Short Reports

Weight Gain Associated With Improved Glycemic Control in Population-Based Sample of Subjects With Type I Diabetes

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Previous studies have suggested that weight gain is an identifiable risk of efforts to lower blood glucose with intensive insulin therapy in type I (insulin-dependent) diabetic subjects. This study examined this relationship in a population-based sample of type I diabetic subjects participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Four hundred five adults (aged ≥21 yr) with type I diabetes, who were diagnosed before age 30 yr, were studied from 1980 to 1982 and in a follow-up examination from 1984 to 1986. Weight gain over the 4-yr interval averaged 1.8 ± 5.9 kg. Weight gain was significantly associated ($r = -0.26$, $P < 0.001$) with improvements in glycosylated hemoglobin levels; the quartile of subjects with the greatest improvements in glycemic control gained 3.4 kg, whereas the quartile of subjects with the smallest improvements in glycemic control lost 0.6 kg. Weight gain was also correlated with increases in the number of shots of insulin per day and change in the treatment regimen from one type of insulin to a combination of short- and long-acting insulins. These results suggest that weight gain may be an adverse consequence of improved glycemic control. Efforts to better understand the mechanism explaining weight gain and to prevent weight gain are needed.
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Recent studies suggest that intensive insulin therapy is associated with weight gain in type I (insulin-dependent) diabetic subjects. For example, in the Diabetes Control and Complications Trial (DCCT; 1), subjects on intensive therapy gained 5.1 kg in the 1st yr, whereas standard-therapy subjects gained 2.4 kg; weight gain on intensive therapy was related to initial HbA_1 level and to the degree of improvement in HbA_1.

The association between improved glycemic control and weight gain in type I diabetic subjects is of concern because weight gain may diminish adherence to the treatment regimen and adversely affect coronary heart disease risk factors, including blood pressure and serum lipid levels (2). Therefore, it is important to know whether improvements in glycemic control are associated with weight gain in other settings. To examine this, we studied the relationship between improvements in glycemic control and weight change over a 4-yr interval in a population-based sample of people with type I diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).

RESEARCH DESIGN AND METHODS

The WESDR population has been described in detail in previous articles (3–5). In brief, 452 of 457 physicians who provided primary care to diabetic patients in an 11-county area in southern Wisconsin participated. These physicians identified 1396 diabetic patients who were diagnosed before age 30 yr and taking insulin. A sample of 1210 of these individuals was selected to participate in the WESDR baseline examinations. Eighty-two percent of these patients ($n = 996$) participated in the baseline examinations from 1980 to 1982, and

89.5% of these (n = 891) participated in the follow-up examination (1984–1986). From this sample of 891, we further selected only those who had C-peptide levels <0.3 nM, were aged ≥21 yr at baseline, were on insulin at both baseline and follow-up, had weight and HbA_1 measured at both examinations, and did not have a history of cancer at either time. This yielded a total sample of 405 subjects (195 men, 210 women). These subjects averaged mean ± SD 33.8 ± 10.2 yr of age at baseline. A sample of nondiabetic control subjects (n = 39), consisting primarily of spouses and having the same age distribution as the diabetic subjects, was also followed over the 4 yr.

Height and weight were assessed with a balance-beam scale with subjects dressed and shoes removed. HbA_1 levels were determined by a resin microcolumn technique from a capillary blood sample (baseline) or a venous blood sample (follow-up). Most determinations at the baseline examination were performed without the labile fraction of HbA_1 removed from the sample. At the follow-up examination, a change in technique resulted in having the labile fraction removed before analysis. To make the results comparable between the two examinations, a correction procedure was applied to the baseline measurements (6). A structured interview was conducted in which subjects were asked about their insulin regimen (type of insulin, doses, and shots/day).

Statistical analysis. Data were analyzed with paired t tests to compare changes from baseline to follow-up examination. McNemar tests were used to compare the proportion of subjects who increased the intensity of the treatment regimen to those who decreased the intensity of treatment (7). Pearson correlations were used to examine the association between continuous variables. Spearman's rank-order correlations were used when discrete ordinal variables were involved.

RESULTS

Body weight increased significantly over the 4 yr (69.7 ± 13.1 vs. 71.5 ± 13.4 kg, $P < 0.0001$); on average, subjects gained 1.8 ± 5.9 kg. HbA_1 decreased significantly (10.8 ± 1.9% at entry and 9.9 ± 1.8% at follow-up, $P < 0.001$). The increase in weight and improvement in glycemic control were similar in men and women.

Changes in body weight correlated significantly (r = −0.26, $P < 0.001$) with changes in HbA_1 (Table 1). The association was stronger in men than in women. The mean ± SE β-coefficient for the effect of change in HbA_1 on change in weight was −0.797 ± 0.147. Thus, a 1% improvement (decrease) in HbA_1 was associated with a weight gain of 0.8 kg. Restricting the analysis to the participants who did not change their smoking status (n = 367) did not affect the mean weight gain or the correlation between change in weight and change in HbA_1.

To more clearly illustrate the relationship between improvement in control and weight change, subjects were divided into quartiles according to the degree of improvement in glycemic control. Subjects in the quartile with the greatest improvement in control (n = 100) had a mean weight change of 3.4 ± 4.3 kg over the 4 yr of follow-up. Those in the second quartile (n = 99) gained 2.7 ± 6.2 kg; those in the third quartile (n = 106) gained 1.9 ± 6.2 kg; and those in the fourth quartile, who had the smallest improvement in glycemic control (n = 100), lost 0.6 ± 5.9 kg. The nondiabetic subjects gained 0.3 ± 7.6 kg over 4 yr, significantly ($P < 0.005$) less than the subjects with the greatest improvement in control.

Moreover, the proportion of subjects who became overweight (i.e., went from ≤120% of ideal body weight to >120% of ideal body weight) was also related to changes in glycemic control (Fig. 1). In the quartile

TABLE 1
Correlation of weight gain with change in HbA_1, baseline variables, and change in treatment regimen

	All	Men	Women
Change in HbA_1	−0.26*	−0.38*	−0.17†
Baseline variables			
HbA_1 (%)	0.07	0.15†	
Age (yr)	−0.07	−0.11	−0.04
Weight (kg)	−0.17*	−0.14	−0.23*
Sex‡	−0.01		
Units (insulin · kg^{-1} · day^{-1})	0.09	0.05	0.11
Doses (1 shot/>1 shot/day)‡	−0.05	−0.04	−0.05
Regimen (single insulin/combination)‡	−0.12†	−0.05	−0.17†
Change in regimen			
Change in units of insulin (kg/day)	−0.04	0.19§	−0.16†
Change in doses/day‡	0.17*	0.14	0.20†
Change in regimen‡	0.23*	0.12	0.32*
Self-monitoring of blood glucose (times/wk)‡	0.07	0.01	0.13

*$P < 0.001$, †$P < 0.05$, §$P < 0.01$.
‡Spearman's rank-order correlations; all other Pearson correlations.

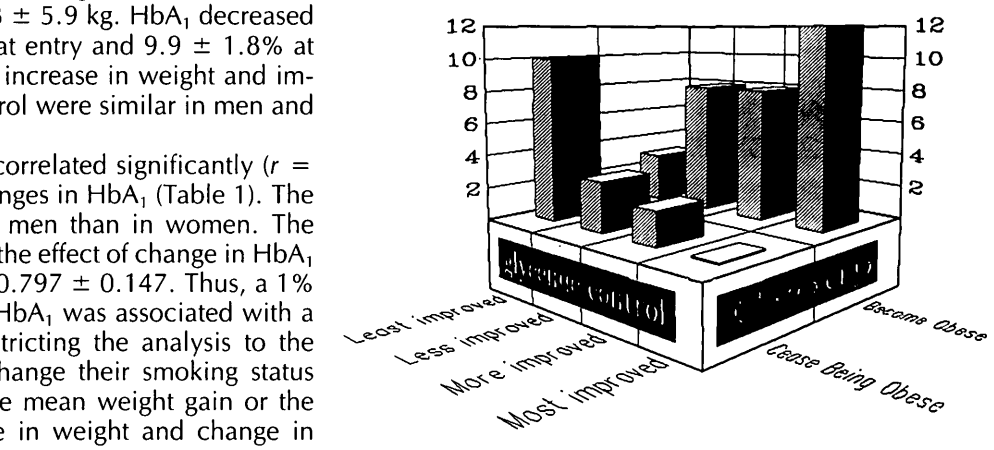

FIG. 1. Percentage of subjects who became obese or ceased being obese as function of improvement in glycemic control.

that had the greatest improvement in control, 12% of the subjects went from ≤120% of ideal body weight to >120% of ideal body weight. In contrast, in the quartile with the smallest improvement in glycemic control, only 3% of the participants went from ≤120% of ideal body weight to >120% of ideal body weight ($P < 0.0001$). Similarly, the percentage of subjects who ceased being obese was related to quartile of glycemic control.

Table 1 shows other baseline characteristics and changes that were associated with weight gain. Thinner subjects tended to gain more weight, as did those who at baseline were on treatment regimens involving only one type of insulin. Over the course of the study, there was an intensification of the general treatment regimen used for type I diabetic subjects. For example, 64% of the subjects were on one dose of insulin per day at baseline, and 60% used only one type of insulin. In contrast, at follow-up, 59% of the subjects took more than one shot of insulin per day, and 64% used a combination of short- and long-acting insulins. Table 1 shows that subjects who increased the number of doses of insulin per day and those who went from a single type of insulin to a combined regimen had the greatest weight gains.

DISCUSSION

This study suggests that weight gain is associated with improvement in glycemic control in a population-based sample, a result that is in agreement with experimental programs of intensive insulin therapy. During the 4-yr interval from 1980 to 1982 and 1984 to 1986, there was a shift toward more intensive treatment regimens, with most subjects in this population sample starting to use more than one shot of insulin per day and combining short- and long-acting insulins. Over this period, there was also a decrease in HbA_1 from 10.8 to 9.9%.

The changes in treatment regimen and the improvement in glycemic control were correlated with increased body weight, as was the number of subjects who became clinically obese (defined as being >120% of ideal body weight). Twelve percent of subjects in the quartile with the greatest improvements in HbA_1 became clinically obese compared with 3% of subjects in the quartile with the smallest improvement in HbA_1. Thus, the weight change is not merely due to underweight subjects attaining normal weight. Moreover, the weight change in the quartile with the greatest improvement in glycemic control was greater than that observed in a nondiabetic control group.

The weight gain reported in this population sample was clearly less than that previously reported in experimental trials of intensive therapy, such as the DCCT. The improvements in HbA_1 were also smaller, and the treatment regimen used in this population-based sample remained less intensive than that used in the DCCT. Thus, this study suggests that weight gain may occur with more complex insulin regimens and improved HbA_1, even when the efforts to improve glycemic control are far less intensive than those found in experimental trials such as the DCCT.

An important step in preventing weight gain is to understand the mechanisms that underlie it. In this study, the best predictors of weight gain were baseline weight, initial use of only one type of insulin, change from one type of insulin to a combined regimen, and increase in the number of shots per day. These data suggest that changes in the type of insulin and frequency of administration affect body weight. It is possible that these changes in insulin lead to greater calorie intake. Perhaps subjects on more intensive regimens feel freer to eat large meals, or, alternatively, intensive insulin therapy may make subjects feel hungrier (8). Intensive insulin therapy may also affect body weight by affecting metabolic rate. Leslie et al. (9) demonstrated that metabolic rate is decreased in intensively treated type I diabetic subjects. Efforts to determine which part of the energy balance equation is affected by intensive therapy may help to determine how best to prevent weight gain when improving glycemic control in type I diabetic subjects.

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Effect of Captopril on Glucose Concentration
Possible Role of Augmented Postprandial Forearm Blood Flow

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The goal of this study was to evaluate the effects of captopril on plasma glucose concentration. The daily profiles of the plasma glucose levels were determined in 12 non-insulin-dependent diabetic normotensive subjects, treated with or without captopril at a dose of 25 mg 3 times/day. Forearm blood flow was also measured by strain-gauge plethysmography. Administration of captopril improved the daily profile of the plasma glucose level. Postprandial forearm blood flow was also augmented 2 h after a meal. These results suggest that angiotensin-converting enzyme inhibitors may improve glucose metabolism in diabetic subjects, possibly through enhancement of blood flow to skeletal muscle. *Diabetes Care* 13:1109–11, 1990

It is well known that diabetic subjects sometimes have associated hypertension. Although many hypotensive agents have adverse effects on glucose tolerance and lipid metabolism (1), it has been reported that angiotensin-converting enzyme inhibitors (ACEIs) do not affect the plasma glucose concentration or insulin level during the oral glucose tolerance test, even in the case of long-term administration of captopril, the first orally available ACEI (2). Rett et al. (3), with a euglycemic-hyperinsulinemic glucose-clamp technique, demonstrated a significant rise in whole-body glucose elimination and glucose utilization rate in the forearm musculature concomitantly with an increase in plasma kinin levels 90 min after administration of 25 mg captopril. Therefore, this study was designed to investigate whether captopril has beneficial effects on glycemic control and acute hemodynamic changes in subjects with non-insulin-dependent diabetes mellitus (NIDDM).

RESEARCH DESIGN AND METHODS

The study was performed on 12 normotensive NIDDM patients (7 men, 5 women) aged 33–76 yr (mean age 53.9 yr). Their mean ± SE body mass index averaged 22.7 ± 0.9. Five subjects were treated by diet alone and the rest with sulfonylurea. The mean HbA_1 level was 13.1 ± 0.7% (normal range 5.5–7.8%). None of the subjects had proteinuria. The daily profile of the plasma glucose level was determined for each subject before and 2 h after each meal and at midnight during 2 consecutive days with administration of captopril (25 mg) or placebo 3 times/day after meals. Plasma glucose levels were measured by a standard glucose oxidase method. Subjects were randomly assigned to a group in which captopril was given on the 1st day followed by placebo on the 2nd day or a group in which the placebo was administered on the 1st day and captopril on the 2nd day. Before and 1 and/or 2 h after breakfast or lunch on 2 consecutive days, forearm blood flow was determined by venous-occlusion plethysmography with strain gauges (Vasculab, Medasonics, Mountain View, CA), excluding the hand circulation with a wrist blood pressure cuff inflated to 200 mmHg (expressed as ml · 100 ml^{-1} · min^{-1}) (4). Vascular resistance was calculated from the equation for mean blood pressure divided by forearm blood flow (mmHg/ml · 100 ml^{-1} · min^{-1}). In a pilot study (n = 4), forearm blood flow tended to decrease after breakfast through 1400. However, when captopril was administered, forearm blood flow increased significantly 2 h after breakfast and returned to basal levels before lunch with a slight but not significant increase 1 and 2 h after lunch. Hematocrit determined 2 h after lunch did not differ from control values before lunch. Based on these findings, forearm blood flow was determined before and 2 h after lunch in the remaining subjects. Plasma insulin levels were also measured in some of the subjects (n = 8) before and 2 h after lunch by a specific radioimmunoassay. Individual daily meals were identical during the 2 days of the study and consisted of 1300–2000 kcal containing 70–90 g protein, 50–55 g fat, and 1200–1550 ml water.

Data are expressed as means ± SE. Statistical difference was evaluated by paired Student's t test or analysis of variance with repeated measurements. To evaluate changes between times, a Scheffe-type criterion was used.