain, components of MetS, and other nontradi-
tional CVD risk factors during the DCCT with carotid IMT
had greater mean waist circumference; increased levels of
low-density lipoprotein (LDL) cholesterol, triglyceride, and
small-dense LDL particles; and lower high-density lipopro-
tein (HDL) cholesterol levels.6 The greater central distribu-
tion of body weight and dyslipidemia associated with this
weight gain is consistent with the hallmark characteristics
of the metabolic syndrome (MetS), typically seen in subjects
with insulin resistance and type 2 diabetes mellitus;7–9 but also
associated with increased risk of CVD events and mortality in
observational studies of T1DM.10,11
In the present analyses we examine relationships between
excess weight gain, components of MetS, and other nontradi-
ctional CVD risk factors during the DCCT with carotid IMT
and CAC during follow-up in EDIC. In addition, based on our
finding of increased susceptibility to weight gain and dyslip-
idemia in INT-treated DCCT subjects with a parental history
of type 2 diabetes mellitus (T2DM),12 we hypothesized that
family histories of T2DM, hypertension, and hyperlipidemia
would be associated with worsening markers of atheroscle-ro-
is in the INT-treated subjects during follow-up in EDIC.

Methods
Subjects
During 1983 to 1989, 1441 subjects were randomly assigned to INT
versus CONV diabetes mellitus therapy in the DCCT and were treated
until the final closeout visit in 1993, a mean of 6.5 years. Annual
follow-up in EDIC was initiated in 1994 (EDIC year 1). Participants
included in this analysis are a subset of the original 1441 DCCT
subjects who were aged ≥18 years at baseline (n = 1168),6 survived,
and who then elected to continue in the EDIC study and underwent
measurements of IMT at years 1 and 6 of EDIC (n = 1015), and CAC
at EDIC year 8 (n = 925; Figure 1 in the online-only Data Supplement).
The average ± SD age for the group at DCCT closeout visit was
35 ± 5.7 years, 45% were female, and 97% were white. Participants
were categorized by quartile change in BMI during the DCCT within
their respective treatment groups.6 The ranges of change in BMI for
each quartile in the INT group were as follows: from −0.27 to 0.95
kg/m² in quartile 1; from 0.96 to 2.44 kg/m² in quartile 2; from 2.45
to 4.37 kg/m² in quartile 3; and from 4.39 to 17.7 kg/m² in quartile 4.
For reference, a change in 1 BMI unit for a male with a height of 1.76
m (5' 9.5") represents 3.1 kg and for a woman with a height of 1.62 m
(5' 4") represents 2.6 kg. In contrast, the highest quartile of change in
BMI in the CONV group was from 2.24 to 8.86 kg/m².

Herein, excess gainers are defined as those whose BMI increased
by at least 4.39 kg/m² during the DCCT, the cutoff for the fourth
quartile of BMI change in the INT group during the DCCT. For the
present study, subjects in the CONV group who met this criterion
were also classified as excess gainers.

In addition, because the amount of weight gain in the first through
third quartiles in the INT therapy group were close in range and
nearly half that of the fourth quartile (Figure 1), data from the first 3
quartiles were combined (minimal gainers, n = 394) for comparison
with the excess gainers (n = 122). In the CONV, 23 (4.6%) subjects
met criteria for excess gainer, and the remaining 476 subjects were
classified as minimal gainers. Baseline ages, duration of diabetes
mellitus, and BMIs were the same in all BMI change quartiles in
both the INT and CONV groups, as were hemoglobin A1c values at
the final DCCT closeout visit with INT after a mean of 6.5 years of
treatment.6 Family histories of T2DM, as well as hypertension and
hyperlipidemia, were obtained at the baseline visit in DCCT.
Measurements of lipid levels, blood pressure, and waist circumfer-
ence obtained at the DCCT closeout visit were classified according to
MetS criteria from the National Cholesterol Education Program.7

Intima-Media Thickness
Carotid ultrasonography was performed ≥1 and 6 years after the ini-
tiation of the EDIC study (approximately 8 and 13 years, respectively,
after the beginning of the DCCT).4,13 Carotid IMT (mm) was mea-
sured by a single longitudinal lateral view of the distal 10 mm of
the right and left common carotid arteries and 3 longitudinal views
in different imaging planes of each internal carotid artery.14 Studies
were read in a central unit (Tufts University, Boston, MA) by a single
reader, who was masked to the subjects’ treatment assignments and
the time of the studies (year 1 versus year 6).

Computed Tomography of Coronary Artery
Calcium
Computed tomography was performed once during approximately
the 8th EDIC year, between 11 to 20 years after enrolment into the

Figure 1. Body mass index (BMI; left graph) and waist circumference (right graph) of subjects treated intensively in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) cohort during the DCCT and study years 1 and 6 of EDIC. P < 0.001 for both BMI and waist circumference comparing the fourth quartile of weight gain during the DCCT (Q4, excess gainers; n = 122) vs quartiles Q1–Q3 (n = 394, minimal-gainers, shown in graphs separately) at each study time point by Mann–Whitney rank sum test. Waist circumference not measured at DCCT baseline. Results are mean ± SE.
Table 1. Glycemic Control, Lipid Levels, and Blood Pressure Among Minimal Gainers (n=394) Versus Excess Gainers (n=122) With Treatment in the EDIC/DCCT Cohort

<table>
<thead>
<tr>
<th></th>
<th>DCCT Closeout</th>
<th>EDIC Year 1</th>
<th>EDIC Year 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimal Gainers</td>
<td>Excess Gainers</td>
<td>P Value</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>7.1 ± 1.1</td>
<td>7.1 ± 1.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Insulin dose, u/kg/day</td>
<td>0.62 ± 0.20</td>
<td>0.74 ± 0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>0.84 ± 0.52</td>
<td>1.0 ± 0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol level, mmol/L</td>
<td>Total</td>
<td>4.6 ± 0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>2.8 ± 0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>1.4 ± 0.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>3.2 ± 0.77</td>
<td>3.6 ± 0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent with LDL&gt;2.59 mmol/L, %</td>
<td>62</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>115 ± 12</td>
<td>119 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74 ± 8.8</td>
<td>77 ± 8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MetS criteria WC, %</td>
<td>4</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MetS criteria HC</td>
<td>24</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>HDL, %</td>
<td>4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>MetS criteria TP, %</td>
<td>15</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>No. of criteria met</td>
<td>0, %</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>1, %</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>2, %</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>3, %</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4, %</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Results are mean ± SD. Metabolic syndrome criteria defined using NCEP criteria. BP indicates blood pressure; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications study; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglyceride; and WC, waist circumference.

*χ² test for proportion of subjects who met 0 to 4 MetS criteria.

Statistical Analyses

Comparisons of quantitative variables between excess gainers versus minimal gainers were made using the Mann–Whitney rank sum test. Proportions of medication use and MetS criteria between groups were tested by χ² analysis. Prospective associations of IMT and CAC scores using lipid and clinical outcome variables determined at the closeout visit of the DCCT, including MetS criteria, were tested using multiple linear regression for IMT and multiple logistic regression for CAC scores. Covariates included in the regression analyses represent updated, weighted (adjusted for differences in sampling schedule between DCCT and EDIC study visits) mean values at the time the imaging measure was obtained—EDIC years 1 and 6 for IMT and EDIC year 8 for the CAC. Bonferroni correction was used for analyses of repeated measures. Statistical analyses were performed using SAS version 9.1.

Results

Change in Weight, Waist Circumference, Lipids, Blood Pressure, and Metabolic Syndrome Criteria Among Excess Gainers Versus Minimal Gainers During EDIC

From the DCCT closeout visit until EDIC year 6, INT and CONV subjects originally categorized as minimal gainers at
the DCCT closeout visit continued to gain weight (P < 0.001 for both treatment groups; Figure 1 and Figure II in the online only Data Supplement). INT and CONV subjects originally categorized as excessive weight gainers experienced slight, but nonsignificant, weight gain during this same time (Figure 1 and Figure II in the online only Data Supplement). All weight gain groups, however, experienced significant increases in waist circumferences (P < 0.001; Figure 1 and Figure II in the online only Data Supplement). In addition, the separations in BMI and waist circumference between the excess gainers and the minimal gainers were maintained during EDIC follow-up (Table I and Table I in the online only Data Supplement).

With INT, although both the excess gainers and minimal gainers had similar glycemic control at the closeout visit in the DCCT and experienced rises in hemoglobin A1c levels during EDIC follow-up (Table 1), the rise in hemoglobin A1c was significantly greater in the excess gainers compared with the minimal gainers despite using greater insulin doses (Table 1). With CONV, insulin dose was higher and hemoglobin A1c level trended lower at the DCCT closeout visit in the excess than the minimal gainers (Table I in the online only Data Supplement); both weight gain groups experienced improvement in glycemic control during EDIC follow-up with similar A1c and insulin doses by EDIC year 6 (Table I in the online only Data Supplement).

At the DCCT closeout visit, levels of total cholesterol, LDL, non-HDL cholesterol, and percent of subjects with LDL > 2.59 mmol/L (100 mg/dL) were higher in excess gainers than minimal gainers with INT, and remained higher at both EDIC follow-up visits (Table 1). HDL cholesterol was lower among excess gainers than minimal gainers at the DCCT closeout visit and EDIC year 1 visits (Table 1). By EDIC year 6, however, HDL cholesterol had increased in both groups such that levels were no longer statistically different between them, which occurred despite the weight gain and significant increases in TG levels experienced by both groups (Table 1). During EDIC follow-up, use of lipid lowering medications was greater in the excess gainers than minimal gainers (7% at EDIC year 1, 26% at EDIC year 6, and 48% by EDIC year 8–9 for excess gainers versus 2%, 11%, and 32% for corresponding time points in minimal gainers, respectively; P = 0.003, < 0.001, and P = 0.04, respectively). Of the lipid values measured only at the DCCT closeout visit, mean (± SD) levels of apolipoprotein B (0.89 ± 0.18 versus 0.81 ± 0.22 g/L; P < 0.001) and LDL peak particle density (Rf, 0.30 ± 0.024 versus 0.31 ± 0.023; P = 0.004) were higher among excess gainers than minimal gainers, but Lipoprotein (a) levels were not different (0.69 ± 0.70 versus 0.66 ± 0.69 mmol/L; P = 0.28). Systolic and diastolic blood pressures were higher among excess gainers than minimal gainers at each study visit (P < 0.001), despite greater use of medications for hypertension in the excess gainers compared with the minimal gain group (17% at EDIC year 1, 44% at EDIC year 6, and 88% by EDIC year 8–9 for excess gainers versus 9%, 27%, and 48% for corresponding time points in minimal gainers, respectively; all comparisons P < 0.001). For the CONV group, there were no significant differences in lipid levels or blood pressure at any time point (Table I in the online only Data Supplement).

### Table 2. Association of Excess Weight Gain With Treatment in the DCCT and Carotid Intima Media Thickness Measured at EDIC Year 1 (n = 1015)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive gainers vs minimal gainers</td>
<td>0.025</td>
<td>0.0073</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intensive vs conventional therapy</td>
<td>-0.0074</td>
<td>0.0063</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>-0.026</td>
<td>0.0053</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Age</td>
<td>0.0052</td>
<td>0.00043</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>0.0015</td>
<td>0.0025</td>
<td>0.56</td>
</tr>
<tr>
<td>Albumin excretion rate</td>
<td>0.0000080</td>
<td>0.000019</td>
<td>0.68</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.00278</td>
<td>0.00072</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.0035</td>
<td>0.00048</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>0.0088</td>
<td>0.0063</td>
<td>0.16</td>
</tr>
<tr>
<td>Site of machine measurement</td>
<td>-0.0016</td>
<td>0.00035</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multiple linear regression analysis. See text for definition of excessive gainers and minimal gainers. Covariates are weighted means. BP indicates blood pressure; DCCT, Diabetes Control and Complications Trial; and EDIC, Epidemiology of Diabetes Interventions and Complications study. *Bonferroni significance threshold, P = 0.025.

At the DCCT closeout visit, among minimal gainers in INT, MetS criteria for HDL cholesterol and blood pressure were most commonly met, whereas excess gainers most commonly met HDL, blood pressure, and waist circumference criteria (Table 1). Similarly, the most frequent MetS criteria met by minimal gainers in CONV at the DCCT closeout visit were HDL cholesterol and blood pressure. On the other hand, excess gainers in CONV had roughly equal proportions meeting waist circumference, lipids, and blood pressure criteria (Table I in the online only Data Supplement). Proportionally more excess weight gainers than minimal gainers met ≥1 MetS criteria at each DCCT and EDIC study visit in both INT (Table 1; P < 0.001 for each time point) and CONV groups (Table I in the online only Data Supplement; P = 0.05, < 0.001, and < 0.05 for DCCT closeout, EDIC year 1, and EDIC year 6, respectively).

### Intima-Media Thickness

IMT at EDIC year 1 was greater among excess gainers than minimal gainers (P < 0.001), remaining significant with adjustments for treatment group (INT versus CONV), age, sex, smoking status, type of scanning machine used, and updated, weighted mean values for urinary albumin excretion rate, hemoglobin A1c, and diastolic and systolic blood pressure levels (Table 2). Both excess and minimal gainers experienced increases in IMT thickness between years 1 and 6 of follow-up (P < 0.001; Figure 2, data shown for INT group only); however, there was an incrementally higher mean IMT among excess gainers versus minimal gainers at year 6 (P = 0.006; Table 3).

When traditional lipid risk factors (eg, LDL cholesterol, HDL cholesterol, and triglyceride levels) measured at the DCCT closeout were added to the multivariable models presented in Tables 2 and 3, excess gainers continued to show significantly greater IMT compared with minimal-gainers at year 1 (P = 0.003) and at year 6 (P = 0.02). Nontraditional
lipid risk factors measured at the DCCT closeout visit were also tested for association with IMT at EDIC years 1 and 6. These included apolipoprotein B, LDL, peak particle density (relative flotation rate or RF), Lipoprotein (a), and non-HDL cholesterol. When each was added individually to a model that included LDL, triglyceride, HDL, as well as adjustments for age, sex, and machine used, none independently reached significance with IMT at either time point or improved the model fit.

Table 3. Association of Excess Weight Gain With Treatment in the DCCT and Carotid Intima Media Thickness Measured at EDIC Year 6 (n = 1015)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Standard Error</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive gainers vs non-gainers</td>
<td>0.0287</td>
<td>0.010</td>
<td>0.006</td>
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<tr>
<td>Intensive vs conventional therapy</td>
<td>-0.0232</td>
<td>0.0082</td>
<td>0.005</td>
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<tr>
<td>Sex (female vs male)</td>
<td>-0.032</td>
<td>0.0076</td>
<td>&lt;0.001</td>
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<td>Age</td>
<td>0.0068</td>
<td>0.00063</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>-0.0000865</td>
<td>0.00358</td>
<td>0.81</td>
</tr>
<tr>
<td>Albumin excretion rate</td>
<td>0.0000024</td>
<td>0.00000187</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.00268</td>
<td>0.000102</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.0042</td>
<td>0.00065</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>0.034</td>
<td>0.0096</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Site of machine measurement</td>
<td>0.00072</td>
<td>0.00050</td>
<td>0.14</td>
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</table>

Multiple linear regression analysis. See text for definition of excessive gainers and minimal gainers. Covariates are weighted means. BP indicates blood pressure; DCCT, Diabetes Control and Complications Trial; and EDIC, Epidemiology of Diabetes Interventions and Complications study. Bonferroni significance threshold, P = 0.025.

Table 4. Association of Excess Weight Gain With Treatment in the DCCT and Presence of Coronary Artery Calcium Accumulation (Score >6.25) in EDIC (n = 925)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive gainers vs minimal gainers</td>
<td>1.55</td>
<td>0.97 to 2.49</td>
<td>0.07</td>
</tr>
<tr>
<td>Intensive vs Conventional Therapy</td>
<td>0.98</td>
<td>0.68 to 1.42</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex (Female vs Male)</td>
<td>0.34</td>
<td>0.24 to 0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.13</td>
<td>1.10 to 1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>1.25</td>
<td>1.06 to 1.49</td>
<td>0.01</td>
</tr>
<tr>
<td>Albumin Excretion Rate</td>
<td>1.001</td>
<td>1.000 to 1.002</td>
<td>0.27</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.97</td>
<td>0.93 to 1.02</td>
<td>0.26</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.024</td>
<td>0.99 to 1.06</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoking (yes/no)</td>
<td>2.19</td>
<td>1.43 to 3.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT scanner type</td>
<td>1.00</td>
<td>0.97 to 1.02</td>
<td>0.86</td>
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</table>

Multiple logistic regression analysis. See text for definition of excessive gainers and minimal gainers. Covariates are weighted means. BP indicates blood pressure; CI, confidence interval; CT, computed tomography; DCCT, Diabetes Control and Complications Trial; and EDIC, Epidemiology of Diabetes Interventions and Complications study.

Coronary Artery Calcium

The likelihood of having an increased CAC score (>6.25) trended higher among excess gainers compared with minimal gainers (odds ratio [OR], 1.55; confidence interval [CI], 0.97–2.49; P = 0.07: Table 4; Figure 3 showing data for INT group only) after accounting for updated, weighted mean values of covariates and lost even borderline significance with further adjustment for traditional lipid risk factors (LDL cholesterol, HDL cholesterol, and triglycerides; OR, 1.48; 95% CI, 0.91–2.40; P = 0.12). None of the nontraditional lipid variables individually added to a model that included LDL, triglyceride, and HDL levels, as well as adjustments for age, sex, and machine used, independently reached significance or improved the model fit.

Mets Criteria

The associations of meeting individual MetS criteria, irrespective of weight gain, using variables measured at the DCCT

Figure 2. Intima media thickness (IMT) of the common carotid of conventionally (CONV; n = 499) and intensively (INT) treated Diabetes Control and Complications Trial (DCCT) subjects, measured at Epidemiology of Diabetes Interventions and Complications Study (EDIC) years 1 and 6. *P < 0.001 vs minimal gainers with intensive therapy (n = 394) in years 1 and 6. †P < 0.001 vs excess gainers with intensive therapy (n = 122) EDIC year 1. ‡P = 0.003 and §P = 0.03 vs excess gainers in year 1 and 6, respectively. Analysis by Mann–Whitney Rank Sum Test (for fully adjusted significance values, see Tables 2 and 3). Box plots respectively. Analysis by Mann–Whitney Rank Sum Test (for fully adjusted significance values, see Tables 2 and 3). Box plots show 5th, 10th, 25th, median, 75th, 90th, and 95th percentiles lines, bottom to top.

Figure 3. Distribution of coronary artery calcification (CAC) scores of subjects treated intensively in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) cohort, excess gainers versus minimal gainers during DCCT. See Table 4 for significance.
closeout visit with IMT thickness and CAC accumulation were tested (Table 5). Including covariates for age, sex, treatment group assignment, study performance site, smoking status, and updated, weighted mean values for hemoglobin A1c, albumin excretion rate, and total and LDL cholesterol, meeting MetSyn criteria for blood pressure and waist circumference was associated with greater IMT at EDIC years 1 ($P=0.02$ and $<0.001$, respectively) and 6 ($P<0.001$ for both). Meeting triglyceride criteria became significantly associated with increased IMT at EDIC year 6 ($P=0.04$). HDL criteria was not associated with IMT at either EDIC year but was the only MetSyn criteria associated with CAC accumulation ($P=0.01$).

### Family History
Most subjects (753 of 1015, or 74%) reported a family history of T2DM, hyperlipidemia, or hypertension. After adjusting for age, sex, machine type, smoking status, urinary albumin excretion rate, and hemoglobin A1c, increasing frequency of ≥1 of these familial diagnoses in the INT group was associated with increasing IMT thickness at both EDIC year 1 (regression coefficient = 0.011, standard error = 0.0038, $P=0.004$) and EDIC year 6 (regression coefficient = 0.014, standard error = 0.0050, $P=0.007$). On the other hand, CAC scores were not significantly associated with these family histories (OR, 1.05; 95% CI, 0.81–1.37; $P=0.70$) in the INT group. Corresponding analyses for CONV were all nonsignificant: IMT EDIC year 1, $P=0.58$; IMT EDIC year 6, $P=0.56$; CAC, $P=0.56$.

### Discussion
The DCCT study previously demonstrated that weight gain and obesity were associated with INT of T1DM, but little is known about the effect of this weight gain on CVD risk factors and outcomes. With longer follow-up of the DCCT subjects during EDIC, we have shown that the original DCCT groups continued to gain weight accompanied by increases in waist circumference and insulin dose (units/kg), and that those in the highest quartile of weight gain (excess weight gainers) maintained their average BMI in the obese range (≥30 kg/m²).

Along with the increase in central obesity and presumed insulin resistance (higher insulin needs for similar or worse hemoglobin A1c levels), lipid and blood pressure levels worsened during EDIC follow-up among excess gainers versus minimal gainers with INT. Of note is the paradoxical rise in LDL cholesterol during EDIC follow-up in both excess gainers and minimal gainers with INT. This occurred despite increases in central adiposity (waist circumference) and triglyceride levels in both groups, conditions usually associated with lower, more atherogenic HDL levels in association with increased activities of the enzymes involved in depleting cholesterol from HDL, including lecithin:cholesterol acyltransferase enzyme activity,17 changes in endothelial lipase,18 or other alterations leading to increased cholesterol efflux or reduced HDL clearance. In addition, the percentage of subjects meeting ≥1 criteria of metabolic syndrome (not including impaired fasting glucose) was greater in excess gainers than minimal gainers at the DCCT closeout visit and remained so during EDIC years 1 and 6.

Increased IMT is a measure of subclinical atherosclerosis and a predictor of cardiovascular events in the general population24 and has been shown to be greater in patients with T1DM compared with controls without diabetes mellitus.13,22,23 Excess weight gain in the DCCT was associated with increased IMT at both years 1 and 6 of follow-up in EDIC compared with the minimal gainers, differences that may have been attenuated by the increased use of blood pressure and lipid-lowering medications in the excess gainers. CAC is another subclinical marker associated with increased risk for cardiovascular disease,24 and like IMT, CAC scores were higher in the excess gainer group, though this relationship only reached borderline significant after adjusting for covariates. With only 1 cross-sectional CAC measurement in EDIC, we were unable to test whether a higher insulin dose and greater BMI predicted greater CAC score progression, as was recently reported in an observational study of patients with T1DM.25 We also explored relationships between individual criteria for MetS, previously described as an independent CVD risk in nondiabetic populations26 and in T1DM,10,11 with both IMT and CAC measures. We found that meeting MetS criteria for blood pressure and waist circumference was associated with increased IMT at both EDIC time points, triglyceride criteria became associated with IMT by EDIC year 6, but only HDL criteria were associated with increased CAC score. Taken
together, these data demonstrate the potentially adverse effect of excess weight gain (and increasing frequency of meeting MetS criteria that accompany this weight gain) with INT on IMT and CAC and are consistent with recent long-term observational studies of patients with T1DM that have found obesity to be predictive of future cardiovascular events and mortality.

In an attempt to understand the risk factors accompanying weight gain with INT in the DCCT that led to the increased IMT and CAC measures, we performed adjusted analyses with traditional (triglyceride, LDL, and HDL) and nontraditional (apoB, LDL particle density, Lipoprotein(a), and non-HDL cholesterol levels) lipid CVD risk factors. The nontraditional risk factors were not associated with increased IMT or CAC in EDIC independent of excess weight gain. Although the traditional risk factors associated with CVD were associated with IMT and INT, excess weight gain remained significantly associated with IMT after their inclusion. However, the same was not true for the association between weight gain and CAC. These data suggest that the effect of excess weight gain on carotid artery disease is not fully explained by accompanying deterioration in lipid levels (or blood pressure levels), whereas traditional lipid risk factors are likely to be mediators of the relationship between weight gain and coronary artery disease.

Obesity, central obesity, dyslipidemia, and hypertension within middle-age populations are known to be strongly influenced by heritability. We have previously demonstrated that patients with T1DM with ≥1 parent with T2DM are more likely to exhibit central obesity and dyslipidemia. Specifically, we showed that subjects in the DCCT with parents with T2DM gained more weight with INT than those with T1DM34 that are otherwise obviated by poor metabolic control. The expression of these traits may promote atherosclerosis and reduce the salutary effects of INT on CVD previously demonstrated.4,5

In conclusion, we have shown that excessive weight gain with INT is sustained during 6 years of EDIC follow-up and remains associated with central obesity, insulin resistance, a progressive rise in blood pressure, and dyslipidemia. Regardless of treatment group assignment, however, subjects with the greatest weight gain had the greatest INT and highest CAC scores. Whether the atherogenic changes associated with weight gain will reduce the long-term benefit of INT on major cardiovascular events needs to be examined with future follow-up. However, based on the results of this study, efforts should be made to limit excess weight gain that accompanies intensive glucose treatment of T1DM.

Acknowledgments
We acknowledge the ongoing dedication of the DCCT/EDIC study researchers, staff, participants, and their families. A complete list of participants in the DCCT/EDIC research group can be found in Archives of Ophthalmology, 2008;126:1713.

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Disclosures
None.

References


34. Deeb SS, Brunzell JD. The role of the pgc1alpha gly482ser polymorphism in weight gain due to intensive diabetes therapy. *PPAR Res*. 2009;694286, 2009.

**CLINICAL PERSPECTIVE**

Unlike other observational studies of patients with type 1 diabetes mellitus, the Diabetes Control and Complications Trial (DCCT) was a randomized, controlled trial. Patients assigned to the intensive treatment arm had better diabetes mellitus–related microvascular and initial macrovascular outcomes compared with the conventionally treated group, but roughly a quarter of the patients became obese. The rationale for this study was to determine whether this excess weight gain and accompanying worsening of cardiovascular risk factors in this subset would persist and be associated with subclinical atherosclerotic disease during long-term follow-up. We found during 8 to 9 years of follow-up that central obesity, increased lipid levels, and increased blood pressures in this group persisted and were associated with more subclinical atherosclerotic disease. We also found evidence for familial influences on atherosclerotic disease in the intensively treated subjects, but not those treated conventionally. The significance of this study is the recognition that obesity-related deterioration of cardiometabolic risk factors can occur in patients with type 1 diabetes mellitus treated with intensive diabetes mellitus management, even those who have experienced improvements in their glycemic control to near normal levels, and that this excessive weight gain can worsen atherosclerotic disease. It highlights the need to develop effective weight control strategies for obesity prevention to maximize the benefits of intensive diabetes mellitus therapy in type 1 diabetes mellitus.
The Effect of Excess Weight Gain With Intensive Diabetes Mellitus Treatment on Cardiovascular Disease Risk Factors and Atherosclerosis in Type 1 Diabetes Mellitus: Results From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) Study
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for the DCCT/EDIC Research Group

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**Supplemental figure 1:** Flow chart of study dates of subjects in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC).
Supplemental figure 2: Body mass index (left graph) and waist circumference (right graph) of subjects treated conventionally in the DCCT/EDIC cohort during the DCCT and study years 1 and 6 of EDIC. BMI was greater in the fourth quartile of weight gain during the DCCT (Q4, excess gainers, open circles) (n=23) vs. quartiles Q1-3 (n=476, minimal-gainers, closed circles) at each study time point \(P < 0.001\). Waist circumference, not measured at DCCT baseline, was greater in Q4 than Q1-3 at DCCT closeout \(P < 0.001\) and EDIC years 1 \(P < 0.001\) and 6 \(P=0.002\). Analysis by Mann-Whitney Rank Sum Test. Results are mean ± SE.
Supplemental Table 1: Glycemic control, lipid levels, and blood pressure among minimal gainers (n=476) vs. excess gainers (n=23) with conventional diabetes treatment in the EDIC/DCCT cohort (n=499).

<table>
<thead>
<tr>
<th></th>
<th>DCCT Closeout</th>
<th>EDIC Year 1</th>
<th>EDIC Year 6</th>
</tr>
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<tr>
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<td>Minimal gainers</td>
<td>Excess gainers</td>
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<td>Hemoglobin A1c (%)</td>
<td>9.0±1.9</td>
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<td>Insulin Dose (u/kg/day)</td>
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<td>Triglyceride (mmol/L)</td>
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<td>Cholesterol level (mmol/L)</td>
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<td>Total</td>
<td>4.7±0.88</td>
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<td>LDL</td>
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<td>Percent with LDL &gt; 2.59 mmol/L (%)</td>
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<td></td>
<td>115±13</td>
<td>118±15</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<td>Diastolic BP (mm Hg)</td>
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<td>Number of criteria met:</td>
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WC-waist circumference. HDL-high density lipoprotein cholesterol. TG-triglyceride. BP-blood pressure. Metabolic syndrome defined as presence of two additional criteria in addition to diabetes using NCEP criteria. *Chi-squared test for proportion of subjects that met 0 to 4 MetS criteria. Results are mean ± SD.

References:


