Improved Glycemic Control Reduces the Impact of Weight Gain on Cardiovascular Risk Factors in Type 1 Diabetes

The Epidemiology of Diabetes Complications Study

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OBJECTIVE — To assess the prevalence and incidence of being overweight in type 1 diabetes, to identify factors associated with weight gain and improved glycemic control, and to examine relationships among weight gain, glycemic control, and cardiovascular risk factors.

RESEARCH DESIGN AND METHODS — The prevalence and incidence of being overweight in the Pittsburgh Epidemiology of Diabetes Complications (EDC) cohort ($n = 441$) were compared with the general population (National Health and Nutrition Examination Survey [NHANES]). Factors associated with weight gain and improved glycemic control were identified, and relationships among weight gain, glycemic control, and cardiovascular risk factors were examined over a 6.9 ± 2.2-year period.

RESULTS — At baseline, the prevalence of being overweight (BMI >27.8 kg/m² for men and >27.3 kg/m² for women) was 10.4 and 11.4%, respectively, and was lower than the age- and sex-specific estimate for the general population ($P < 0.05$). The incidence of being overweight was comparable in men (12.6%) and women (11.8%) and did not differ from the general population ($P = 0.98$). Weight gain correlated with improvements in HbA_{1c} ($r = -0.21$, $P < 0.001$). Patients with the highest baseline HbA_{1c} levels gained the most weight and had the greatest improvement in glycemic control. A lower baseline BMI was also associated with a greater improvement in glycemic control. Weight gain favorably influenced the lipid profile in the setting of improved glycemic control, but adversely influenced the lipid profile in the absence of improved glycemic control. Weight change was directly associated with blood pressure change, but the incidence of hypertension was more strongly influenced by the development of nephropathy.

CONCLUSIONS — The prevalence of being overweight in type 1 diabetes remains lower than that in the general population. Moderate weight gain did not adversely affect the cardiovascular risk profile in the setting of improved glycemic control.

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Intensive therapy to improve glycemic control in type 1 diabetes reduces microvascular complications (1). Weight gain is a potential consequence of improved glycemic control (2–6). In the Diabetes Control and Complications Trial (DCCT), the prevalence of being overweight (BMI >27.8 kg/m² for men and >27.3 kg/m² for women) reached 33.1% in the intensively treated subjects, compared with only 19.1% in the conventionally treated subjects >6.5 years (6). To further assess the impact of weight gain, more recent reports from the DCCT have examined subgroups that have experienced the most weight gain. In both treatment groups, subjects who gained the most weight had the greatest increases in systolic blood pressure, total cholesterol levels, LDL cholesterol levels, apolipoprotein(B) [apo(B)] levels, and insulin dose (4). Moreover, weight gain was independently associated with adverse effects on the lipid profile regardless of glycemic control (4).

In the general population, gaining weight and being overweight are common (7). In the period 1988–1991, 33.4% of U.S. adults ≥20 years of age were estimated to be overweight, according to the same criteria used to define being overweight in the DCCT (7). Weight gain is particularly common between the ages of 25 and 44 years (8). In nondiabetic subjects, obesity is associated with dyslipidemia and hypertension (9) and with increased mortality (10,11). Adults with type 1 diabetes thus may experience the same rate of weight gain and be subject to the same adverse effects of weight gain as the remainder of the general population. The relationship between the effects of weight gain and glycemic control on cardiovascular risk factors in the absence of a direct study intervention in type 1 diabetes is also unclear.

Cardiovascular disease is a leading cause of mortality in type 1 diabetes (12). Therefore, a greater understanding of being overweight, of the predictors and pattern of weight gain, and of the relationships among weight gain, glycemic control, and cardiovascular risk in type 1 diabetes are urgently needed. The Epidemiology of Diabetes Complications (EDC) Study is a prospective study of a representative cohort of subjects with childhood-onset type 1 diabetes. This cohort provides an opportunity to examine the natural history of body weight, weight change, and the interaction between body weight and glycemic control on cardiovascular risk factors. The objectives of this

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Abbreviations: apo(B), apolipoprotein(B); DCCT, Diabetes Control and Complications Trial; EDC, Epidemiology of Diabetes Complications; NHANES, National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

study are to *1*) compare the prevalence of being overweight and the incidence of weight gain with the general population, *2*) identify factors associated with weight gain and improved glycemic control, and *3*) examine the relationships among weight gain, glycemic control, and cardiovascular risk factors in subjects with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study population

The Pittsburgh EDC Study was a 10-year prospective study of a well-defined cohort of childhood-onset (<17 years) type 1 diabetic subjects. Subjects (*n* = 325 women, 333 men) diagnosed between 1 January 1950 and 30 May 1980 were first seen at the baseline examination (1986–1988) and then biennially for a maximum of 8 years. The design and methods of the study have been previously described (13–15). For this analysis, 441 individuals who were ≥20 years of age at baseline, had at least two examinations, and had no more than a digital amputation were included. Data presented are from the baseline and the most recent follow-up examination. No subjects were pregnant at the time of their examination.

Comparison of rates of the prevalence and incidence of being overweight were taken from the National Health and Nutrition Examination Survey (NHANES). To use the most recent data, the prevalence of being overweight was obtained from NHANES III (1988–1991) (7), while incidence rates were taken from the follow-up of NHANES I (follow-up examination, 1981–1984) (8).

Clinical measurements

Details regarding the clinical and metabolic evaluation for the EDC Study have been previously reported (13,14). Weight was measured using a balance-beam scale, and height was measured using a wall-mounted stadiometer with subjects in hospital gowns and without shoes. On the basis of the NHANES reports (7,8), being overweight was defined as >27.8 kg/m² for men and >27.3 kg/m² for women. Blood pressure readings were measured by a random-zero sphygmomanometer according to the Hypertension Detection Follow-up Protocol (16) after a 5-min rest period. Subjects were considered to have hypertension if they had a blood pressure >140 mmHg systolic, 90 mmHg diastolic, or were receiving antihypertensive medication. Coronary artery disease comprised angina diagnosed by a clinic physician, confirmed myocardial infarction (validated hospital records), or death certificate. A family history of presumed type 2 diabetes, defined as diabetes diagnosed after age 30 years in a first-degree relative, was further evaluated to validate the diagnosis and type of diabetes as previously reported (17). Assessment of leisure time physical activity was obtained through a self-administered questionnaire originally developed for the Harvard alumni study (18) and internally validated in the EDC population (19).

Laboratory measurements

Fasting blood samples were for the measurement of lipids, lipoproteins, HbA_1, and fibrinogen as previously reported (13,14). Subjects were considered to have dyslipidemia if the LDL cholesterol level was ≥4.14 mmol/l (160 mg/dl) or the triglyceride level was ≥2.26 mmol/l (200 mg/dl) based on prior definitions established in the DCCT (4,20). Overt nephropathy was defined as an albumin excretion rate >200 μg/min (consistent results from at least two of three timed urine specimens), end-stage renal disease (renal dialysis or transplant), a urinary albumin-to-creatinine ratio (mg/mg) of >0.31 (if only one urine specimen was available), or a serum creatinine level >2 mg/dl (in the absence of urine specimens) as previously described (15).

Statistical methods

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago). Cross-sectional comparisons included the Student's *t* test for continuous variables and χ^2 tests for categorical variables. Paired *t* tests were used to compare differences in relevant variables over the follow-up period. Rates of incidence and prevalence of being overweight were compared using the χ^2 test for trend. Logistic regression was used to assess interrelationships between variables. For those variables that were highly intercorrelated (e.g., age and duration of type 1 diabetes, total and LDL cholesterol levels) only one variable was chosen (e.g., duration of type 1 diabetes and LDL cholesterol level) for multivariate analyses. Variables that were not normally distributed were log-transformed for analyses.

Table 1—*Baseline characteristics*

	Men	Women	All
n	225	216	441
Age (years)	29.2 ± 6.0	29.9 ± 6.5	29.6 ± 6.3
Duration of diabetes (years)	20.6 ± 6.7	20.9 ± 7.1	20.7 ± 6.9
Caucasian	98.9 (223)	95.4 (206)	97.7 (440)
Duration of follow-up (years)	6.8 ± 2.2	6.9 ± 2.1	6.9 ± 2.2
Weight (kg)	72.7 ± 9.8	60.6 ± 9.6†	66.8 ± 11.4
BMI (kg/m²)	24.2 ± 2.8	23.5 ± 3.3*	23.9 ± 3.0
Waist circumference (cm)	84.6 ± 7.9	76.2 ± 8.4†	80.5 ± 9.2
Waist-to-hip ratio	0.88 ± 0.05	0.78 ± 0.06†	0.83 ± 0.07
Prevalence of overweight	10.4 (23)	11.4 (24)	10.9 (47)
HbA_1 (%)	10.1 ± 1.5	10.1 ± 1.7	10.1 ± 1.6
Education (> high school graduate)	30.8 (66)	36.7 (76)	33.7 (142)
Ever smoker	42.6 (92)	40.2 (84)	41.4 (176)

Data are means ± SEM or % (*n*). For between-sex comparisons, *$P < 0.05$, †$P < 0.001$.

RESULTS

Comparison to NHANES population

To compare the EDC population to the NHANES population, subjects were first stratified based on sex (Table 1). Men had a higher mean BMI and a greater waist circumference (84.6 ± 6.9 vs. 76.2 ± 8.4 cm, $P < 0.001$) than women. The prevalence of being overweight was similar across the two sexes. When compared with the age- and sex-specific estimate for non-Hispanic whites in the general population from NHANES III, the prevalence of being overweight was lower in the EDC population ($P < 0.001$ for men and $P < 0.05$ for women) as shown in Fig. 1.

Subjects were followed for a mean duration of 6.9 ± 2.2 years. Men and women did not differ in overall change in weight (+3.17 ± 6.29 kg), overall change in HbA_1 (+0.55 ± 1.92), or inci-

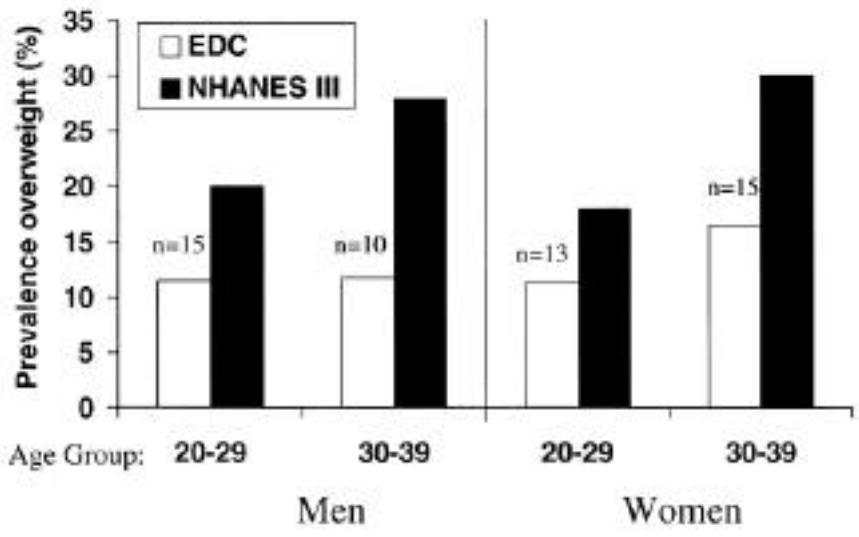

Figure 1—*Prevalence of being overweight by age-group and sex in the EDC cohort (□) and NHANES III groups (■). The x axis represents age in years and the number above each bar represents the number of overweight subjects in the EDC cohort.*

dence of being overweight (men 12.6%, women 11.8%: $P = 0.98$) in the EDC population. The incidence of being overweight was also comparable to the general population from NHANES I (Fig. 2). While the incidence of being overweight in the 35- to 44-year-old age-group was nearly twice as high in EDC women compared with EDC men, this level did not reach statistical significance ($P = 0.35$).

Correlation analyses

Partial correlations between weight change and both baseline characteristics and changes in cardiovascular risk factors, controlling for duration of follow-up, are shown in Table 2. Weight change was directly related to baseline HbA_1 ($r = 0.12$, $P < 0.05$), suggesting that subjects who had a higher HbA_1 level at baseline were more likely to gain weight (Table 2). No other baseline factors were significantly associated with change in weight. When changes during follow-up (as opposed to baseline values) were considered, weight change was inversely related to change in HbA_1 ($r = -0.21$, $P < 0.001$) and directly associated with change in systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, and triglycerides.

Subgroup analyses

To examine the relationship between improved glycemic control and weight gain, the characteristics of a subgroup of patients with excessive weight gain (top tertile of weight change, gain ≥4.8 kg) were compared with patients who had lesser weight gain. To further examine the HbA_1 and weight change association, analyses were performed to compare differences between subjects who had a major improvement in HbA_1 (>2% decrease in HbA_1) and those who did not. A level of 2% was chosen to approximate the overall 2% decline in HbA_{1c} observed in the intensively treated group in the DCCT (1). These subgroup analyses are shown in Tables 3 and 4 and are discussed below.

Baseline predictors of weight gain and improved glycemic control

At baseline, subjects who subsequently had a major improvement in glycemic control over the period of follow-up had a lower baseline BMI (22.9 ± 3.0 vs. 24.0 ± 3.0 kg/m², $P < 0.05$). When examined by weight change category, this trend persisted in the group that gained ≥4.8 kg ($P < 0.10$), as shown in subgroup analyses in Table 3. Regardless of weight change category, subjects who had a major improvement in glycemic control had higher HbA_1 levels at baseline ($P < 0.001$). Subjects who had a major improvement in glycemic control also took fewer insulin injections per day. Subjects who gained <4.8 kg and had a major improvement in glycemic control had the lowest systolic blood pressure. Among subjects who had the greatest weight gain, baseline total cholesterol and LDL cholesterol levels were significantly higher in those who had gained ≥4.8 kg ($P < 0.01$).

Changes in risk factors as a function of weight change and glycemic control

Overall, subjects who had a major improvement in glycemic control gained more weight (8.2 ± 6.8 vs. 2.7 ± 6.0 kg, $P < 0.001$) and had a greater incidence of being overweight (25.6 vs. 10.8%, $P < 0.01$) than those with no major improvement in glycemic control over the follow-up period. While follow-up BMI (25.7 ± 5.1 vs. 24.7 ± 3.7 kg/m²) and prevalence of being overweight (29.3 vs. 22.9%) were higher in subjects who had a major improvement in

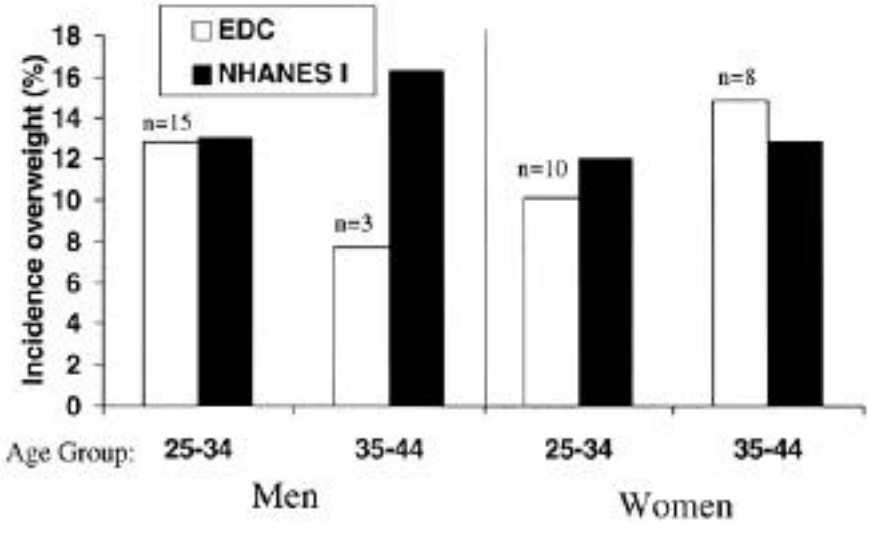

Figure 2—*Incidence of being overweight by age-group and sex in the EDC cohort (□) and NHANES I (■). The x axis represents age in years and the number above each bar represents the number of overweight subjects in the EDC cohort.*

Table 2—*Variables associated with weight change (correlations) adjusted for years of follow-up*

	Baseline characteristics	Change over follow-up period
Age	−0.06	—
Duration of diabetes	−0.04	—
Weight	−0.03	—
BMI	−0.05	—
Waist-to-hip ratio	0.08	—
HbA_1	0.12†	−0.21‡
Insulin dose	0.03	0.07
Systolic blood pressure	0.06	0.11†
Diastolic blood pressure	0.02	0.22‡
Total cholesterol	−0.02	0.24‡
LDL cholesterol	−0.01	0.24‡
HDL cholesterol	−0.08*	−0.10*
Triglycerides	0.05	0.13†
Fibrinogen	0.04	0.06
Physical activity	−0.01	0.02

*$P < 0.10$, †$P < 0.05$, ‡$P < 0.001$.

glycemic control, this difference did not reach statistical significance ($P > 0.10$). Regardless of weight change category (Table 4), subjects who had a major improvement in glycemic control had a greater increase in the number of insulin injections per day ($P < 0.01$). As a group, subjects who had a major improvement in glycemic control had a greater increase in physician visits per year (+1.7 ± 1.4 vs. +0.3 ± 3.1, $P < 0.05$). This trend persisted, but did not reach statistical significance, in subgroup analysis (Table 4, $P > 0.10$).

Subjects who had a major improvement in glycemic control had greater increases in the incidence of overt nephropathy (24.1 vs. 8.7%, $P < 0.01$), in the levels of both systolic (9.5 ± 19.8 vs. 3.9 ± 17.7 mmHg) and in diastolic (11.6 ±

Table 3—*Baseline characteristics by weight change status and improvement in HbA_1 status*

	Gained ≥4.8 kg		Gained <4.8 kg	
	Major improvement in HbA_1	No major improvement in HbA_1	Major improvement in HbA_1	No major improvement in HbA_1
n	28	124	13	273
Demographics				
Men	57.1 (16)	54.8 (68)	53.9 (7)	48.3 (132)
Age (years)	28.3 ± 5.9	29.6 ± 6.5	28.4 ± 6.8	29.7 ± 6.2
Duration of diabetes (years)	20.1 ± 6.9	20.4 ± 6.8	20.8 ± 9.1	20.8 ± 6.8
Education (>high school graduate)	33.3 (9)	32.2 (127)	38.5 (5)	34.2 (88)
Income (>$40,000/year)	80.0 (20)	70.5 (74)	50.0 (5)	73.3 (162)
Follow-up (years)	7.2 ± 1.8	7.4 ± 1.8	6.8 ± 2.1	6.6 ± 2.3
Weight characteristics				
Weight (kg)	65.5 ± 11.4	68.2 ± 10.8	63.1 ± 8.9	66.6 ± 11.6
BMI (kg/m^2)	23.1 ± 3.3	24.3 ± 3.1*	22.6 ± 2.1	23.8 ± 3.0
Prevalent overweight	10.5 (2)	22.8 (21)	0 (0)	12.3 (33)¶
Diabetes characteristics				
HbA_1	12.5 ± 1.5	9.7 ± 1.3§	12.1 ± 1.7	9.9 ± 1.5§
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.70 ± 0.2	0.76 ± 0.2	0.77 ± 0.3	0.75 ± 0.2
Insulin injections per day	1.33 ± 0.5	1.85 ± 1.0‡	1.31 ± 0.5	1.70 ± 1.0
Physician visits per year	2.1 ± 2.4	3.2 ± 3.5	2.2 ± 1.8	3.1 ± 2.9
Overt nephropathy	28.6 (8)	23.4 (29)	30.8 (4)	29.3 (80)
Family history of type 2 diabetes	14.3 (4)	24.2 (30)	0 (0)	17.2 (47)
Cardiovascular risk				
Systolic blood pressure (mmHg)	116.3 ± 17.8	114.8 ± 15.6	105.8 ± 13.5‖	114.8 ± 15.5†
Diastolic blood pressure (mmHg)	73.1 ± 12.5	74.3 ± 10.7	70.5 ± 11.1	73.5 ± 10.3
Prevalent hypertension	17.9 (5)	18.6 (23)	0 (0)	18.3 (50)*
Total cholesterol (mmol/l)	5.50 ± 1.25	4.85 ± 1.00‡	5.20 ± 1.00	5.00 ± 1.05
LDL cholesterol (mmol/l)	3.45 ± 0.85	2.90 ± 0.76‡	3.10 ± 0.85	3.05 ± 0.90
HDL cholesterol (mmol/l)	1.35 ± 0.25	1.40 ± 0.35	1.45 ± 0.30	1.40 ± 0.35
Triglycerides (mmol/l)	3.60 ± 3.20	2.70 ± 1.80	3.00 ± 1.90	2.60 ± 1.90
Prevalent dyslipidemia	34.6 (9)	10.7 (12)	23.1 (3)	15.1 (39)
Smoker	37.0 (10)	45.9(56)	46.2 (6)	39.2 (102)
Fibrinogen (mg/dl)	303.9 ± 95.2	278.5 ± 74.0	252.3 ± 69.5‖	287.2 ± 94.2
Physical activity (kcal/week)	2,558 ± 2,190	2,172 ± 2,740	3,753 ± 4,944	2,426 ± 2,540
Prevalent coronary artery disease	3.6 (1)	4.8 (6)	7.7 (1)	8.4 (23)

Data are means ± SEM or % (*n*). Major improvement, HbA_1 decrease of >2 U during follow-up period; *$P < 0.10$, †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$, comparisons between HbA_1 change category: ‖$P < 0.10$, ¶$P < 0.05$, comparisons within HbA_1 change category and between weight gain category.

Table 4—*Changes in characteristics by weight change status and improvement in HbA_1 status*

	Gained ≥4.8 kg		Gained <4.8 kg	
	Major improvement in HbA_1	No major improvement in HbA_1	Major improvement in HbA_1	No major improvement in HbA_1
n	28	124	13	273
Weight characteristics				
Weight change (kg)	11.5 ± 5.2	9.4 ± 4.4†	1.2 ± 3.4	−0.4 ± 3.8**
BMI at follow-up (kg/m²)	26.9 ± 4.1	27.5 ± 3.7	23.0 ± 2.6**	23.6 ± 3.0**
Incidence of overweight	34.6 (9)	31.1 (32)	7.7 (1)‖	2.1 (5)**
Prevalence of overweight	39.3 (11)	42.7 (53)	7.7 (1)	13.9 (38)
Diabetes characteristics				
HbA_1	−3.16 ± 1.0	0.8 ± 1.4§	−2.9 ± 1.1	1.0 ± 1.6§
Insulin dose (U · kg^{-1} · day^{-1})	−0.06 ± 0.1	−0.05 ± 0.3	−0.07 ± 0.3	−0.08 ± 0.2
Insulin injections per day	1.2 ± 1.4	0.4 ± 0.8‡	2.0 ± 2.4	0.5 ± 1.0§
Physician visits per year	1.9 ± 1.5	0.7 ± 3.4	1.0 ± 0.7	−0.01 ± 2.9
Incident overt nephropathy	20 (4)	12.6 (12)	33.3 (3)	6.7 (13)‡‖
Cardiovascular risk				
Systolic blood pressure (mmHg)	7.4 ± 13.1	6.3 ± 16.1	14.1 ± 29.8	2.7 ± 18.2†‖
Diastolic blood pressure (mmHg)	9.5 ± 20.1	7.3 ± 2.7	16.1 ± 29.1	4.6 ± 19.0†
Incident hypertension	34.8 (8)	18.8 (19)*	30.8 (4)	18.4 (41)
Total cholesterol (mmol/l)	−0.35 ± 1.00	0.55 ± 1.25§	−0.15 ± 2.5	−0.05 ± 0.95**
LDL cholesterol (mmol/l)	−0.20 ± 0.85	0.45 ± 1.00‡	−0.00 ± 2.30	−0.05 ± 0.70**
HDL cholesterol (mmol/l)	−0.05 ± 0.35	−0.05 ± 0.25	−0.05 ± 0.40	0.05 ± 0.30¶
Triglycerides (mmol/l)	−1.20 ± 2.80	0.95 ± 3.75‡	0.00 ± 2.45	0.01 ± 2.15**
Incidence dyslipidemia	5.9 (11)	17.8 (19)	20.0 (2)	8.7 (19)‖
Fibrinogen (mg/dl)	58.3 ± 155.1	85.4 ± 126.8	78.5 ± 99.4	43.1 ± 120.7#
Physical activity (kcal/week)	−1,020 ± 3,428	−934 ± 2,057	−2,573 ± 5,017	−1,134 ± 2,945
Incident coronary artery disease	7.1 (2)	16.1 (20)	15.4 (2)	12.1 (33)

Data are means ± SEM or % (*n*). Major improvement, HbA_1 decrease of >2 U during follow-up period. For incidence rates, prevalent cases at baseline were excluded from the denominator. *$P < 0.10$, †$P < 0.05$, ‡$P < 0.01$, §$P < 0.001$, comparisons between HbA_1 change category. ‖$P < 0.10$, ¶$P < 0.05$, #$P < 0.01$, **$P < 0.001$, comparisons within HbA_1 change category and between weight-gain category.

23.2 vs. 5.4 ± 20.3 mmHg) blood pressure ($P < 0.10$), and in the incidence of hypertension (33.3 vs. 18.5%, $P < 0.05$) than subjects with no major improvement in glycemic control. Medication-controlled hypertension was comparable between the two groups (12.3%, $P = 0.38$). In subgroup analysis (Table 4), the primary differences in these variables were in subjects who gained <4.8 kg and had a major improvement in HbA_1. These subjects had a higher incidence of overt nephropathy ($P < 0.01$) and greater increases in both systolic and diastolic blood pressure ($P < 0.05$) than subjects with no major improvement in HbA_1. After excluding subjects who developed overt nephropathy from this weight change category, increases in systolic (7.8 ± 26.5 mmHg) and diastolic blood pressure (12.3 ± 28.7 mmHg) and the incidence of hypertension (20.0%) were less marked. These levels were higher, but did not differ significantly, from subjects in lowest weight-gain category with no major improvement of glycemic control and no overt nephropathy (systolic blood pressure 2.6 ± 18.2 mmHg, diastolic blood pressure 4.2 ± 19.1 mmHg, incidence of hypertension 16.9%).

Among subjects who gained ≥4.8 kg, reductions in total cholesterol, LDL cholesterol, and triglycerides occurred in those who had a major improvement in glycemic control, while those with no major HbA_1 improvement had increases in these factors (Table 4). Among subjects who had no major improvement in glycemic control, those who gained ≥4.8 kg also had greater increases in these factors (Table 4). Among subjects who gained <4.8 kg, those who had a major improvement in glycemic control had greater reductions in total cholesterol (−0.92 ± 1.21 vs. −0.09 ± 0.95 mmol/l, $P < 0.001$) and LDL cholesterol (−0.71 ± 1.19 vs. −0.06 ± 0.72 mmol/l, $P < 0.01$) than subjects who had no major improvement in glycemic control, after excluding subjects who developed nephropathy.

Baseline and follow-up LDL cholesterol by weight change and improvement in HbA_1 categories for all subjects are shown graphically in Fig. 3. For the groups that experienced the most weight gain, LDL cholesterol levels were highest at baseline ($P < 0.02$) and declined over the period of follow-up in the group that had a major improvement in glycemic control, while LDL cholesterol levels increased in the absence of a major improvement in glycemic control. Subjects who gained the least weight had the lowest LDL cholesterol levels at the follow-up period regardless of changes in HbA_1 category ($P < 0.01$).

Multivariate analysis

Because hypertension is associated with the development of nephropathy, we were concerned by the finding that improved glycemic control was associated with a higher incidence of hypertension, which in turn could be related to a higher incidence of nephropathy. Logistic regression was performed to further assess the relationship among development of overt nephropathy, improvement in glycemic control, and weight change on the development of hypertension. After controlling for duration of follow-up, development of overt nephropathy and initial systolic blood pres-

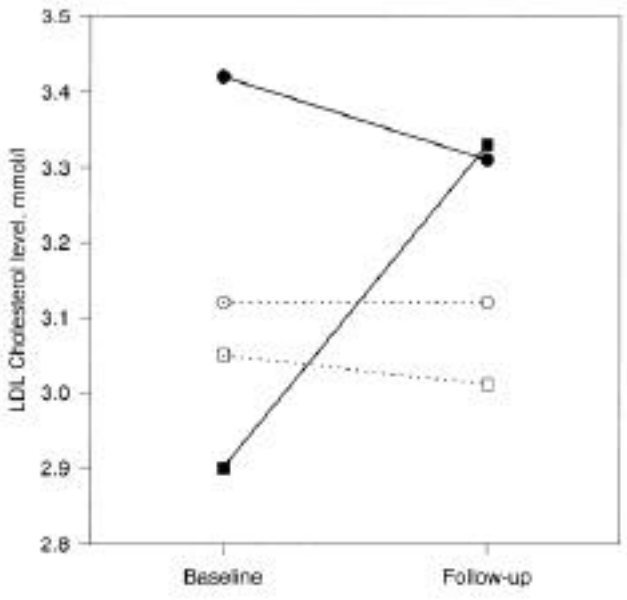

Figure 3—*Baseline and follow-up LDL cholesterol by weight change and improvement in HbA_1 categories for all subjects. Categories are weight gain ≥4.8 kg (—) with major improvement in glycemic control (●) or no major improvement in glycemic control (■) and weight gain <4.8 kg (- - -) with major improvement in glycemic control (○) or no major improvement in glycemic control (□).*

sure were the only factors independently associated with development of hypertension. No significant interaction for duration of diabetes was found.

While improvement in HbA_1 is known to be associated with weight gain, the association between increased number of insulin injections per day and weight gain was of concern. Logistic regression was performed to further assess these relationships. Using the level of weight gain (<4.8 kg or >4.8 kg) as the dependent variable and controlling for duration of follow-up, only the decrease in HbA_1 was an independent predictor of greater weight gain. No significant interaction for duration of diabetes was found.

CONCLUSIONS — Being overweight and gaining weight are recognized increasingly as a problem in type 1 diabetes, particularly among adolescents (21–23). In the current study, being overweight was less common in adults with type 1 diabetes when compared to the general population. Despite weight gain during the period of follow-up, the incidence of being overweight was comparable to that of the general population. Because our cohort was in the age-group at high risk for weight gain (8), weight gain could be related to trends observed in the general population as well as the effect of changes in glycemic control. However, while the NHANES III report was concurrent in time with the baseline assessments in the present study, the only available population incidence estimates of being overweight were based on the earlier NHANES I reports. Temporal shifts in the general population incidence of being overweight could have occurred, resulting in an over- or underestimate of the current trend for being overweight in the general population. While current clinical guidelines define being overweight as a BMI of ≥ 25 kg/m² for both men and women (24), similar patterns were observed in all analyses, regardless of which cutpoint was used.

Identification of factors related to improved glycemic control could help maximize the benefits and minimize the side effects of intensive glycemic therapy. One of the strengths of this study is that it represents community care, rather than a select trial population. Thus, the improvement in control is consistent with general clinical practice and may reflect more closely the type of patient who will change control. Indeed, subjects who had a major improvement in glycemic control (when compared with those who did not) weighed less at baseline, had higher baseline HbA_1 levels, and took fewer insulin injections. The DCCT excluded patients with hypertension, dyslipidemia, and obesity at baseline, and the only baseline characteristic that distinguished the group that gained the most weight with intensive therapy from the group that gained the least amount of weight was a higher baseline HbA_{1c} in the former (4).

At the follow-up period, EDC subjects who had a major improvement in glycemic control gained more weight, had a higher incidence of being overweight, and had a greater increase in the number of insulin injections per day. However, while the BMI and prevalence of being overweight in those who had a major improvement in glycemic control was higher at the follow-up period, these differences did not reach statistical significance. Thus, the weight gain observed with major improvement in glycemic control could be related in part to attainment of the subjects' naturally determined body weight (i.e., that initially they were inadequately treated). Possible explanations for weight gain with improvement in glycemic control include elimination of caloric loss from glycosuria, reduced metabolic rate (25,26), shift in fuel use from fatty acids to glucose (potentially resulting in reduced fat mobilization and increased fat storage [26]), and an insulin-induced increase in appetite (27).

While no relationship was observed between change in insulin dose or number of insulin injections per day, patients who saw their doctor more frequently had more weight gain, independent of changes in glycemic control. Regular patient-provider contact is clearly required to optimally manage type 1 diabetes. One possible explanation for weight gain with more frequent patient-provider contact is that more frequent patient-provider contact helps to maintain glycemic control and that maintenance of glycemic control, per se, is associated with weight gain as previously observed in both treatment groups in the DCCT (1,3). Thus, patients should be monitored for weight gain even in the absence of improvement in glycemic control.

In the current study, weight gain overall was associated with an adverse effect on the lipid profile. In the DCCT, the intensively treated group had greater overall improvements in their lipid profile (5), but the lipid panel was adversely affected in both treatment groups in patients with the greatest weight gain (4). In contrast, among patients in this study who gained weight, those who improved glycemic control had favorable lipid profile changes, while those who did not improve glycemic control had unfavorable lipid profile changes. Thus, weight gain in the absence of improvement of glycemic control should be avoided. The milder

impact of weight gain in this study may be due to the lower mean BMI at follow-up among those who gained the most weight (25.7 kg/m^2), compared with patients in the DCCT who experienced the most adverse lipid profile effects (BMI 27 and 31 kg/m^2 in the conventionally and intensively treated groups, respectively) (4). This observation is consistent with a study in normal volunteers that showed a threshold for an adverse effect of obesity on insulin sensitivity at a BMI of 26.8 (28). Thus, patients who exceed this threshold may be more insulin resistant and have changes similar to those seen in insulin resistance, as described in the DCCT population (4).

The association between weight gain and hypertension in this study was slightly more complex. While changes in weight were directly associated with changes in blood pressure, multivariate analysis showed that the development of overt nephropathy and the baseline systolic blood pressure were the primary determinants of the incidence of hypertension. Interestingly, the small subgroup of subjects who gained the least amount of weight and had a major improvement in glycemic control had a higher incidence of nephropathy and hypertension. While caution must be taken in interpreting the results of a small number of patients, this may be a subgroup of subjects worthy of future study regarding the cause of nephropathy. However, the multivariate analyses suggest that a higher incidence of hypertension and nephropathy is not a general feature of the intensification of glycemic control. In the DCCT, the systolic blood pressure was higher in the intensively treated group, but the incidence of hypertension between the two groups was comparable (5). Blood pressure was also higher in DCCT subjects who gained the most weight, but the incidence of hypertension and nephropathy in this subgroup was not reported (4).

In conclusion, despite the overall increase in obesity in the general population, the prevalence of being overweight in type 1 diabetes remains lower than the general population, and the incidence of overweight in type 1 diabetes does not differ from the general population. Patients who had major improvements in glycemic control weighed less and had a worse metabolic profile at baseline. Weight gain in the setting of improved glycemic control favorably influenced the lipid profile, while weight gain in the absence of improved glycemic control adversely influenced the lipid profile. On the basis of prior DCCT findings (4), it remains prudent to avoid excessive weight gain in type 1 diabetes.

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