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The evaluation of serum leptin level and other hormonal parameters in children with severe malnutrition

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Abstract

Objectives: Protein–energy malnutrition (PEM) is a clinical problem caused by inadequate intake of one or more nutritional elements, and remains as one of the most important health problems in developing countries. The aim of this study is to determine the relationship among leptin concentrations, body weight and concentrations of some serum hormones, e.g., basal GH, IGF-1, basal cortisol and IGF-BP3, in severe malnourished children, and to determine the effects of leptin in malnourished children.

Design and methods: The study group consisted of 36 children diagnosed with PEM. Thirty healthy children were enrolled as the control group. After an overnight fast and before initiation of feedings, fasting venous blood samples were obtained from a forearm vein with needle technique for routine tests, and leptin, IGF-1, IGF-BP3, basal GH and cortisol levels were measured. Tests were carried out in the laboratories of the Department of Biochemistry by commercial kits.

Results: Serum leptin levels of infants with marasmus and kwashiorkor were significantly lower than that of the controls (2.09 ± 0.93 and 2.27 ± 1.01, 6.82 ± 2.28 ng/ml, respectively, $P < 0.001$). However, there was no significant difference between serum leptin levels in children with marasmus and those with kwashiorkor ($P > 0.05$). Serum IGF-1 and IGF-BP3 levels were significantly lower in malnourished children ($P < 0.001$, both). Also, basal GH and cortisol levels were significantly higher in malnourished children ($P < 0.001$, both). There was a positive correlation among serum leptin levels and IGF-1 and IGF-BP3 levels and also a negative correlation among serum leptin levels and basal GH and cortisol levels in children diagnosed with marasmus or kwashiorkor and the control group.

Conclusions: The decrease of energy intake and adipose tissue and serum IGF-1 levels in children with PEM may result in decrease of leptin secretion. Decrease in serum leptin levels may initiate food intake by increasing appetite and stimulating the secretion of cortisol and GH that might increase energy expenditure through an autocrine mechanism. Moreover, serum leptin level may be an important signal to reflect the metabolism of children with PEM.

Keywords: Malnutrition; Leptin; IGF-1; Growth hormone; Cortisol

Introduction

Protein–energy malnutrition (PEM) is a clinical problem caused by inadequate intake of one or more nutritional elements, and remains as one of the most important health problems in developing countries [1]. Severe form of PEM affects 2–3% of the pediatric population worldwide, and PEM prevalence is approximately 20% in our country [2,3].

Leptin, a product of the *ob* gene, is expressed in adipocytes and secreted in pulses and in a nyctohemeral rhythm into circulation [4,5]. Leptin level reaches the maximum values in the morning and the minimum values in the afternoon [6]. Factors controlling the nyctohemeral rhythm of leptin secretion include sleep and sleep-induced elevations in glucose, insulin and growth hormone (GH) concentrations [7–9]. Leptin has a suppressive effect on neuropeptide Y (NPY) expression and secretion by neurons in the arcuate nucleus. NPY is a strong stimulator of appetite and is known to be involved in the regulation of various pituitary hormones, e.g., stimulation of insulin like growth factor 1 (IGF-1) through suppression of GH [5,10,11]. Human studies have shown that serum leptin

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Table 1
Anthropometric data of malnourished children and control group

Measurements	Control (n = 30)	Marasmus (n = 21)	Kwashiorkor (n = 15)
Age (months)	10.33 ± 2.36	8.95 ± 1.81	9.87 ± 3.51
Sex			
Male	16	14	9
Female	14	7	6
Weight (kg)	10.35 ± 1.65	4.77 ± 1.43	6.10 ± 1.12
Height (cm)	76.2 ± 6.96	65.07 ± 7.1	65.5 ± 4.87
Weight for age (%)	106.03 ± 3.59	54.42 ± 6.98	68.01 ± 3.91
Height for age (%)	102.6 ± 2.95	95.8 ± 3.87	92.3 ± 5.93
Weight for height (%)	100.8 ± 3.12	58.71 ± 9.04	72.33 ± 6.79
Triceps skinfold thickness (mm)	9.21 ± 2.23	1.81 ± 1.13	5.83 ± 1.96
Body mass index (kg/m^2)	17.82 ± 1.78	10.56 ± 1.67	14.89 ± 2.15
Z score (for weight)	0.71 ± 0.41	−3.31 ± 0.76	−2.83 ± 0.57

concentrations increase with food intake and decrease with fasting at a more rapid rate and greater magnitude than the change in adiposity. Long-term insufficient nutrition influences decrease of leptin concentration [12–14]. Insulin-like growth factor 1 secretion depends on GH and also on nutritional status, and is stimulated by increase of blood glucose after feeding. In studies on malnourished children, IGF-1 concentrations are found decreased. The biological effects of IGF-1 are regulated by insulin-like growth factor binding proteins (the most important of which is IGF-BP3), which are responsible for its transport in the blood [15,16].

The aims of this study are to determine the relationship among leptin concentrations, body weight and some serum hormone concentrations, e.g., basal GH, IGF-1, basal cortisol and IGF-BP3 in severe malnourished children, and to evaluate the effects of leptin in malnourished children.

Methods

The study group consisted of 36 children diagnosed with PEM. The body weight and height percentiles of these children were until the third percentile and they did not have any other chronic disease or infection other than nutritional insufficiency. Marasmus and kwashiorkor were identified according to the Wellcome classification of PEM types. Kwashiorkor was identified on children whose body weight to age ratio (according to Gomez) was between 60% and 80%, whose body weight to height ratio (relative weight) was below 75%, and had edema of the scrotum, anterior surface of the tibia and hepatomegaly on physical examination; on the other hand, marasmus was identified on children whose body weight to age ratio (according to Gomez) was below 60% and whose body weight to height ratio (relative weight) was below 70%, and with no physical examination findings [17].

The control group consisted of 30 children who had normal physical examination findings and normal routine laboratory data and who were followed in Healthy Children Outpatient Department. Their body weight, height and head circumference were between 50 and 97 percentiles.

Physical history data, anthropometric measurements [body weight, height, evaluation of head circumference, body weight to age, height to age and body weight to height, body mass index (BMI), triceps skinfold thickness and Z score for weight], physical examination findings, laboratory results and clinical follow-up of all the children in the study and the control groups were recorded on separate forms.

After an overnight fast and before initiation of feedings, fasting venous blood samples were obtained from a forearm vein with needle technique for routine tests; leptin, IGF-1, IGF-BP3, basal GH and cortisol levels were then measured. The serum was separated and kept frozen at −24°C until analysis of hormones. The tests were carried out in the

Table 2
Laboratory data of malnourished children and control group

Measurements	Control (Group I), n = 30	Marasmus (Group II), n = 21	Kwashiorkor (Group III), n = 15	P[a] value
Leptin (ng/ml)	6.82 ± 2.28	2.09 ± 0.93	2.27 ± 1.01	<0.001 (Groups I–II, I–III)
Leptin (μg/l)	6.82 ± 2.28	2.09 ± 0.93	2.27 ± 1.01	
IGF-1[b](ng/ml)	35.48 ± 5.87	12.63 ± 3.38	14.24 ± 4.03	<0.001 (Groups I–II, I–III)
IGF-1 (nmol/l)	4.63 ± 0.76	1.65 ± 0.44	1.86 ± 0.52	
IGF–BP3[c](ng/ml)	1695 ± 358	1047 ± 196	1135 ± 184	<0.001 (Groups I–II, I–III)
IGF–BP3 (nmol/l)	221.5 ± 46.8	136.8 ± 25.6	148.3 ± 24.0	
Growth hormone (ng/ml)	3.51 ± 0.98	5.44 ± 1.53	4.88 ± 1.49	<0.001 (Groups I–II); <0.01 (Groups I–III)
Growth hormone (μg/l)	3.51 ± 0.98	5.44 ± 1.53	4.88 ± 1.49	
Cortisol (μg/dl)	11.35 ± 3.15	19.87 ± 4.93	16.41 ± 4.31	<0.001 (Groups I–II, I–III); <0.05 (Groups II–III)
Cortisol (nmol/l)	313.1 ± 86.9	548.2 ± 136.0	452.7 ± 118.9	

Conversion factors for IGF-1 is 0.1307, for IGF-BP3 is 0.1307, for growth hormone is 1.0 and for cortisol is 27.59.
[a] Post hoc t tests, Tukey-B and Scheffe.
[b] Insulin-like growth factor-1.
[c] Insulin-like growth factor binding protein 3.

laboratory of the Department of Biochemistry. Serum leptin levels were determined by ELISA using commercial kits (Leptin kit, DRG international, Inc., USA). Serum IGF-1 and IGF-BP3 levels were also determined by ELISA using commercial kits (IGF-1 ELISA kit, IGF-BP3 ELISA kit, BioSource, Europa S.A., France). Cortisol and basal GH levels were evaluated with chemiluminoassay technique by Immulite 2000 hormone autoanalyzer and using commercial kits (Bio-DPC, USA).

Results are expressed as mean ± standard deviation (SD). The difference between groups was evaluated by one-way analysis of variance (ANOVA) and Tukey-B and Scheffe tests, from Post-ANOVA tests. When the P value was <0.05, the hypothesis is accepted as statistically significant. The relationships between the data in the study and the control groups were investigated by nonparametric Pearson and Spearman rank correlation coefficient.

Results

In the study group, 21 cases (7 females and 14 males) were diagnosed as marasmus and 15 cases (6 females and 9 males) as kwashiorkor; in the control group, of the 30 cases, 14 were females and 16 were males. Anthropometric data for the study and control groups are presented in Table 1. Patients with PEM (marasmus and kwashiorkor) had significantly lower weights, heights, weights for age, weights for height, triceps skinfold thickness, BMI and Z score for weight compared with the control group ($P < 0.05$).

Serum leptin levels of infants with marasmus were significantly lower than that of the controls (mean ± SD: 2.09 ± 0.93 vs. 6.82 ± 2.28 ng/ml, respectively); also, serum leptin levels of infants with kwashiorkor were significantly lower than that of the controls (2.27 ± 1.01 vs. 6.82 ± 2.28 ng/ml, respectively). However, there was no significant difference between serum leptin levels of cases with marasmus and serum leptin levels of cases with kwashiorkor ($P > 0.05$).

Serum IGF-1 and IGF-BP3 levels were significantly lower in malnourished children when compared to controls ($P < 0.001$). Also, the lowest serum IGF-1 and IGF-BP3 levels were measured in the marasmus group (12.63 ± 3.38 and 1047 ± 196 ng/ml, respectively). Basal serum GH levels were significantly higher in children with marasmus when compared with controls (5.44 ± 1.53 and 3.51 ± 0.98 ng/ml, respectively); also, basal serum GH levels were significantly higher in children with kwashiorkor when compared with controls (4.88 ± 1.49 and 3.51 ± 0.98 ng/ml, respectively). Similarly, the highest levels of serum cortisol were measured in marasmic children (19.87 ± 4.93 μg/dl). Data on levels of serum leptin and other hormones are presented in Table 2.

There was a positive correlation between serum leptin levels and BMI of children with marasmus and control group ($R^2 = 0.252$, $P < 0.05$ and $R^2 = 0.334$, $P < 0.01$, respectively). However, there was no significant relationship between BMI and serum leptin levels of the infants with kwashiorkor ($R^2 = 0.058$, $P > 0.05$). These correlations were shown in Fig. 1.

Z score and levels of serum leptin were significantly correlated in infants with marasmus and control group ($R^2 = 0.231$, $P < 0.05$ and $R^2 = 0.447$, $P < 0.001$, respectively) and in infants with kwashiorkor and control group ($R^2 = 0.295$, $P < 0.05$ and $R^2 = 0.447$, $P < 0.001$, respectively). Also, triceps skinfold thickness and levels of serum leptin were significantly correlated in infants with marasmus and control

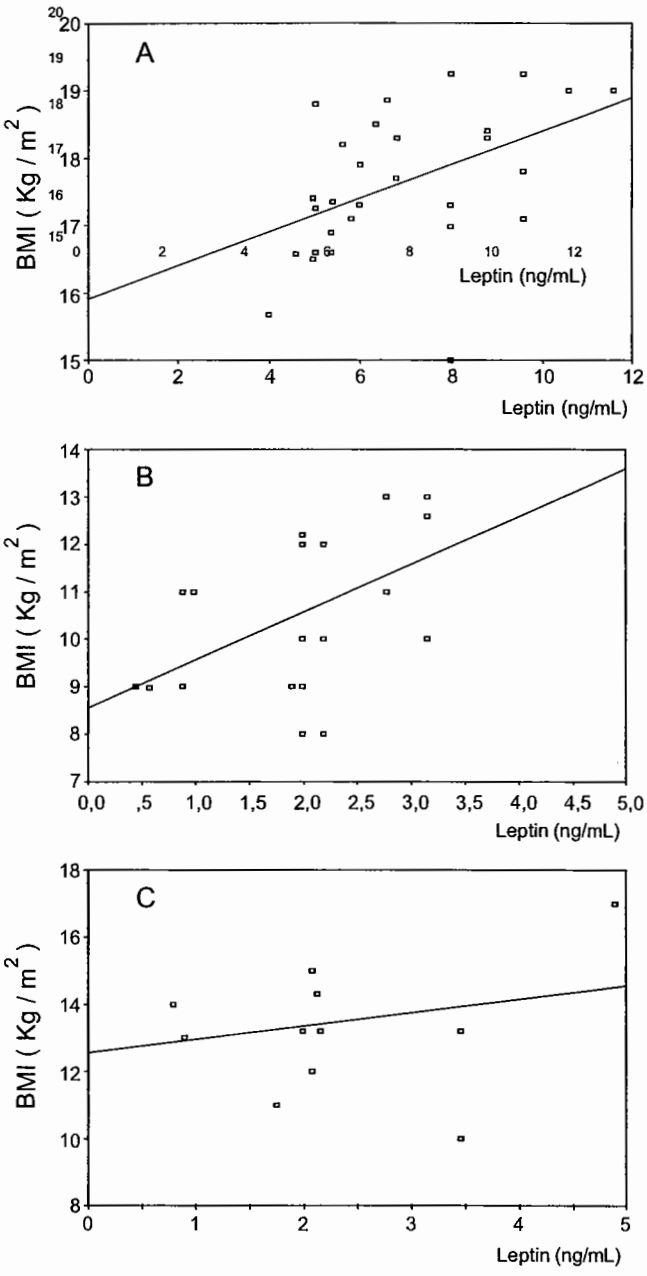

Fig. 1. The positive correlation of serum leptin levels and body mass index (A) in the control group ($R^2 = 0.334$, $P < 0.01$), (B) in children with marasmus ($R^2 = 0.252$, $P < 0.05$) and (C) in children with kwashiorkor ($R^2 = 0.058$, $P > 0.05$).

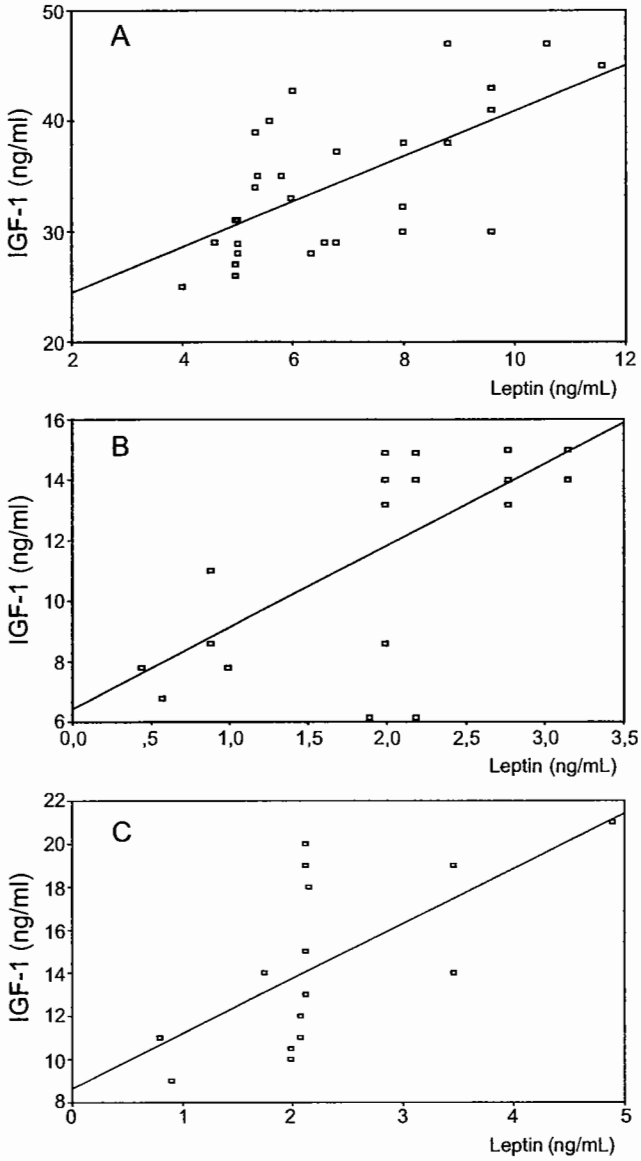

Fig. 2. The positive correlation of serum leptin and IGF 1 levels (A) in the control group ($R^2 = 0.421$, $P < 0.001$), (B) in children with marasmus ($R^2 = 0.446$, $P < 0.001$) and (C) in children with kwashiorkor ($R^2 = 0.414$, $P < 0.01$).

group ($R^2 = 0.429$, $P < 0.01$ and $R^2 = 0.582$, $P < 0.01$, respectively) and in infants with kwashiorkor and control group ($R^2 = 0.293$ $P < 0.01$ and $R^2 = 0.582$, $P < 0.01$, respectively).

Positive correlations were determined between serum leptin and IGF-1 levels in the control group and the children with marasmus ($R^2 = 0.421$, $P < 0.001$ and $R^2 = 0.446$, $P < 0.001$, respectively), and in the control group and the children with kwashiorkor ($R^2 = 0.421$, $P < 0.001$ and $R^2 = 0.414$, $P < 0.01$, respectively). These correlations were shown in Fig. 2.

Similarly, there was a positive correlation between serum leptin and IGF-BP3 levels in the control group and the children with marasmus ($R^2 = 0.281$, $P < 0.01$ and $R^2 = 0.329$, $P < 0.01$, respectively) and in the control group and the children with kwashiorkor ($R^2 = 0.281$, $P < 0.01$ and $R^2 = 0.330$, $P < 0.05$, respectively).

However, a negative relationship was evaluated between serum leptin and basal GH levels in children with marasmus and control group ($R^2 = 0.197$, $P < 0.05$ and $R^2 = 0.157$, $P < 0.05$, respectively), and in children with kwashiorkor and control group ($R^2 = 0.237$, $P < 0.05$ and $R^2 = 0.157$, $P < 0.05$, respectively). These correlations were shown in Fig. 3.

When serum leptin levels were compared with basal cortisol levels, a negative relationship was found in the control group and in infants with marasmus ($R^2 = 0.170$, $P < 0.05$ and $R^2 = 0.211$, $P < 0.05$, respectively), and in the control group and in infants with kwashiorkor ($R^2 =$

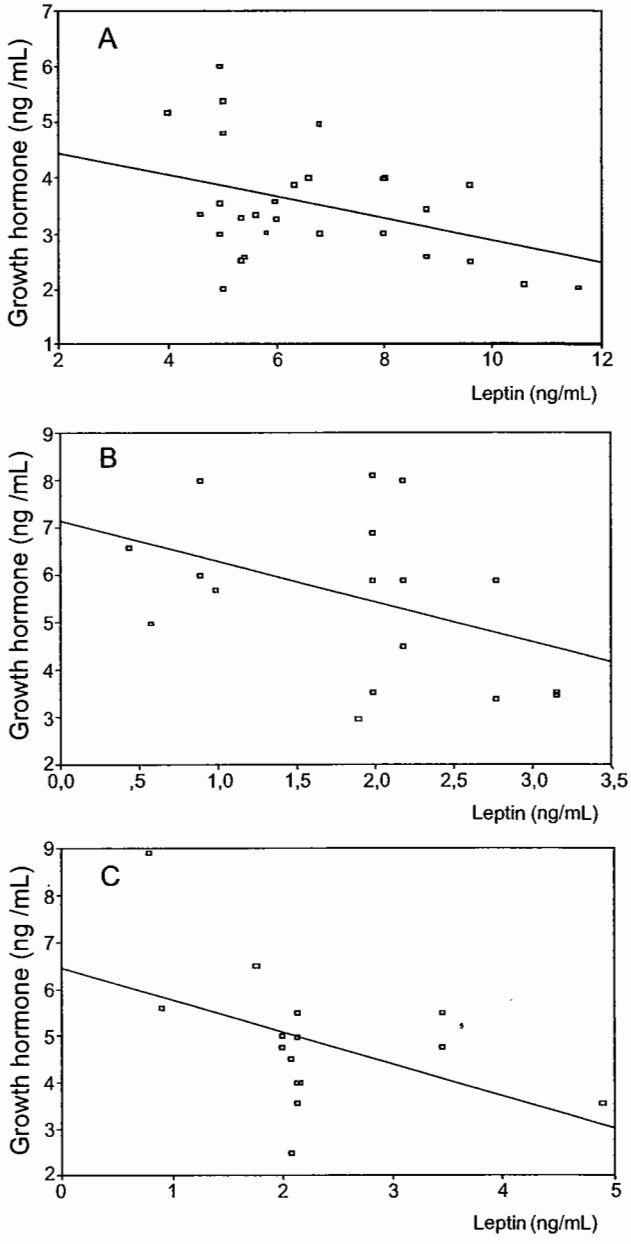

Fig. 3. The negative correlation of serum leptin and growth hormone levels (A) in the control group ($R^2 = 0.157$, $P < 0.05$), (B) in children with marasmus ($R^2 = 0.197$, $P < 0.05$) and (C) in children with kwashiorkor ($R^2 = 0.237$, $P < 0.05$).

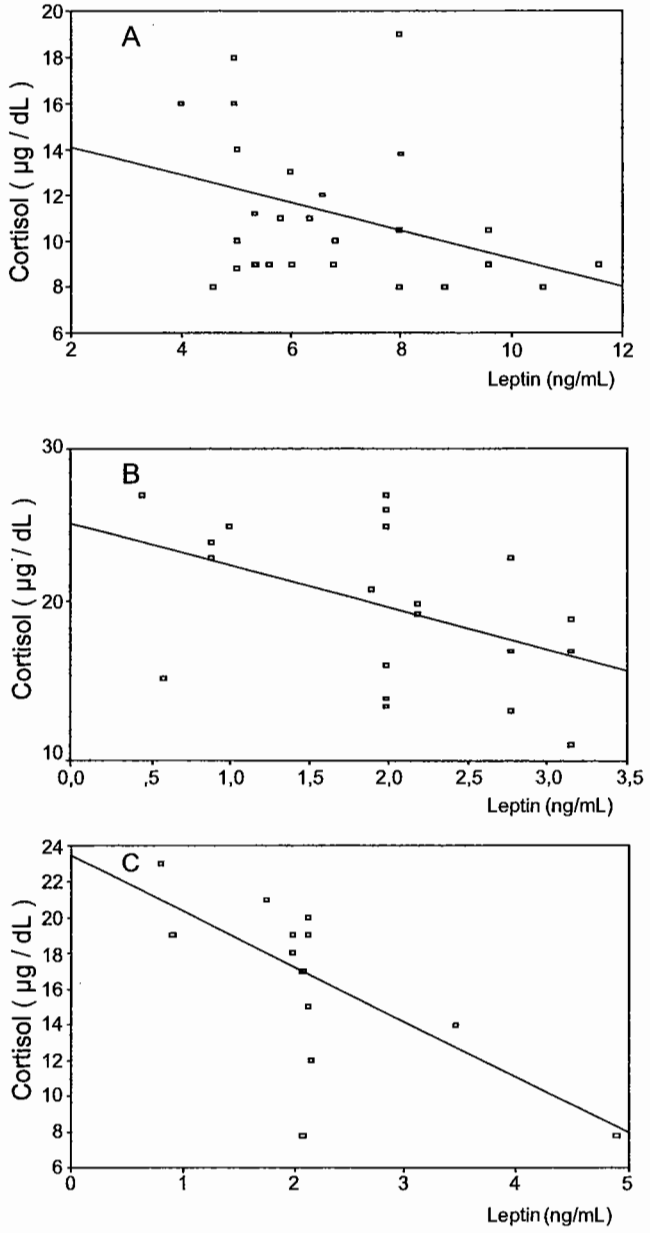

Fig. 4. The negative correlation of serum leptin and cortisol levels (A) in the control group ($R^2 = 0.170$, $P < 0.05$), (B) in children with marasmus ($R^2 = 0.211$, $P < 0.05$) and (C) in children with kwashiorkor ($R^2 = 0.465$, $P < 0.01$).

0.170, $P < 0.05$ and $R^2 = 0.465$, $P < 0.01$; respectively). These correlations were shown in Fig. 4.

Discussion

Several anthropometric and biochemical parameters are utilized to establish the diagnosis and the identification of malnourished children as having marasmus or kwashiorkor. In this study, the serum leptin level of severely malnourished children was measured and its diagnostic significance was assessed. Leptin is a sensitive marker of nutritional status.

Serum leptin levels changes with nutritional status and energy intake. Thus, it may be an indicator of excess storage of energy or chronic fasting. The available information shows that in prolonged and severe malnutrition, the suppressed production of leptin might promote increased energy intake and partitioning of energy toward fat (stimulation of cortisol and GH) [18].

In several studies on malnourished children, serum leptin levels were found to be lower than that of the control group and showed positive correlation with BMI [14,18,19]. Additionally, in patients with malnutrition and anorexia nervosa, low serum leptin levels were increased following weight gain [16,20]. In this study, Palacio et al. [20] identified low levels of serum leptin in malnourished children when compared to normal children, and thought that this increase was due to the suppression of the secretion of leptin due to the diminished subcutaneous adipose tissue resulting from decreased energy intake.

In the current study, we found serum leptin levels of malnourished children to be lower than the control group ($P < 0.001$). Additionally, the serum leptin levels in children with marasmus were not significantly lower than in children with kwashiorkor ($P > 0.05$). In children with PEM, the loss in adipose tissue due to decreased food intake results to a decrease in the secretion of leptin. The loss of adipose tissue in children with marasmus is higher than that in children with kwashiorkor; consequently, we might expect low levels of serum leptin in these children. Also, several researchers found decreases in the levels of serum leptin in correlation with the degree of malnutrition in children with PEM and observed that to be a reflection of loss of adipose tissue [21–23]. Although we have identified a positive correlation between the serum leptin levels and BMI in the control group and in patients with marasmus, the same correlation was not found in children with kwashiorkor. However, there was a significant correlation among serum leptin levels, Z score and triceps skinfold thickness in all groups. Body mass index is a very powerful indicator of body composition and body fat ratio. The loss of positive correlation between serum leptin concentrations and BMI in patients with kwashiorkor is probably the result of the body composition changes. In this group of patients, BMI correlates with the body fat contents less precisely than in healthy children [14].

Serum IGF-1 and IGF-BP3 levels were positively correlated with nutritional status [24–26]. Different research reports demonstrated that serum IGF-1 levels in patients with PEM is positively correlated with serum leptin levels and BMI. The decrease in the levels of IGF-1 in malnourished patients decrease energy and oxygen utilization and the catabolic process, thus creating a protective mechanism for survival [16,18–20]. In the current study, the levels of IGF-1 and IGF-BP3 in children with PEM was lower when compared to controls, and a positive correlation was observed between these parameters and serum leptin levels. Moreover, in patients with PEM, there was a negative relationship between the levels of basal GH and IGF-1. The increased levels of GH in patients with PEM can be explained by the

decrease in the secretion of IGF-1, which stimulates the secretion of GH through the classic negative feedback regulation [27]. Under the light of these findings, in patients with PEM, decreases observed in the serum leptin concentrations and serum IGF-1 concentrations and their positive correlation show the role of IGF-1 in the secretion of leptin.

The cortisol had an anti-insulinic effect and increases in its serum levels was observed in children with PEM. Cortisol levels were thought to increase as a result of the stimulation of the hypothalamo–pituitary–adrenal axis due to low levels of leptin [18]. In the current study, the levels of basal serum cortisol and GH were higher in malnourished children versus that in controls. There was negative correlation between these hormones and the serum leptin levels in all groups. Elevated levels of cortisol mediate many important mechanisms during PEM, including augmentation of lipolysis, enhancement of muscle protein catabolism, inhibition of IGF-1-dependent actions of GH and anti-insulin action on peripheral tissues [28–30].

In conclusion, the decrease of energy intake and reduction of adipose tissue and serum IGF-1 levels in children with PEM might result with decrease in the secretion of leptin. The decrease of serum leptin levels might initiate food intake by increased appetite and stimulate the secretion of cortisol and GH that might increase energy expenditure through an autocrine mechanism. Moreover, serum leptin level may be an important signal to reflect the metabolism of children with PEM. It is in positive correlation with several biochemical and anthropometric parameters; it can also be used to assess the nutritional status of these children.

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