Serum Leptin Concentrations in Children With Type 1 Diabetes Mellitus: Relationship to Body Mass Index, Insulin Dose, and Glycemic Control

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Although obesity is a frequent feature of type 2 diabetes mellitus (DM), many patients with type 1 DM are prone to high body mass index (BMI). We measured serum leptin concentrations in a cohort of children (n = 55) with type 1 diabetes mellitus (DM), as well as their anthropometric parameters including BMI, skin fold thickness at multiple sites, and midarm circumference. Glycemic control was assessed by blood glucose (BG) monitoring before meals, and measurement of glycated hemoglobin (HbA_{1c}) and insulin dose/kg/d was recorded. Dietary evaluation and assessment of caloric intake (kg/d) was performed by an expert dietitian. In the newly diagnosed children (n = 10) before initiation of insulin therapy, circulating leptin concentration was significantly lower (1.1 ± 0.8 ng/dL) versus 5 days after insulin therapy (1.45 ± 0.7 ng/dL). The decreased leptin level appears to be related to insulinopenia in these patients. In 45 children with type 1 DM on conventional therapy (2 doses of insulin mixture (NPH and regular) subcutaneous (SC) before breakfast and dinner for more than 2 years), serum leptin concentration was significantly higher (2.15 ± 1 ng/dL) compared with age-matched normal children (1.3 ± 1 ng/dL). Diabetic children were further divided into 2 groups according to their HbA_{1c} level: group 1 with HbA_{1C} less than 7.5% (less than 2 SD above the mean for normal population) (n = 29) and group 2 with HbA_{1c} greater than 7.5%. (greater than 2 SD above the mean for normal population) (n = 16). Patients with a higher HbA_{1c} level (group 2) had a higher leptin concentration (2.3 ± 0.8 ng/dL), higher BMI (17.8 ± 1.7), and were receiving higher insulin dose/kg (0.92 ± 0.2 U/kg/d) compared with group 1 (lower HbA_{1c}) (1.78 ± 0.8 ng/dL, 16.7 ± 1.5, and 0.59 ± 0.2 U/kg/d, respectively). Group 2 patients had a higher incidence of late morning hypoglycemia (9/29) versus group 1 patients (2/16). Analysis of dietary intake showed that patients with a higher HbA_{1c} (group 2) consumed more calories (73.5 ± 10.5 kcal/kg/d) versus patients with lower HbA_{1c} (64.2 ± 8.7 kcal/kg/d). These findings pointed to the unphysiologic nature of injecting a mixture of insulin twice daily. To cover the relatively big lunch meal (40% to 50% of the total caloric intake in the Arab countries) and prevent afternoon hyperglycemia, there is a great tendency to increase NPH dose before breakfast. This, in turn, induces late-morning hypoglycemia and increases appetite and food intake at that time. Multiple regression analysis showed that circulating leptin concentrations (the dependent variable) were best correlated with the mean skinfold thickness (SFT), BMI, and caloric intake/kg/d (together they explained 65% of the variability in leptin concentrations). It appears that oversubstitution by insulin and increased food intake stimulate fat synthesis and subsequently BMI. Increased appetite and BMI contribute to increased leptin secretion and explains the higher leptin levels in undercontrolled diabetic children (higher circulating HbA_{1c} concentrations) who were oversubstituted by insulin.

TYPE 1 DIABETES MELLITUS (DM) is characterized by severe insulinopenia and dependence on exogenous insulin to preserve life. Although obesity is a frequent feature of type 2 DM, many patients with type 1 DM are obese, and children and adolescents with type 1 DM are more prone to high body mass index (BMI) than their nondiabetic counterparts and unaffected siblings.[1-3] Obesity by itself leads to insulin resistance and increases the requirements of insulin to attain good glycemic control.[4,5] Many factors might affect the BMI in patients with type 1 DM. These include: (1) glycemic control, (2) insulin dose, (3) quality and quantity of food consumed, and (4) different daily activities and exercise.

In many in vivo studies, a strong positive correlation was detected between circulating leptin concentration on the one hand and BMI and body fat on the other hand.[6-10] Human obesity is suggested to be, in part, due to desensitization of leptin receptors within the hypothalamus resulting in hyperphagia.[5,11] Sustained elevation of plasma leptin levels is proposed to uncouple leptin action on its receptors in the hypothalamus and thereby attenuates signal transduction pathway that exerts the effects of leptin on satiety and energy expenditure.[12] In diabetic children, leptin secretion can be changed by multiple factors. Overfeeding, increased insulin dose/kilogram, and elevated cortisol (in response to frequent hypoglycemia) might increase leptin secretion, whereas insulin deficiency and dietary restriction (underfeeding) might decrease it.[11-18]

We studied serum leptin concentrations in a cohort of children with type 1 DM in relationship to their anthropometric data BMI and skinfold thickness (SFT), the degree of glycemic control, their qualitative and quantitative food intake, and insulin dose/kg/d.

PATIENTS AND METHODS

This study included 55 prepubertal children with type 1 DM, aged between 3 and 10 years (29 males and 26 females) attending the Diabetes Clinic of Alexandria University Children's Hospital, Alexandria, Egypt. Ten of them were newly diagnosed patients who were studied before and after correction of ketoacidosis and hyperglycemia. The other 45 children were children with type 1 DM on conventional therapy (2 injections of insulin mixture, NPH and regular insulin, before breakfast and dinner) for 2 years or more. Ten age-matched healthy children served as controls. Informed consent was obtained from the parents of all the children and when appropriate from the

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children. The protocol of the study was approved by the ethical committee of Alexandria University.

All children were subjected to: (1) case history including the onset of the disease, insulin dose/kg/d, and detailed daily activities. (2) Full clinical examination including anthropometric measurements (height, weight, BMI, and SFT at multiple sites (abdominal, scapular, and triceps) using the Holtain caliper, and midarm circumference (MAC) using a metal tape. (3) Qualitative and quanititative evaluation of dietary intake using the counting method for 3 days was performed by an expert dietitian. Each patient was offered a dietary sheet to record food intake (quality, quantity, and time). (4) Self-glucose monitoring was performed by the parents before meals, snacks, at midnight, and at 3:00 AM to 4:00 AM for each patient using the 1-touch glucometers offered to them. (5) A fasting venous blood sample was collected at 8:00 AM to 9:00 AM for measuring serum cortisol (by radioimmunoassay [RIA]), leptin (using kits purchased from Diagnostic System Laboratories, Los Angeles, CA) (enzyme-linked immunosorbent assay [ELISA] method), and glycated hemoglobin (HbA_{1c}) (ELISA method).

Data are presented as mean ± SD. Statistical analyses were performed using the analysis of variance (ANOVA) test to compare anthropometric and analyte concentrations among study groups when data were normally distributed, and the Wilcoxon test was used when the data were not normally distributed. The linear regression equation was used to test the relationship between variables. A multiple regression analysis for all subjects was performed to study the total contribution of all parameters, including BMI, SFT, insulin dose/kg/d, HbA_{1C} concentration, and caloric intake to the leptin variation. Data are presented as means ± SD.

RESULTS

Anthropometric and lab data of diabetic children on conventional insulin therapy and normal children (Table 1) showed that diabetic children had significantly higher BMI, circulating leptin, 8:00 AM cortisol, and fasting blood glucose (BG) concentrations versus normal children.

Patients were divided according to their HbA_{1c} levels into 2 groups (group 1 with $HbA_{1c} \geq 2$ SD above the mean for the general population [7.5%, n = 16] and group 2 with $HbA_{1c} <$ 7.5%). Children in group 1 had significantly higher BMI, insulin dose/kg/d, and leptin concentration compared with group 2 patients) (Table 2). They consumed significantly higher amounts of calories/kg/d (73 ± 10.5 kcal/kg/d) versus patients in group 2 (63.8 ± 9.3 kcal/kg/d). Analysis of self-glucose monitoring records showed a higher incidence of hypoglycemia (BG below 3 mmol/L) in group 1 patients (9/29) versus group 2 patients (2/16) in the late morning hours (between 10:30 AM and 11:30 AM). Symptoms of hypoglycemia (hunger, drowsiness, headache, and sweating) were reported in 7/29 patients in group 1 and 1 patient in group 2. Circulating leptin concentrations were significantly higher in diabetic girls (2.3 ± 1.2 ng/dL) versus boys (1.8 ± 0.9 ng/dL).

Table 1. Anthropometric and Laboratory Data for Diabetic and Normal Children

	Type 1 DM	Controls
No.	45	10
Age (yr)	7.9 ± 1.5	7.38 ± 1.9
HtSDS	(−)0.51 ± 0.6	(−)0.2 ± 0.4
BMI	17.2 ± 1.7*	16.1 ± 2.1
MAC	17.7 ± 1.7	16.7 ± 1.9
Leptin (ng/dL)	2.1 ± 1.4*	1.3 ± 1.5
HbA_{1c} (%)	8.1 ± 1.8*	5.8 ± 0.8
FBG (mg/dL)	176 ± 61*	88.5 ± 8.8
Cortisol (nmol/L)	453 ± 78*	375 ± 88

NOTE. Data are mean ± SD.

Abbreviation: FBG, fasting blood glucose, cortisol at 8 AM; HtSDS, height standard deviation score.

*$P < .05$.

Table 2. Anthropometric and Laboratory Data of Patients With HbA_{1c} Above and Below 7.5%

	$HbA_{1c} > 7.5\%$	$HbA_{1c} > 7.5\%$
No.	16	29
HtSDS	(−)0.4 ± 0.7	(−)0.7 ± 0.8
BMI	17.8 ± 1.7*	16.7 ± 1.5
Caloric intake (kcal/kg/d)	73.5 ± 10.5*	64.2 ± 8.7
Duration of DM (yr)	3.5 ± 2.5	2.9 ± 1.8
Insulin dose (U/kg/d)	0.92 ± 0.2*	0.59 ± 0.2
Mean BG (mg/dL)	185 ± 65*	162 ± 56
Leptin (ng/dL)	2.28 ± 1.1*	1.76 ± 0.8
Cortisol (nmol/L)	495 ± 85	449 ± 79

NOTE. Mean BG, mean of recorded BG before meals, snacks, midnight, and 4 AM. $HbA_{1c} > 7.5\%$ (2 SD above the mean for general population). Data presented are mean ± SD.

*$P < .05$.

Table 3 compares BMI and lab data among the studied groups. In the newly diagnosed children, the BMI and serum leptin concentrations were significantly lower, and fasting BG and cortisol concentrations were higher before versus after 5 days of starting insulin therapy. Children with type 1 DM on conventional therapy for more than 2 years had higher BMI and serum leptin concentrations and lower HbA_{1c} and cortisol concentrations versus the newly diagnosed group.

Circulating leptin concentration was significantly correlated with BMI ($r = .439$, $P < .001$), abdominal SFT ($r = .47$, $P < .001$), triceps abdominal fat thickness ($r = .39$, $P < .001$), and insulin dose/kg (0.32, $P < .05$). Insulin dose/kg/d was correlated significantly with BMI ($r = .43$, $P < .001$) and triceps and abdominal SFT ($r = .37$ and .3, respectively, and $P < .01$) (Table 4, Fig 1). No significant correlation was found between leptin concentration on the one hand and age, duration of the disease, fasting BG, average BG (average of 7 readings/day) or HbA_{1c} concentration on the other hand. No correlation was detected between insulin dose and HbA_{1c} concentration in diabetic children.

DISCUSSION

In this study, newly diagnosed children with type 1 DM (during insulinopenia) had significantly lower leptin concentration compared with normal children. One in vivo study confirmed that ob mRNA and leptin protein levels decreased to barely detectable levels with fasting (low insulin status), but were restored to normal within 4 hours after refeeding or administration of insulin.[19,20] Streptozotocin-treated mice had low leptin levels that increased significantly after insulin injection.[20-22] Decreased leptin secretion stimulates appetite and contributes to hyperphagia in these patients.

Leptin concentrations increased markedly 5 days after starting insulin therapy even before significant change in BMI or

Table 3. BMI, Glycemic Data, Leptin, and Cortisol Levels in Diabetics and Controls

	New Type 1 (b)	New Type 1 (a)	Type 1 (>2 years)	Controls
No.	10	10	45	10
BMI	15.9 ± 2.1*	16.3 ± 1.9	17.2 ± 1.6†	16.1 ± 2.1
Leptin (ng/dL)	1.1 ± 0.8*	1.45 ± 0.7	2.1 ± 1.8†	1.3 ± 1.2
FBG (mg/dL)	312 ± 155*	189 ± 75†	176 ± 61†	88.5 ± 88
Mean BG (mg/dL)	ND	210 ± 52	170.5 ± 65	ND
HbA_{1c} (%)	10.5 ± 2.9*	10.3 ± 2.7†	8.1 ± 1.8†	5.8 ± 0.8
Cortisol (nmol/L)	599 ± 102*	469 ± 92†	453 ± 78†	375 ± 88

NOTE. Mean BG, mean of recorded BG before meals, snacks, midnight, and 4 AM, cortisol at 8 AM.

Abbreviation: ND, not done.

*$P < .05$ new type 1 before (b) *v* after (a) insulin therapy.

†$P < .05$ patients *v* controls.

SFT. In support of these data, Saad et al[23] have shown that low-dose infusions of insulin can prevent the decrease of leptin during fasting in humans with type 1 and type 2 diabetes. These data support a direct relationship between the circulating insulin concentration and leptin secretion.[19,24-27] Rats rendered hyperinsulinemic in clamp studies showed a marked increase in ob mRNA compared with controls.

The circulating leptin concentrations were higher in children with type 1 DM on long-term insulin therapy (more than 2 years) compared with normal children. Those diabetic children who had a higher HbA_{1c} (> 7.5%) (less compliant patients, group 1) had higher BMI, fasting BG and average BG concentrations, and higher insulin dose/kg/d compared with those with lower HbA_{1c} (< 7.5%) (more compliant, group 2). Analysis of dietary intake showed that patients in group 1 consumed more calories/kg/d (73 ± 10.5 kcal/kg/d) versus group 2 patients (63.8± 9.3 kcal/kg/d). Group 1 patients had a higher incidence of late-morning hypoglycemia (9/29 *v* patients in group 2 [2/16]).

In normal children during the fasting state, basal insulinemia (relatively low insulin status) controls and allows fine adjustment of glycolysis and possibly gluconeogenesis to supply enough glucose to keep an adequate BG level. It is important to emphasize that the liver is more sensitive than muscle or fat to a given concentration of insulin, ie, endogenous glucose production from the liver through glycolysis and gluconeogenesis can be restrained at insulin concentrations that do not fully augment glucose utilization by peripheral tissues.[28] Prandial insulin secretion (relatively high insulin status) inhibits glycolysis, lipolysis, and gluconeogenesis[28,29] and facilitates glycogen synthesis and glucose uptake by tissues to keep the BG level within a normal range.[28] In our diabetic patients receiving 2 injections of insulin mixture (NPH and regular) before breakfast (7:00 AM to 9:00 AM) and dinner (9:00 PM to 11:00 PM), it appears that increasing the morning basal insulin (NPH) above the physiologic limit is necessary to cover the big lunch meal (the main meal in Arab countries, taken between 1:00 PM and 3:00 PM and constitutes 40% to 50% of the total caloric intake of the day) and to avoid late afternoon hyperglycemia. This increase in NPH dose is associated in many patients with a tendency to hypoglycemia (through inhibiting proper glycolysis and gluconeogenesis) during late morning hours (10:30 AM to 11:30 AM) when the effects of NPH and regular insulin overlap (higher basal insulinemia). This also stimulates hunger and induces the intake of a big snack, which markedly increases the total caloric intake of the patient.

This basal hyperinsulinemia and increased caloric intake appear to stimulate lipogenesis and consequently increase BMI and fat mass. This view is supported in our patients who were receiving higher doses of insulin/kg/d. They had a higher incidence of hypoglycemia during the late morning hours, consumed more calories/kg/d, had significantly higher BMI, and increased subcutaneous fat thickness compared with those on a lower insulin dose/kg/d. In addition, insulin dose/kg/d was correlated significantly with BMI and SFT in these diabetic children. Multiple linear regression analysis showed that the mean SFT, BMI, and caloric intake together explained 65% of the variability in leptin concentrations (mean SFT, 32%; BMI, 18.5%, and caloric intake/kg/d, 15.2%). Luna et al[30] demonstrated that both obesity and insulin dose were correlated with leptin levels. However, in our study, the addition of insulin dose/kg/d to these independent variables did not improve prediction of the leptin level. In agreement with previous studies,[30-32] leptin concentrations were not correlated significantly with HbA_{1c} levels and the addition of HbA_{1c} as an independent variable to the multiple regression study variables did not improve the prediction of leptin level. These findings were in support of the indirect role of insulin on leptin secretion through increasing caloric intake, fat thickness, and BMI.

Table 4. BMI, Glycemic Data, Leptin, and Cortisol Levels in Males and Females With DM

	DM Females	DM Males	DM All	Controls
No.	21	24	45	10
BMI	17.5 ± 1.5*	16.9 ± 1.1*	17.2 ± 1.6*	16.1 ± 2.1
Leptin (ng/dL)	2.3 ± 1.6*†	1.9 ± 1.7*	2.1 ± 1.8*	1.3 ± 1.2
FBG (mg/dL)	179 ± 64*	173 ± 58*	176 ± 61*	88.5 ± 88
Mean BG (mg/dL)	172 ± 69*	169 ± 59*	170.5 ± 65	ND
HbA_{1c} (%)	8.2 ± 2*	7.9 ± 1.6*	8.1 ± 1.8*	5.8 ± 0.8
Cortisol (nmol/L)	473 ± 82*	432 ± 56*	453 ± 78*	375 ± 88

NOTE. Mean BG, mean of recorded BG before meals, snacks, midnight, and 4 AM, cortisol 8 AM. Data are presented as mean ± SD.

Abbreviation: ND, not done.

*$P < .05$ patients *v* controls.

†$P < .05$ males *v* females.

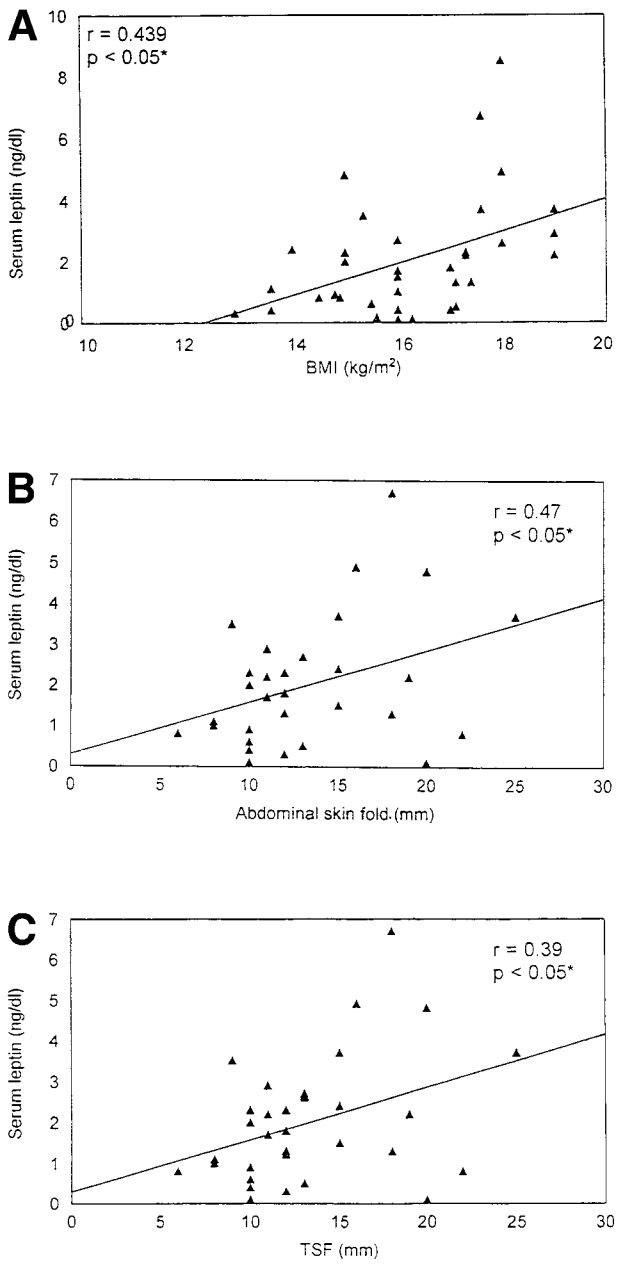

Fig 1. (A) Correlation with serum leptin level and BMI (r = .439, P < .05). (B) Correlation between serum leptin level and triceps SFT (r = .39, P < .05). (C) Correlation between serum leptin level and abdominal SFT (r = .47, P < .05).

It is suggested that in our diabetic patients basal hyperinsulinemia increases fat mass, with consequent increase in leptin secretion. In concert with this view, the serum leptin concentration was correlated significantly with BMI, abdominal and scapular SFT, and insulin dose/kg/d in these patients (Table 5). In addition to this indirect effect of insulin, basal hperinsulinemia might directly stimulate leptin secretion by adipose tissue. Multiple linear regression analysis showed that the BMI and mean SFT can explain 43% of the variabilities of leptin values. Addition of caloric intake to the mean SFT and BMI together can explain 0.65 of the variability in leptin concentrations. However, addition of insulin dose/kg/d to these independent variables did not add to the R^2 value. These findings are in support of the indirect role of insulin on leptin secretion through increasing caloric intake, fat thickness, and BMI.

Contrary to the expectation that patients with higher insulin doses might have lower HbA_{1c}, our patients with higher HbA_{1c} were receiving higher insulin doses. In addition, insulin dose/kg/d was not correlated significantly with either HbA_{1c} levels (r = .13, P > .05) or to fasting BG level (r = .09, P .05). This can be explained by the importance of other factors in the glycemic control of these patients including the regimen and type of insulin used in relationship to food intake, quality and quantity of their meals, amount of exercise they perform, and compliance to these aspects of control. It is expected that increasing the insulin doses as described above would stimulate appetite and increase food intake and consequently increase fat synthesis and BMI. The increased BMI and fat mass might produce a state of insulin resistance that disturbs glycemic control in these patients.

Multiple dose insulin therapy (basal insulin, once or twice daily, plus 3 prandial short-acting insulin doses) by adjusting the prandial short or ultrashort insulin dose to the specified caloric content of the meal and avoiding prolonged basal hyperinsulinemia appears more physiologic. In one study, patients with type 1 DM on multiple insulin doses had normal leptin concentrations compared with controls.[30] The normal diurnal pattern of leptin, which peaks in the nighttime, appears to be "entrained" to the normal rise and fall of insulin during the usual daytime meal cycle, and this can be disrupted by altering the patterns of meals and spikes of insulin. In addition, there are indications that dietary composition can affect leptin production by the adipocyte, because a high-fat diet reduces leptin levels more than a high-carbohydrate diet does, and fructose reduces leptin levels more than glucose. These findings have obvious implications for the relationship of dietary composition, insulin doses and types, and the schedule of insulin in relationship to meals to weight gain.[23,31]

In summary, subcutaneous insulin substitution using twice daily injections of insulin mixtures before breakfast and dinner is not physiologic. A nondiabetic circulating insulin profile cannot be simulated with this regimen. Many of the patients

Table 5. Correlations Between Leptin and Other Variables

	r	P
Age (yr)	.052	>.05
Duration of disease	.04	>.05
BMI	.439*	<.01
HtSDS	.15	>.05
Triceps SFT (mm)	.4	<.01
Abdominal SFT (mm)	.47*	<.01
Insulin dose (kg/d)	.32*	<.01
Fasting BG (mg/dL)	.1	>.05
HbA_{1c} (%)	.027	>.05

NOTE. Data presented are mean ± SD.

Abbreviations: HtSDS, height standard deviation score; SFT, skinfold thickness; BG, blood glucose.

*P < .05.

treated with this method have significant late morning hypoglycemia denoting high basal insulinemia, which stimulates increased food intake, BMI, and fat mass. Increased fat mass and basal hyperinsulinemia appear to stimulate leptin secretion to a higher level in these patients. It is hopeful that with strategies aimed at more physiologic circulating insulin (basal and prandial) levels that these metabolic abnormalities would be minimized.

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