

Effect of Low-Dose Insulin Treatment on Body Weight and Physical Development in Children and Adolescents at Risk for Type 1 Diabetes

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OBJECTIVE— Insulin's role in body weight regulation is controversial. We evaluated the effect of parenteral insulin on body weight and physical development in children and adolescents at risk for type 1 diabetes.

RESEARCH DESIGN AND METHODS— We performed a secondary analysis of the parenteral arm of the Diabetes Prevention Trial–Type 1 Diabetes (DPT-1), a randomized controlled trial of low-dose parenteral insulin (human ultralente insulin at 0.25 units · kg⁻¹ · day⁻¹) in subjects with a >50% 5-year risk of diabetes. Analysis was limited to 100 subjects (55 intervention, 45 closely monitored) aged <19 years at randomization whose weight was followed for at least 2 years by study end after excluding subjects who were noncompliant within 2 years or developed diabetes within 36 months of randomization.

RESULTS— Subjects ranged in age from 4.07 to 18.98 years. There were no significant differences at randomization between subjects in each group with respect to sex, age, weight, height, BMI, Tanner stage, or glucose tolerance. We found no differences over 2 years between the intervention and closely monitored groups in the change in weight (median 6.8 vs. 6.0 kg, $P = 0.65$), height (median 10.7 vs. 10.1 cm, $P = 0.66$), BMI (median 0.9 vs. 1.0 kg/m², $P = 0.79$), or Tanner stage (median 0 vs. 0, $P = 0.35$). Multiple regression showed no effect of insulin on change in weight ($P = 0.53$) or BMI ($P = 0.95$) over 2 years after adjustment for relevant covariates.

CONCLUSIONS— Low-dose insulin treatment for 2 years did not affect the weight, BMI, or physical development of nondiabetic children and adolescents.

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Abbreviations: CMG, closely monitored group; DPT-1, Diabetes Prevention Trial–Type 1 Diabetes; HOMA-IR, homeostasis model assessment of insulin resistance; IG, intervention group; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

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

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The effect of insulin on body weight has been the subject of much debate. Peripheral insulin action may promote weight gain by facilitating storage of metabolic fuels, thereby leading to hunger and increased caloric intake (2,3). Weight gain, for example, is a known complication of exogenous insulin treatment for both type 1 and type 2 diabetes (4,5). Normal rats treated with exogenous insulin also demonstrate increased food intake and weight gain despite only mild hypoglycemia (6). Insulin's central action on appetite regulation, however, strongly supports an anorectic effect (7). Animal studies show increased food intake and weight gain with disruption in the brain insulin receptor (8) and decreased food intake and weight loss with intracerebroventricular insulin infusion (9).

Longitudinal observational studies exploring the relationship between endogenous insulin secretion and sensitivity (S_i) and changes in weight and body composition show inconsistent results (10–20). Studies among normal glucose tolerant Pima Indian adults demonstrated that both insulin secretion (14) and insulin resistance (15) were negatively associated with weight gain. Higher fasting insulin was also associated with a decreased likelihood of weight gain among normal glucose tolerant Hispanic and non-Hispanic white subjects (16). In contrast, high acute insulin secretion during an intravenous glucose tolerance test (IVGTT) predicted weight gain among normal glucose tolerant offspring of two type 2 diabetic parents (12). Differences in length of follow-up, expression of change in weight, and baseline weight have been proposed as potential explanations for these conflicting results (12).

Fewer studies have addressed these issues in children (18–20), and changes in insulin resistance associated with puberty further complicate this relationship (21). Fasting hyperinsulinemia was associated with an increased adjusted rate of

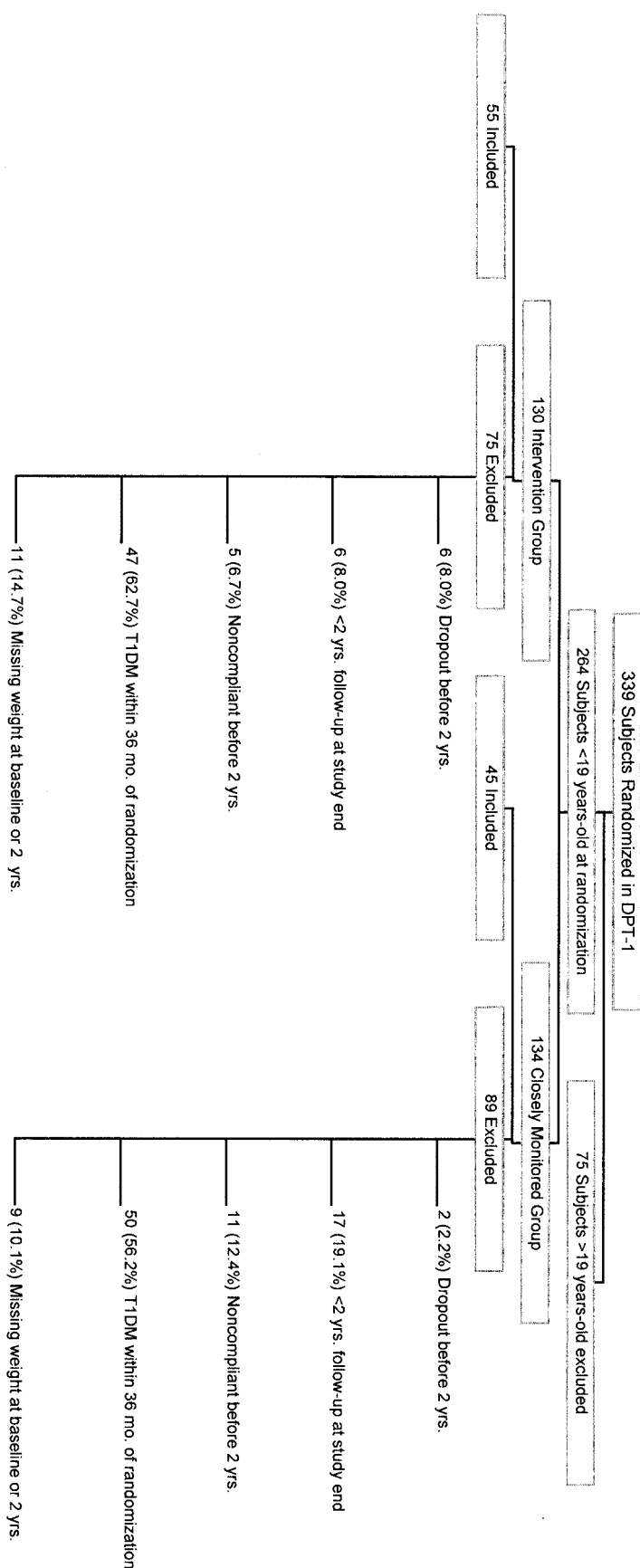


Figure 1—Identification of eligible subjects. T1DM, type 1 diabetes.

weight gain among nondiabetic Pima Indian children (18) and with an adjusted increase in body fat in white and African-American children (19). However, among healthy nondiabetic children, the most insulin-resistant subjects (lowest tertile of S_1) either maintained (girls) or decreased (boys) their percentage of body fat, assessed by skinfold thickness over 3 years (20).

Prior studies in this area have methodological limitations including their observational nature, inability to distinguish between primary and secondary hyperinsulinemia (the latter compensatory to insulin resistance), inability to account for divergent action of insulin centrally versus peripherally, and, in children, limited availability of data. The parenteral insulin arm of the Diabetes Prevention Trial—Type 1 Diabetes (DPT-1), a randomized controlled trial of low-dose insulin treatment for prevention of type 1 diabetes in relatives at high risk (1), afforded a unique opportunity to evaluate the effect of exogenous insulin treatment on body weight and physical development in nondiabetic children and adolescents in an experimental setting. The primary hypothesis under consideration was that body weight among children and adolescents receiving low-dose parenteral insulin would differ from that of a closely monitored group not receiving insulin.

RESEARCH DESIGN AND METHODS

The study design was a secondary analysis of data collected in the parenteral insulin arm of the DPT-1, a randomized controlled trial of parenteral insulin for prevention of type 1 diabetes conducted between 1994 and 2001 (1).

Recruitment of DPT-1 subjects has been previously described (1). Briefly, 3- to 45-year-old first-degree relatives and 3- to 20-year-old second-degree relatives of patients with type 1 diabetes, who had islet cell antibody titers ≥ 10 Juvenile Diabetes Foundation units, underwent a staging procedure including IVGTT and oral glucose tolerance tests (OGTTs). Subjects with estimated 5-year risk of type 1 diabetes $>50\%$ were eligible (1).

We limited our study to subjects <19 years old at randomization to focus on physical development. We also excluded subjects with <2 years of follow-up because of dropout or study end (21 May 2001), with weight missing at baseline or 2 years, or who were noncompliant

Table 1—Baseline characteristics of subjects included in the analysis

	n	IG	n	CMG	P
Sex	55	53% male	45	64% male	0.24*
Age (years)	55	10.3 (8.1, 15.0)	45	9.7 (8.4, 11.8)	0.33†
Weight (kg)	55	32.6 (24.4, 55.1)	45	31.1 (25.7, 42.0)	0.48‡
Weight Z-score	55	0.17 (−0.49, 0.69)	45	−0.08 (−0.62, 0.74)	0.55†
Height (cm)	54	141.3 (121.9, 166.4)	43	136.8 (128.7, 151.1)	0.45†
Height Z-score	54	0.34 (−0.29, 1.04)	43	0.06 (−0.55, 0.96)	0.20†
BMI (kg/m ²)	54	17.0 (15.2, 19.7)	43	17.0 (15.4, 19.1)	0.81‡
BMI Z-score	54	0.09 (−0.66, 0.43)	43	0.01 (−0.60, 0.40)	0.94†
Tanner stage	52	1 (1, 4)	42	1 (1, 2)	0.69*
HOMA-IR	55	1.9 (1.7, 2.6)	45	1.7 (1.3, 2.4)	0.05‡
Impaired/indeterminate glucose tolerance§	55	27%	45	22%	0.56*

Data are medians (25th percentile, 75th percentile) or %. * χ^2 test. †t test. ‡Wilcoxon's rank-sum test. §Indeterminate glucose tolerance defined as glucose ≥ 200 mg/dl at 30, 60, or 90 min but fasting plasma glucose < 110 mg/dl and 120-min glucose < 140 mg/dl during an OGTT (1).

within 2 years or developed diabetes within 36 months of randomization (among subjects with 36 months of follow-up available). The latter exclusion was intended to limit the impact of early diabetes on anthropometric measures. For the intervention group (IG), noncompliance was defined as refusal to take parenteral insulin, and for the closely monitored group (CMG), as refusal to participate in all visits or participation in another diabetes prevention therapy. Figure 1 shows the algorithm to identify eligible subjects.

Protocol

The DPT-1 study protocol has been previously described (1). Subjects in the IG received twice-daily subcutaneous insulin injections and annual intravenous insulin infusions. Subcutaneous injections consisted of recombinant human ultralente insulin (Humulin U; Eli Lilly) at 0.25 units \cdot kg^{−1} \cdot day^{−1} divided twice daily with adjustment for weight and hypoglycemia. At baseline and every 12 months, subjects also received continuous intravenous infusions of recombinant human regular insulin (Humulin R; Eli Lilly) for 4 days at 0.015 units \cdot kg^{−1} \cdot h^{−1} with adjustments for meals and hypoglycemia. CMG subjects were not treated with placebo. Subjects had an OGTT at 6-month intervals and either a mixed-meal tolerance test or IVGTT at yearly intervals (1). OGTT results were interpreted according to American Diabetes Association guidelines (22). Indeterminate glucose tolerance was defined as a blood glucose ≥ 200 mg/dl at 30, 60, or 90 min

but normal fasting and 120-min glucose (1). This definition is based on the classification system used by the 1979 National Diabetes Data Group, which required intermediary glucose measurements during an OGTT and recognized that abnormalities of glucose homeostasis are a continuum (23,24). We felt these OGTT profiles reflected some evidence of impairment and categorized these results together with impaired glucose tolerance.

Measurements

Anthropometric and physical examination data were collected at participating sites at 6-month intervals. Weight was measured in kilograms and height in centimeters. Weight, height, and BMI Z-scores were calculated based on data from the Centers for Disease Control and Prevention (25). Pubertal development was assigned a Tanner stage from one (prepubertal) to five (adult) (26,27). Glucose and insulin were measured after an overnight fast. Plasma glucose was measured by the glucose oxidase method and plasma insulin by radioimmunoassay. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) defined as the product of fasting glucose (mmol/l) and fasting insulin (μ U/ml) divided by 22.5 (28).

Statistical analysis

Analyses were performed using SAS (Version 8.2; SAS Institute, Cary, NC). We did not perform an intention-to-treat analysis. Primary outcome measures were change in weight and BMI from 0 to 2

years. Secondary outcome measures were change in height and Tanner stage from 0 to 2 years.

Averaged insulin dose (units \cdot kg^{−1} \cdot day^{−1}) in the IG was defined as the average of doses at the 0-, 6-, 12-, 18-, and 24-month visits. Insulin doses > 0.5 units \cdot kg^{−1} \cdot day^{−1} ($n = 2$) were presumed to be recording errors and were excluded. Average rate of hypoglycemic events was defined as the average of interval definite hypoglycemic events reported at the 6-, 12-, 18-, and 24-month visits.

Data are summarized as a proportion or median (25th percentile, 75th percentile). We used the χ^2 test for categorical variables, *t* test for normally distributed continuous measures, and Wilcoxon's rank-sum test for non-normally distributed continuous measures. Hierarchical multiple linear regression models were used to assess the independent effect of insulin treatment on change in weight and BMI. Residual diagnostics were performed to confirm the appropriateness of model assumptions. Tests of significance were two-tailed with $P < 0.05$ considered significant in all analyses.

RESULTS

Subjects

Out of 339 subjects participating in the parenteral insulin arm of the DPT-1, 264 were < 19 years old at randomization and approximately evenly split between the IG and CMG. We further excluded subjects based on the criteria outlined above, leaving 55 IG subjects and 45 CMG subjects (Fig. 1). Table 1 shows the characteristics of these subjects. Over 2 years, IG subjects received a median averaged insulin dose of 0.243 (0.236, 0.249) units \cdot kg^{−1} \cdot day^{−1}, and the groups had comparable average rates of hypoglycemic events ($P = 0.15$).

At baseline, there were no significant differences between included subjects in the two groups with respect to sex, age, weight, weight Z-score, height, height Z-score, BMI, BMI Z-score, Tanner stage, and glucose tolerance (Table 1). Difference in HOMA-IR was of borderline statistical significance ($P = 0.05$) with highly skewed distributions in both groups. Because 93.5% of DPT-1 subjects were non-Hispanic white (1), race/ethnicity was not considered as a covariate.

Among pediatric subjects, there were

Table 2—Change from 0 to 2 years

	n	IG	n	CMG	P
ΔWeight (kg)	55	6.8 (4.8, 10.0)	45	6.0 (5.3, 8.6)	0.65*
ΔWeight Z-score†	55	0.09 (−0.29, 0.34)	45	−0.07 (−0.22, 0.23)	0.40‡
ΔHeight (cm)§	54	10.7 (6.8, 14.0)	43	10.1 (7.2, 12.5)	0.66
ΔHeight Z-score†	54	0.04 (−0.26, 0.37)	43	−0.04 (−0.29, 0.30)	0.57‡
ΔBMI (kg/m ²)	54	0.9 (0.1, 1.7)	43	1.0 (0.4, 1.9)	0.79
ΔBMI Z-score†	54	0.01 (−0.29, 0.25)	43	−0.02 (−0.30, 0.30)	0.88‡
ΔTanner stage#	51	0 (0, 1)	40	0 (0, 0.5)	0.35**

Data are medians (25th percentile, 75th percentile). **t* test with unequal variance. †Z-scores for subjects >20 years of age at 2 years (*n* = 5) were calculated using data available for 20-year-olds (25). ‡*t* test with equal variance. §Height was used as recorded without adjustment for changes from 0 to 2 years that were negative. ||Wilcoxon's rank-sum test. #Eight subjects had Tanner stage measurement that decreased by 1 from baseline to 2 years (seven of these were from Tanner stage 5 to Tanner stage 4). These eight measurements of −1 were reassigned to 0. ** χ^2 test.

also no significant differences in sex or baseline age between individuals included compared with individuals excluded from either group (data not shown). However, a significantly higher proportion of excluded subjects in both groups had impaired/indeterminate glucose tolerance (IG: 47% of excluded vs. 27% of included, *P* = 0.02; CMG: 53% of excluded vs. 22% of included, *P* < 0.001).

Changes in anthropometric measures

No significant differences were noted between groups in the change in weight, weight Z-score, height, height Z-score, BMI, BMI Z-score, or Tanner stage over 2 years (Table 2). The effect of insulin on change in weight (0.51 ± 0.81 kg, *P* = 0.53) and BMI (0.02 ± 0.25 kg/m², *P* =

0.95) over 2 years remained nonsignificant when adjusted for relevant covariates (Table 3). Adjustment for baseline HOMA-IR did not change the results, and there were no significant interactions between insulin treatment and baseline glucose tolerance or baseline HOMA-IR (data not shown). Comparable analyses with weight and BMI at 2 years as outcomes adjusted for baseline weight or BMI, respectively, produced similar results (data not shown).

CONCLUSIONS— We found no significant differences between the change in weight, BMI, height, or Tanner stage over 2 years in nondiabetic children and adolescents treated with low-dose parenteral insulin compared with an untreated closely monitored group. Therefore, we did not find support for either the conten-

tion that insulin promotes or protects against weight gain at the low dose used in this study.

There are several possible explanations for the absence of an observed effect of insulin on weight and BMI in our study. First, low-dose insulin administration may have caused a commensurate reduction in endogenous insulin secretion, resulting in no actual increase in circulating insulin among IG subjects. This possibility is supported by a comparably low rate of hypoglycemic events in the two groups. Second, any increase in circulating insulin in IG subjects may have been insufficient to produce physiological changes at peripheral sites (causing weight gain [2,3]) or in the central nervous system (causing weight loss [7–9]). Third, at the low insulin dose used in this study, the central and peripheral effects of insulin may be mutually offset. Because of the narrow insulin dose range used in this study, we could not evaluate a dose-response relationship. Fourth, IG subjects may have developed compensatory insulin resistance in response to insulin administration limiting insulin's peripheral effects, which might otherwise have contributed to weight gain. Experimental studies in healthy human subjects have demonstrated that chronic insulin infusion under euglycemic conditions can lead to insulin resistance, as demonstrated by decreased whole-body glucose disposal (29). The development of insulin antibodies in the IG, however, may interfere with accurate measurement of insulin

Table 3—Adjusted effect of insulin treatment on change in weight (kg) and change in BMI (kg/m²) from 0 to 2 years

Model	Covariates	Weight models			BMI models		
		n	ΔWt ± SE due to insulin treatment	<i>P</i> *	n	ΔBMI ± SE due to insulin treatment	<i>P</i> †
1	Unadjusted	100	0.38 ± 0.86	0.66	97	0.04 ± 0.25	0.89
2	Model 1 + sex, baseline age, and baseline Tanner stage	94	0.79 ± 0.90	0.38	91	0.01 ± 0.26	0.96
3	Model 2 + baseline BMI	91	0.71 ± 0.93	0.44	91	0.01 ± 0.26	0.98
4	Model 3 + baseline glucose tolerance	91	0.85 ± 0.92	0.36	91	0.07 ± 0.25	0.79
5	Model 4 + Δ Tanner stage from 0 to 2 years‡	88	0.40 ± 0.80	0.61	88	0.002 ± 0.25	0.99
6	Model 5 + average rate of hypoglycemic events from 0 to 2 years	88	0.51 ± 0.81	0.53	88	0.02 ± 0.25	0.95

**P* value for effect of insulin treatment on change in weight from multiple regression. †*P* value for effect of insulin treatment on change in BMI from multiple regression. ‡Eight subjects had Tanner stage that dropped by 1 from baseline to 2 years (seven of these were from Tanner stage 5 to Tanner stage 4). These eight measurements of −1 were reassigned to 0.

in this group (30). Because polyethylene glycol extraction was not performed before assaying plasma insulin concentrations (30), we did not assess change in insulin levels over time as an indicator of change in insulin resistance.

To explain the contradictory findings of prior studies concerning the relationship between insulin resistance and weight gain in children (18–20), others have highlighted potentially relevant differences in the populations studied and measurements used (20). Such differences should also be considered when placing our study in the context of other pediatric studies. DPT-1 subjects were predominantly non-Hispanic white and had a high risk of type 1 diabetes. To be included in the DPT-1, subjects had either a low first-phase insulin response on an IVGTT on two occasions and/or an abnormal OGTT (1). Indeed, although not overweight or insulin resistant at baseline, approximately one-quarter of our subjects had impaired/indeterminate glucose tolerance, suggesting relative insulin deficiency in some subjects. These characteristics contrast with the study in Pima Indian children, for example, in which subjects were, on average, overweight (relative weight $119 \pm 24\%$) with high risk of type 2 diabetes, had high fasting insulin at baseline, and had normal glucose tolerance (18). Our study also assessed change in weight over 2 years, a shorter interval than some pediatric observational studies (18–20). How long subjects treated with low-dose insulin would need to be followed to see a differential effect on weight is not known. However, in subjects with type 1 diabetes participating in the Diabetes Control and Complications Trial, significantly greater weight gain in the intensively treated group was evident within the first year of therapy (5). We therefore felt that 2 years may be a sufficient period of observation for our analysis. The possibility remains that this may not be the case. Finally, we used weight and BMI as our primary outcome measures. BMI is considered a valid approximation of body fatness in pediatric patients (31), although critics note that it may be affected by changes in lean body mass as well as fat mass (20,32).

There are several methodological limitations to our study, which merit comment. Although this was a randomized controlled trial, there was no blinding or placebo. Had weight and BMI been the

primary end points of the original study, then an information bias could have been introduced with this design. However, as these were not the original focus, such a bias is unlikely. Based on adjusted analyses, a difference of 2.3 kg in weight and 0.7 kg/m^2 in BMI over 2 years would have been detected with 80% power had it been present.

We also did not include all randomized subjects in our analysis. However, we applied the same exclusion criteria to both the IG and CMG. Among the pediatric subjects, development of diabetes was the primary reason for further exclusion in both groups, and comparison of subjects included in each group indicated no significant differences at baseline. In each group, included subjects were also of comparable age and sex to excluded subjects. Both findings suggest that introduction of a selection bias was unlikely. Missing data were assumed to be missing at random. While residual confounding due to unmeasured confounders could theoretically be present, this is unlikely to explain our negative findings.

Because early diabetes may influence anthropometric measures and endogenous insulin, we could not reliably compare baseline weight, height, BMI, pubertal development, or HOMA-IR between included and excluded subjects because a significant proportion developed type 1 diabetes within the first 12 months. However, it does appear that included subjects in both groups were healthier at baseline than excluded subjects given the lower prevalence of impaired/indeterminate glucose tolerance. This suggests that our findings may not be generalizable to pediatric subjects with more significant impairments in glucose homeostasis. However, the finding that included subjects in the two groups were comparable with regard to glucose tolerance should not have biased our conclusions. Finally, among the 100 included subjects, 17 (9 IG [16%], 8 CMG [18%]) did not have follow-up between 24 and 36 months. Theoretically, some of these subjects may have developed diabetes during this time and, if so, should have been excluded. However, after excluding these 17 subjects, there was still no significant effect of insulin treatment on change in weight ($n = 83$, $P = 0.47$) or BMI ($n = 80$, $P = 0.73$) over 2 years in unadjusted models (as in Table 3, Model 1), suggesting that

their inclusion was also unlikely to have introduced bias.

This study's major strength is the unique experimental design whereby exogenous insulin was administered to nondiabetic subjects who were followed prospectively for at least 2 years. We found that low-dose parenteral insulin treatment for 2 years did not affect body weight or physical development in nondiabetic children and adolescents at high risk for type 1 diabetes. Future research is needed to validate these findings in other pediatric groups with different baseline risk characteristics and in other racial/ethnic groups. Evaluation of whether similar findings with regard to weight extend to adults in this population should also be explored.

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References

1. Diabetes Prevention Trial—Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002
2. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB: High glycemic index foods, overeating, and obesity. *Pediatrics* 103:E26, 1999
3. Campfield LA, Smith FJ, Rosenbaum M, Hirsch J: Human eating: evidence for a physiological basis using a modified paradigm. *Neurosci Biobehav Rev* 20:133–137, 1996
4. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 di-

- abetes (UKPDS 33). *Lancet* 352:837–853, 1998
5. DCCT Research Group: Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. *Diabetes Care* 11:567–573, 1988
 6. Cusin I, Rohner-Jeanrenaud F, Terretaz J, Jeanrenaud B: Hyperinsulinemia and its impact on obesity and insulin resistance. *Int J Obes Relat Metab Disord* 16 (Suppl. 4):S1–S11, 1992
 7. Woods SC, Seeley RJ: Insulin as an adiposity signal. *Int J Obes Relat Metab Disord* 25 (Suppl. 5):S35–S38, 2001
 8. Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR: Role of brain insulin receptor in control of body weight and reproduction. *Science* 289: 2122–2125, 2000
 9. Woods SC, Lotter EC, McKay LD, Porte D Jr: Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 282: 503–505, 1979
 10. Folsom AR, Vitelli LL, Lewis CE, Schreiner PJ, Watson RL, Wagenknecht LE: Is fasting insulin concentration inversely associated with rate of weight gain? Contrasting findings from the CARDIA and ARIC study cohorts. *Int J Obes Relat Metab Disord* 22:48–54, 1998
 11. Hodge AM, Dowse GK, Alberti KG, Tuomilehto J, Gareeboo H, Zimmet PZ: Relationship of insulin resistance to weight gain in nondiabetic Asian Indian, Creole, and Chinese Mauritians: Mauritius Non-communicable Disease Study Group. *Metabolism* 45:627–633, 1996
 12. Sigal RJ, El-Hashimy M, Martin BC, Soeldner JS, Krolewski AS, Warram JH: Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. *Diabetes* 46:1025–1029, 1997
 13. Gould AJ, Williams DE, Byrne CD, Hales CN, Wareham NJ: Prospective cohort study of the relationship of markers of insulin resistance and secretion with weight gain and changes in regional adiposity. *Int J Obes Relat Metab Disord* 23:1256–1261, 1999
 14. Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C: Reduced insulin secretion: an independent predictor of body weight gain. *J Clin Endocrinol Metab* 80: 1571–1576, 1995
 15. Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC, Lillioja S, Bogardus C, Ravussin E: Insulin resistance associated with lower rates of weight gain in Pima Indians. *J Clin Invest* 88:168–173, 1991
 16. Hoag S, Marshall JA, Jones RH, Hamman RF: High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: the San Luis Valley Diabetes Study. *Int J Obes Relat Metab Disord* 19:175–180, 1995
 17. Valdez R, Mitchell BD, Haffner SM, Hazuda HP, Morales PA, Monterrosa A, Stern MP: Predictors of weight change in a bi-ethnic population: the San Antonio Heart Study. *Int J Obes Relat Metab Disord* 18:85–91, 1994
 18. Odeleye OE, de Courten M, Pettitt DJ, Ravussin E: Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes* 46:1341–1345, 1997
 19. Johnson MS, Figueroa-Colon R, Huang TT, Dwyer JH, Goran MI: Longitudinal changes in body fat in African American and Caucasian children: influence of fasting insulin and insulin sensitivity. *J Clin Endocrinol Metab* 86:3182–3187, 2001
 20. Travers SH, Jeffers BW, Eckel RH: Insulin resistance during puberty and future fat accumulation. *J Clin Endocrinol Metab* 87: 3814–3818, 2002
 21. Roemmich JN, Clark PA, Lusk M, Friel A, Weltman A, Epstein LH, Rogol AD: Pubertal alterations in growth and body composition. VI. Pubertal insulin resistance: relation to adiposity, body fat distribution and hormone release. *Int J Obes Relat Metab Disord* 26:701–709, 2002
 22. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
 23. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
 24. Bennett PH: Definition, diagnosis, and classification of diabetes mellitus and impaired glucose tolerance. In *Joslin's Diabetes Mellitus*. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger, 1994, p. 193–200
 25. 2000 CDC Growth Charts: United States. Available from <http://www.cdc.gov/growthcharts>. Accessed 21 March 2005
 26. Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 44:291–303, 1969
 27. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45:13–23, 1970
 28. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
 29. Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA: Effect of sustained physiologic hyperinsulinemia and hyperglycemia on insulin secretion and insulin sensitivity in man. *Diabetologia* 37:1025–1035, 1994
 30. Armitage M, Wilkin T, Wood P, Casey C, Loveless R: Insulin autoantibodies and insulin assay. *Diabetes* 37:1392–1396, 1988
 31. Pietrobello A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB: Body mass index as a measure of adiposity among children and adolescents: a validation study. *J Pediatr* 132:204–210, 1998
 32. Maynard LM, Wisemandle W, Roche AF, Chumlea WC, Guo SS, Siervogel RM: Childhood body composition in relation to body mass index. *Pediatrics* 107:344–350, 2001