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Serum Leptin Concentrations During Severe Protein-Energy Malnutrition: Correlation With Growth Parameters and Endocrine Function

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Circulating leptin, insulin, insulin-like growth factor-I (IGF-I), cortisol, and albumin concentrations and the growth hormone (GH) response to provocation were measured in 30 children with severe protein-energy malnutrition (PEM), 20 with marasmus and 10 with kwashiorkor, as well as 10 age-matched normal children (body mass index [BMI] >50th and <90th percentile for age and sex) and 10 prepubertal obese children (BMI >95th percentile for age and sex). Patients with PEM had a significantly lower BMI, midarm circumference (MAC), and skinfold thickness (SFT) compared with the age-matched control group. Basal cortisol and GH concentrations were significantly higher in the malnourished groups versus controls. Leptin and IGF-I were significantly lower in the marasmic and kwashiorkor groups versus normal children. Fasting insulin levels were significantly decreased in the kwashiorkor group compared with marasmic and normal children. The BMI correlated significantly with leptin ($r = .77$, $P < .001$), basal insulin ($r = .61$, $P < .001$), and IGF-I ($r = .77$, $P < .001$) and negatively with basal GH ($r = -.52$, $P < .001$). These findings suggest that during prolonged nutritional deprivation, the decreased energy intake, diminished subcutaneous fat mass, and declining insulin (and possibly IGF-I) concentration suppress leptin production. In support of this view, serum leptin levels were positively correlated with triceps, scapular, and abdominal SFT ($r = .763$, .75, and .744, respectively, $P < .0001$) in all of the children. Moreover, basal insulin and circulating IGF-I were correlated significantly with leptin concentrations ($r = .47$ and .62, respectively, $P < .001$). Basal levels of cortisol and GH were significantly elevated in the 2 groups with severe PEM. It is suggested that low leptin levels can stimulate the hypothalamic-pituitary-adrenal (HPA) axis and possibly the hypothalamic-pituitary-GH axis to maintain the high cortisol and GH levels necessary for effective lipolysis to ensure a fuel (fatty acids) supply for the metabolism of brain and peripheral tissue during nutritional deprivation. In summary, during prolonged PEM, the decreased synthesis of IGF-I and the low level of insulin and/or its diminished effect due to an insulin-resistant status in the presence of high circulating GH and cortisol levels ensure substrate diversion away from growth toward metabolic homeostasis. Leptin appears to be an important signal in the process of metabolic/endocrine adaptation to prolonged nutritional deprivation.

THE IDENTIFICATION of the ob gene[1] and the discovery that its encoded protein, leptin, is an adipocyte-derived hormone that is essential for normal regulation of body weight[2-4] have permanently altered the field of metabolic physiology. Leptin has been considered a signal of energy deficiency and an integrator of neuroendocrine function.

Leptin regulates adipose tissue mass through hypothalamic effects on satiety and energy expenditure. It is detectable in fetal cord blood as early as 18 weeks of gestation and dramatically increases after 34 weeks. In newborns, the serum leptin concentration is positively correlated with the body weight, fat mass, and body mass index (BMI).[5] Although leptin correlates with the fat mass, the circulating concentration is altered by extremes in energy intake such as fasting and overfeeding.[6] Experiments in animals provide evidence that the full-strength leptin receptor is expressed in hypothalamic, anterior pituitary, and adipose tissue, and within the hypothalamus, the receptor form is differentially expressed in well-fed versus feed-restricted animals.[7] In obese adults, leptin levels are high and correlate well with fat mass. Within 24 hours of fasting, leptin declines to approximately 30% of the initial basal value. Massive overfeeding increases leptin over 12 hours by approximately 50% of the initial basal value.[8] Serum leptin levels are low in many forms of malnutrition, including intrauterine growth retardation, untreated anorexia nervosa, and malnourishment in chronically ill elderly patients.[5,9-11] During starvation,

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leptin also correlates with the insulin-like growth factor-I (IGF-I) concentration.[11,12] In pigs and other animal species, leptin modulates growth hormone (GH) secretion and suppresses feed intake.[13-15] However, further studies are necessary to elucidate the relationship of leptin to neuroendocrine abnormalities found in the different forms of severe protein-energy malnutrition (PEM), namely marasmus and kwashiorkor, and to evaluate the relationship, if any, between the leptin concentration and other hormones controlling the adaptation process (GH, IGF-I, insulin, and cortisol) in these patients.

This study was performed to measure basal serum levels of leptin in children with severe PEM (marasmus and kwashiorkor) and their relationship to growth parameters, GH secretion, and circulating concentrations of insulin, IGF-I, and cortisol.

SUBJECTS AND METHODS

Thirty patients between the ages of 6 and 36 months with severe PEM (10 with kwashiorkor and 20 with marasmus; 17 males and 13 females) were the subjects of this study. They were admitted to Alexandria University Children's Hospital, Alexandria, Egypt, for clinical management and nutritional rehabilitation. All patients were examined thoroughly with special emphasis on the nutritional history, anthropometric measurements (weight, length, head and midarm circumference [MAC], biceps, triceps, and subscapular skinfold thickness [SFT], and body mass index [BMI]), and clinical signs of malnutrition including edema, hair and skin changes, mental changes, and hepatomegaly. Ten normal age-matched children (BMI >50th and <90th percentile for age and sex, randomly selected from those undergoing minor surgical procedures) served as controls. Informed consent for the testing procedure was obtained from the parents of the children, and the Ethics Committee of Alexandria University approved the protocol of the study.

On the night of admission to the hospital, the malnourished children were fed diets similar to the diets they consumed at home (protein-deficient diets brought by the parents). All patients with PEM were treated with antibiotics, vitamins, and, when indicated, intravenous fluids. After an overnight fast and before initiation of protein-rich feedings, a fasting venous blood sample (8 AM) was obtained via a polyethylene catheter inserted in a forearm vein. The serum was separated and kept frozen at −20°C until analysis for cortisol, GH, insulin, IGF-I, and leptin by radioimmunoassay and serum albumin and glucose. A standard glucagon test for GH secretion (0.1 mg/kg intramuscularly; maximum dose, 1 mg) was performed and serum samples were obtained at 0, 30, 60, 90, and 120 minutes were glucagon injection for determination of GH levels. Samples were kept frozen at −20°C till analysis for hormone levels. The intraassay coefficient of variation was 6.4% for the range of cortisol values, 7.2% for GH, 5.8% for insulin, 8% for IGF-I, and 6.8% for leptin.

Statistical analyses were performed using the ANOVA and *t* tests to compare results among different groups when the data were normally distributed, and the Wilcoxon test was used when the data were not normally distributed. Linear regression was used to investigate the correlation between different variables. Data are presented as the mean ± SD.

RESULTS

Anthropometric data for the 2 malnourished groups and controls are presented in Table 1. Patients with PEM had a significantly lower BMI, percent average weight for age, % average height for age, MAC, and SFT compared with the age-matched control group.

The serum albumin concentration was significantly decreased in the kwashiorkor group versus marasmic and normal children. Basal cortisol and GH were significantly higher in malnourished groups versus controls. Leptin and IGF-I were significantly lower in the marasmic and kwashiorkor groups versus normal children. Fasting insulin was significantly decreased in the kwashiorkor group compared with marasmic and normal children (Table 2).

Serum leptin levels were positively correlated with the BMI ($r = .77$, $P < .001$), MAC ($r = .764$, $P < .0001$), and triceps, scapular, and abdominal fat thickness ($r = .763$, .75, and .744, respectively, $P < .0001$). Basal insulin and circulating IGF-I were correlated significantly with leptin concentrations ($r = .47$ and .62, respectively, $P < .001$). Basal and peak GH concentrations after provocation were correlated negatively with leptin levels ($r = -.43$ and $-.44$, respectively, $P < .01$). The BMI was correlated significantly with basal insulin ($r = .61$, $P < .001$) and IGF-I ($r = .77$, $P < .001$) and negatively with basal GH ($r = .52$, $P < .001$) (Table 3 and Figs 1 to 3).

DISCUSSION

This study describes changes in the leptin concentration and other hormonal changes in two forms of severe PEM (marasmus and kwashiorkor). Because leptin levels parallel changes in nutritional status and energy storage across a broad range from starvation to obesity, leptin is well positioned to signal energy insufficiency or energy excess, causing responses that could counter the adverse consequences of either starvation or obesity.

Table 1. Anthropometric Data for the Malnourished Children and Controls

Group	Age (yr)	BMI (kg/m²)	MAC (cm)	Tri-SFT (mm)	Scap-SFT (mm)	Abd-SFT (mm)	% of Average Weight	% of Average Height
Marasmus (n = 20)								
Mean	0.63	10.4*†	8.13*†	1.78*†	1.29*†	1.24*†	55.5*†	87.5*
SD	0.14	1.8	1.58	1.1	0.6	0.36	5.2	4.4
Kwashiorkor (n = 15)								
Mean	0.84	12.2*	10.25*	5.7*	3.4*	3.2*	71.5*	90.1*
SD	0.52	1.04	1.11	1.76	0.8	0.63	6.22	4.4
Controls (n = 10)								
Mean	0.99	16.76	13.97	8.87	6.56	7	111.2	103.5
SD	0.72	1.95	1.3	2.02	1.67	2.92	5.3	4.3

Abbreviations: Tri, triceps; Scap, scapular; Abd, abdominal.

*$P < .05$, PEM *v* control.

†$P < .05$, kwashiorkor *v* marasmus.

Table 2. Laboratory Data for the Malnourished and Normal Children

Group	Leptin (ng/mL)	Insulin (mU/L)	Cortisol 8 AM (μg/mL)	B-GH (ng/mL)	P-GH (ng/mL)	IGF-I (ng/mL)	Albumin (g/L)
Marasmus (n = 20)							
Mean	0.41*	14.6	30.1	6.3*	29.2*†	19.8*	3.1*
SD	0.18	3.86	17.4	2.6	6.82	7.2	0.8
Kwashiorkor (n = 15)							
Mean	0.95*†	9.2*†	27.3	6.48*	15.2	7.2*†	2.4*†
SD	0.2	4.1	14.3	3.55	3.55	3.6	0.7
Controls (n = 10)							
Mean	6.84	13.8	15.2	2.18	14.2	38	3.8
SD	1.1	4.75	9.2	1.1	2.26	9	0.45

Abbreviations: B, basal; P, peak response.

*$P < .05$, PEM *v* control.

†$P < .05$, kwashiorkor *v* marasmus.

In adult humans, plasma leptin levels respond slowly to fasting[7-9] and begin to decrease after 12 to 14 hours. Leptin gene transcription is reduced by longer starvation.[17,18] Animal studies showed that leptin most likely exerts this important effect through the central nervous system, specifically within the hypothalamus, and that leptin seems to be a molecule linking the periphery and central regulation of energy balance.[19-22] Collectively, these data suggest that in addition to being a signal of energy stores, the leptin level is a sensor of energy balance.[23] Whether a similar mechanism might work in malnourished children is still unclear.

The effect of prolonged nutritional deprivation on serum leptin was studied in a large group of children with severe PEM. In this group of patients, chronic energy insufficiency was associated with a marked decrease in circulating serum leptin and IGF-I concentrations and an increase in basal GH and cortisol levels. The kwashiorkor group had significantly low basal insulin concentrations. Other studies reported glucose intolerance with delayed glucose disposal and diminished insulin release after an oral glucose load and after arginine infusion in patients with kwashiorkor.[24,25] In this situation, the decreasing insulin appears to be a major factor producing increased lipolysis, decreased uptake of glucose in muscle and fat, and increased hepatic glucose production, which characterize starvation. This process is critical to the metabolic switch from carbohydrate- to fat-based metabolism.[25-27] In support of this view, the BMI, SFT (triceps, abdominal, and scapular), and MAC were correlated significantly with serum insulin levels in our malnourished and normal children ($r = .60$, .662, .686, .589, and .6, respectively, $P < .001$).

The decreasing insulin level may also play a direct and important role in the decrease of leptin production by the adipocyte during starvation, as insulin has been observed to stimulate leptin gene expression in vitro and leptin levels increase in vivo during a prolonged euglycemic insulin clamp.[28,29] A number of reports in humans[28] and animals[29,30] support a BMI/fat mass–independent regulatory influence of insulin on serum leptin levels. Our finding of a significant correlation between serum insulin and leptin ($r = .478$, $P < .001$) supports this view. Although children with marasmus had normal basal insulin levels, many studies showed a defective insulin response to different stimuli in these patients.[25,31,32]

It has been suggested that in animals[22,33,34] and humans[35,36] leptin may act as a starvation signal, such that low levels trigger the hypothalamic-pituitary-adrenal (HPA) axis. It is reasonable to hypothesize that leptin may have a role in the normal negative-feedback function of the HPA axis. Such a relationship would explain the fact that states of severe leptin deficiency (including PEM) are associated with activation of the HPA axis. In support of this concept, our malnourished patients (marasmic and kwashiorkor groups) had significantly elevated 8 AM cortisol levels associated with leptin deficiency. Elevated levels of cortisol mediate many important mechanisms during PEM, including (1) augmentation of lipolysis through potentiation of catecholamine action on hormone-sensitive lipase, (2) enhance-

Table 3. Correlations Between Different Variables in Malnourished and Well-Nourished Children

	Age	BMI	MAC	Tri-SFT	Scap-SFT	Abd-SFT	Leptin	Insulin	Cortisol	B-GH	P-GH	IGF-I
Age	1											
BMI	.755	1										
MAC	.829	.903	1									
Tri-SFT	.804	.896	.927	1								
Scap-SFT	.745	.876	.883	.968	1							
Abd-SFT	.784	.88	.872	.962	.936	1						
Leptin	.508	.77	.757	.764	.75	.7441	1					
Insulin	.549	.604	.597	.662	.58	.6868	.4786	1				
Cortisol	−.19	−.101	−.23	−.18	−.11	−.1412	−.14	−.141	1			
B-GH	−.48	−.537	−.55	−.48	−.43	−.4314	−.434	−.376	.221	1		
P-GH	−.52	−.618	−.61	−.55	−.485	−.5005	−.436	−.237	.302	.55	1	
IGF-I	.712	.774	.761	.777	.76	.8196	.6204	.4833	−.02	−.4	−.4	1

Abbreviations: Tri, triceps; Scap, scapular; Abd, abdominal.

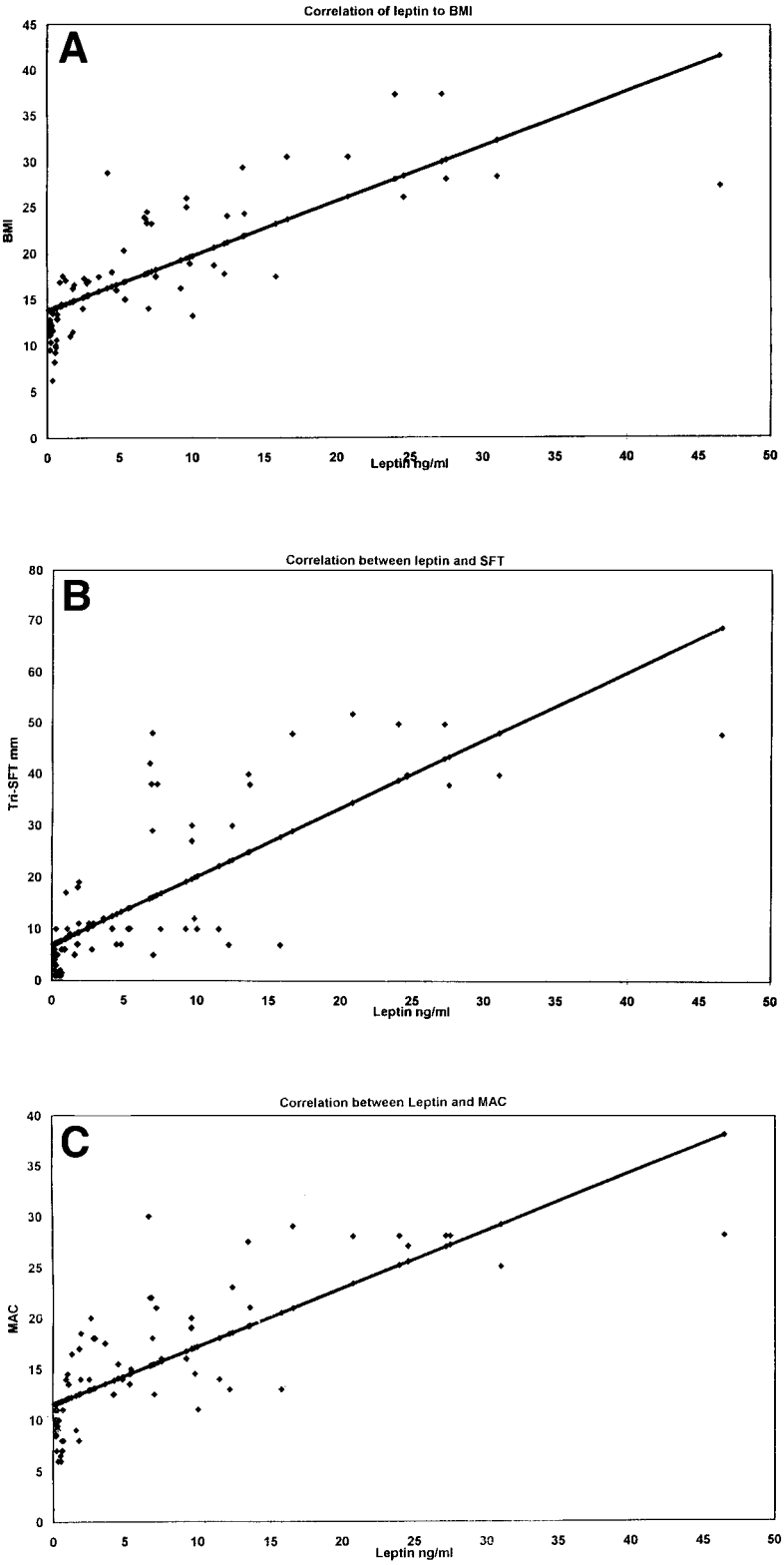

Fig 1. Correlation between leptin concentration and (A) BMI ($r = .77$, $P < .0001$), (B) abdominal SFT ($r = .744$, $P < .0001$), and (C) MAC ($r = .764$, $P < .0001$).

ment of muscle protein catabolism to provide the body with the amino acids necessary for hepatic gluconeogenesis and albumin synthesis, (3) inhibition of IGF-I–dependent actions of GH, and (4) anti-insulin action on peripheral tissues.[37-39]

IGF-I is a GH-dependent polypeptide with a 3-fold function as a mediator of the growth-promoting action of GH, a potent mitogenic factor, and a metabolic regulator with insulin-like activity.[40,41] In addition, serum IGF-I levels are positively

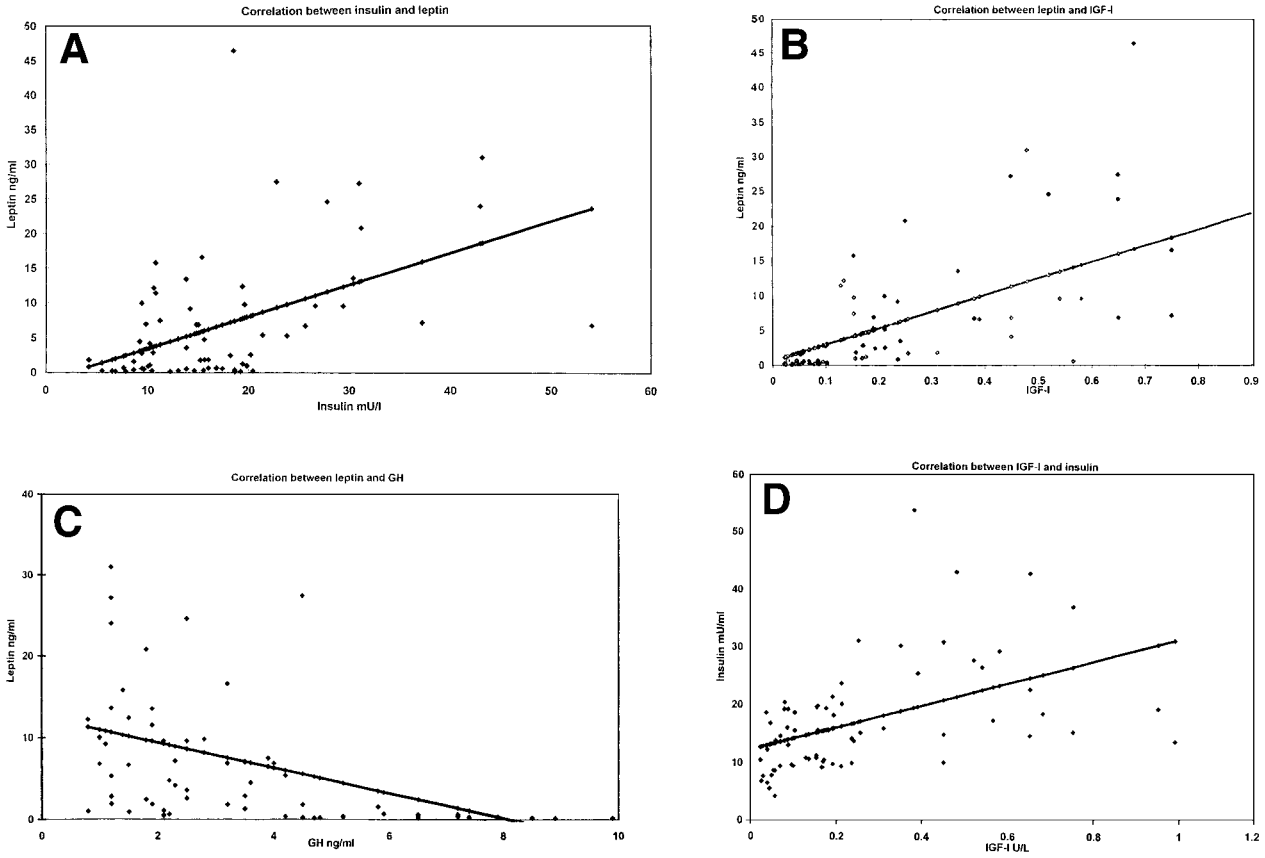

Fig 2. Correlation between (A) insulin and leptin ($r = .47$, $P < .001$), (B) IGF-I and leptin ($r = .62$, $P < .001$), (C) leptin and GH ($r = -.43$, $P < .01$), and (D) insulin and IGF-I ($r = .483$, $P < .001$).

related to nutritional status[25,42] and affected by other hormones like insulin.[43-44] In this study, circulating IGF-I concentrations were significantly correlated with the basal insulin level, BMI, SFT (triceps, abdominal, and scapular), and MAC ($r = .483$, .774, .777, .819, .76, and .76, respectively, $P < .001$). This selective decrease in IGF-I acts to decrease energy and oxygen utilization in general and to spare glucose, fatty acids, and amino acids by reducing protein synthesis in muscle and lipogenesis in fat depots which would consume these fuels when life itself may be in the balance. The positive correlation between circulating IGF-I and leptin levels ($r = .62$, $P < .0001$) and the marked reduction of circulating concentrations of leptin and IGF-I in the two forms of severe PEM (marasmus and kwashiorkor) suggest that IGF-I plays an important role also in the control of leptin secretion in these children. In support, other investigators found a significant correlation between leptin and IGF-I in malnourished humans.

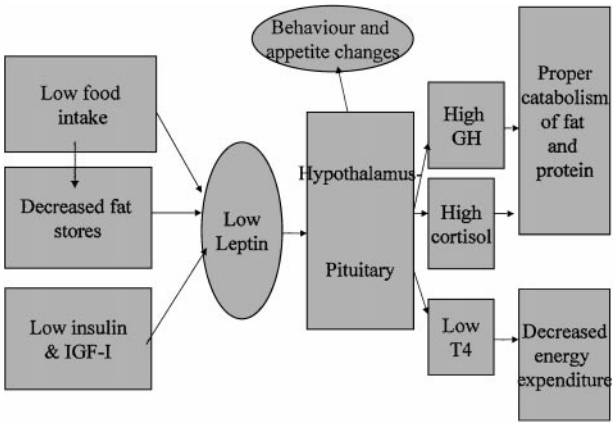

Fig 3. Suggested important role of leptin in mediating the adaptation process during prolonged nutritional deprivation.

The diminished IGF-I generation leads to further GH secretion through classic negative-feedback regulation.[25] This could explain the high basal and provoked GH levels in our malnourished children and the negative correlation between IGF-I and basal GH concentrations ($r = -.432$, $P < .001$). Studies in humans and swine showed a relation between GH status and circulating leptin concentrations.[13-16] Whether low leptin secretion could stimulate GH secretion in these children is still unknown. In this study, basal and provoked GH concentrations correlated negatively with the serum leptin concentration ($r = -.43$, $P < .01$). The metabolic effects of the high circulating GH concentration, namely mobilization of fatty acids from adipose tissue and inhibition of glucose uptake by muscle tissue, would help to ensure fuel supply to the brain and to defend the organism against hypoglycemia.[11,12]

It appears that during prolonged nutritional deprivation, the decreased energy intake and decreasing insulin and possibly

IGF-I suppress leptin production. It is possible that leptin plays an important role in defending the thrifty phenotype by decreasing with starvation. The decreasing leptin might promote increased energy intake and partitioning of energy toward fat (through stimulation of cortisol and possibly GH secretion).

Hepatic albumin synthesis depends on the serum concentration of amino acids, especially the branched-chain amino acids (BCAAs).[44] During starvation, despite muscle protein catabolism under the effect of hypercortisolemia, the supply of BCAAs is usually low.[45] The high dietary carbohydrate to protein ratio (ie, excessive sugars) characteristic of patients with kwashiorkor further disturbs this amino acid pattern.[46,47] In the absence of adequate insulin secretion to direct hepatic albumin synthesis, hypoalbuminemia develops with subsequent edema.[25] On the other hand, the diet of marasmic children is usually quantitatively deficient in calories but has a normal carbohydrate to protein ratio that could partially supply essential amino acids. The presence of better insulin secretion in these children in comparison to those with kwashiorkor supports hepatic albumin synthesis and prevents the development of hypoalbuminemia and edema. Insulin inhibits adipose tissue lipolysis and decreases free fatty acid (FFA) flux into the plasma. The reduced availability of FFAs favors a decline in hepatic VLDL-triglyceride (TG) synthesis. In addition, insulin stimulates hepatic esterification of FFA to form TG, coupling of TG to apoprotein B, and secretion of VLDL.[48] In kwashiorkor, hypoinsulinemia could explain all of the biochemical changes that lead to fatty liver.[49] Plasma FFA levels are elevated due to increased adipose tissue lipolysis.[50] The increased FFAs stimulate hepatic synthesis of VLDL-TG. In the absence of adequate insulin secretion, the liver cannot adequately couple TG to apoprotein B or secrete VLDL-TG.[51,52] This leads to an accumulation of TG in the liver (hepatic steatosis). In support of this view, studies on perfused liver demonstrate that increasing the FFA concentration of the medium results in an increase of VLDL-TG production only in animals with partial insulin deficiency, not those rendered completely insulin-deficient,[53] and that this stimulatory effect of insulin on hepatic lipogenesis is most apparent when preceded by high-carbohydrate feeding.[54] Moreover, the liver of patients with kwashiorkor shows extensive zone-1 fatty changes analogous to the fatty liver of pancreatectomized dog.[55]

In summary, during prolonged PEM, the decreased synthesis of IGF-I and the low level of insulin and/or its decreased effect due to an insulin-resistant status in the presence of high circulating GH and cortisol levels ensure the diversion of substrate away from growth toward metabolic homeostasis. Low leptin levels help to increase appetite and food intake during malnutrition, and stimulate the HPA axis and possibly the GH axis to maintain the high cortisol and GH levels necessary for effective catabolism (Fig 3).

REFERENCES

1. Zhang Y, Proenca R, Maffei M, et al: Positional cloning of the mouse ob gene and its human homologue. Nature 372:425-432, 1994
2. Halaas J, Gajiwala K, Maffei M: Weight reducing effect of the plasma protein encoded by the obese gene. Science 269:543-546, 1995
3. Campfield L, Smith F, Guisez Y, et al: Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. Science 269:546-548, 1995
4. Pellymounter M, Cullen M, Baker M: Effects of the obese gene product on body weight regulation in ob/ob mice. Science 269:540-543, 1995
5. Jaquet D, Leger J, Levy-Marchal C, et al: Ontogeny of leptin in human fetuses and newborns: Effect of intrauterine growth retardation on serum leptin concentration. J Clin Endocrinol Metab 83:1243-1246, 1998
6. Considine RV: Weight reduction, leptin and growth hormone. Horm Res 48:116-121, 1997 (suppl 5)
7. Dyer CJ, Simmons JM, Matteri RL, et al: Leptin receptor mRNA is expressed in ewe anterior pituitary and adipose tissues and is differentially expressed in hypothalamic regions of well-fed and feed-restricted ewes. Domest Anim Endocrinol 14:119-128, 1997
8. Caro JP: Clinical aspects of leptin. Vitam Horm 54:1-30, 1998 (review)
9. Boden G, Chen X, Mozzoli M, et al: Effect of fasting on serum leptin in normal human subjects. J Clin Endocrinol Metab 81:3419-3423, 1996
10. Boguszewski M, Dahlgren J, Bjarnason R, et al: Serum leptin in short children born small for gestational age: Relationship with the growth response to growth hormone treatment. The Swedish Study Group for Growth Hormone Treatment. Eur J Endocrinol 137:378-395, 1997
11. Eckert ED, Pomeroy C, Raymond N, et al: Leptin in anorexia nervosa. J Clin Endocrinol Metab 83:791-795, 1998
12. Cederholm T, Arner P, Palmblad J: Low circulating leptin levels in protein-energy malnourished chronically ill elderly patients. J Intern Med 242:377-382, 1997
13. Seck T, Englaro P, Blum WF: Leptin concentrations in serum from a randomly recruited sample of 50- to 80-year-old men and women: Positive association with plasma insulin-like growth factor (IGF-s) and IGF-binding protein 3 in lean, but not obese, individuals. Eur J Endocrinol 138:70-75, 1998
14. Barb CR, Yan X, Azain MJ, et al: Recombinant porcine leptin reduces feed intake and stimulates growth hormone secretion in swine. Domest Anim Endocrinol 15:77-86, 1998
15. Gill MS, Toogood AA, O'Neill PA, et al: Relationship between growth hormone (GH) status, serum leptin and body composition in healthy and GH deficient elderly subjects. Clin Endocrinol (Oxf) 47:161-167, 1997
16. Carro E, Senaris R, Considine RV, et al: Regulation of in vivo growth hormone secretion by leptin. Endocrinology 138:2203-2206, 1997
17. Maffei M, Halaas J, Ravussin E: Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1:1155-1161, 1995
18. Kolaczynski JW, Considine RV, Ohannesian J: Responses of leptin to short-term fasting and refeeding in humans: A link with ketogenesis but not ketones themselves. Diabetes 45:1511-1515, 1996
19. Ahima RS, Prabakaran D, Mantzoros C: Role of leptin in the neuroendocrine response to fasting. Nature 382:250-252, 1996
20. Chehab FF, Mounzih K, Lu R, et al: Early onset reproductive function in normal female mice treated with leptin. Science 275:88-90, 1997
21. Barash IA, Cheung CC, Weigle DS: Leptin is a metabolic signal to the reproductive system. Endocrinology 137:3144-3147, 1996
22. Frederich RC, Lollmann B, Hamann A: Expression of ob mRNA and its encoded protein in rodents: Impact of nutrition and obesity. J Clin Invest 96:1658-1663, 1995

23. Flier JS: What's in a name? In search of leptin's physiologic role. J Clin Endocrinol Metab 83:1407-1421, 1998

24. Weinkove D, Weinkove EA, Pimstone BL: Glucose tolerance and insulin release in malnourished rats. Clin Sci Mol Med 50:153-163, 1976

25. Soliman AT, Hassan AEH, Aref KM, et al: Serum insulin-like growth factor I and II concentrations and growth hormone and insulin responses to arginine infusion in children with protein energy malnutrition before and after nutritional rehabilitation. Pediatr Res 20:1122-1129, 1986

26. Chipkin S, Kelly K, Ruderman N: Hormone-fuel interrelationships: Fed state, starvation, and diabetes mellitus, in Kahn C, Weir G (eds): Joslin's Diabetes Mellitus. Philadelphia, PA, Lea & Febiger, 1994, pp 97-115

27. Soliman AT, AlSalmi I, Asfour M: Hypoinsulinaemia has an important role in the development of oedema and hepatomegaly during malnutrition. J Trop Pediatr 42:297-299, 1996

28. Boden G, Chen X, Kolaczynski JPM: Effects of prolonged hyperinsulinemia on serum leptin in normal human subjects. J Clin Invest 100:1107-1113, 1997

29. Saladin R, De Vos P, Guerre-Millo M: Transient increase in obese gene expression after food intake or insulin administration. Nature 377:527-529, 1995

30. Zheng D, Jones JP, Usala SJ, et al: Differential expression of ob mRNA in rat adipose tissues in response to insulin. Biochem Biophys Res Commun 218:434-437, 1996

31. Smith IF, Lathman MC, Azubuike JA, et al: Blood plasma levels of cortisol, insulin, growth hormone and somatomedin in children with marasmus, kwashiorkor, and intermediate forms of protein energy malnutrition. Proc Soc Exp Biol Med 167:607-611, 1981

32. Milner RDG: Metabolic and hormonal responses to glucose and glucagon in patients with infantile malnutrition. Pediatr Res 5:33-39, 1971

33. Yu WH, Kimura M, Walczewska A, et al: Role of leptin in hypothalamic-pituitary function. Proc Natl Acad Sci USA 94:1023-1028, 1997

34. Heiman ML, Ahima RS, Craft LS, et al: Leptin inhibition of the hypothalamic-pituitary-adrenal axis in response to stress. Endocrinology 138:3859-3863, 1997

35. Licinio J, Masntzoros C, Negarao AB: Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Nat Med 3:573-579, 1997

36. Korbonits M, Trainer PJ, Little CF: Leptin levels do not change acutely with food administration in normal or obese subjects, but are negatively correlated with pituitary-adrenal activity. Clin Endocrinol (Oxf) 46:751-757, 1997

37. Grodsky GM: Chemistry and functions of the hormones: Thyroid, pancreas, adrenal and gastrointestinal tract, in Martin DW, Mayes PA, Rodwell VW (eds): Harper's Review of Biochemistry (ed 18). Los Altos, CA, Lange Medical, 1981, pp 468-503

38. Unterman TG, Phillips LS: Glucocorticoid effects on somatomedins and somatomedin inhibitors. J Clin Endocrinol Metab 61:618-626, 1985

39. Luo J, Murphy LJ: Dexamethasone inhibits growth hormone induction of insulin-like growth factor-I messenger RNA abundance in the intact rat. Endocrinology 125:165-171, 1989

40. Rutanen EM, Pekonen F: Insulin-like growth factors and their binding proteins. Acta Endocrinol (Copenh) 123:7-13, 1990

41. Rechler MM, Nissley SP: Insulin-like growth factors, in Sporn MB, Robert AB (eds): Peptide Growth Factors and Their Receptors. Handbook of Pharmacology. Heidelberg, Germany, Springer, 1990, pp 263-267

42. Clemmons DR, Underwood LE, Dickerson RN: Use of plasma somatomedin-C/insulin-like growth factor-I measurements to monitor the response to nutritional repletion in malnourished patients. Am J Clin Nutr 41:191-198, 1985

43. Eigenmann JE, Becker M, Kammermann B: Decrease of non-suppressible insulin-like activity after pancreatectomy and normalization by insulin therapy. Acta Endocrinol (Copenh) 85:818-822, 1977

44. Kirsh RE, Saunders SJ, Frith L, et al: Effect of amino acid levels on hepatic protein synthesis. Am J Clin Nutr 22:1559-1562, 1969

45. Thomas FM, Murray AJ, Jones LM: Modification of glucocorticoid induced changes in myofibril apoprotein turnover in rats by protein and energy deficiency as assessed by urinary excretion of *N*-methylhistidine. Br J Nutr 51:323-333, 1984

46. Tew JK, Bradford AM, Harper AE: Induction of lysine imbalance in rats: Relationships between tissue amino acids and diet. J Nutr 111:968-978, 1981

47. Soliman AT, Hassan AH, Rogol AD: Endocrine and amino acid changes in malnutrition (PEM). J Trop Pediatr 37:331-332, 1991

48. Kissebah AH: Insulin actions in vivo: Insulin and lipoprotein metabolism, in Alberti KGMM, DeFronzo RA, Keen H, Zimmet P (eds): International Textbook of Diabetes Mellitus. New York, NY, Wiley, 1992, pp 439-466

49. Soliman AT, AlSalmi I, Asfour M: Hypoinsulinemia has important role in the development of edema and hepatomegaly during malnutrition. J Trop Pediatr 42:32-34, 1996

50. Passmore R, Eastwood MA: Davidson and Passmore Human Nutrition and Dietetics (ed 8). London, UK, Churchill Livingstone, 1986, pp 279-310

51. Ginsberg H, Mok H, Grundy S, et al: Increased production of very low density lipoprotein triglyceride in insulin-deficient diabetics. Diabetes 26:399-341, 1977 (suppl 1)

52. Greenfield M, Kolterman O, Olfsky J, et al: Mechanism of hypertriglyceridemia in diabetic patients with fasting hyperglycemia. Diabetologia 18:441-446, 1980

53. Lunn PG, Whitehead RG, Coward WA: Two pathways to kwashiorkor? Trans R Soc Trop Med Hyg 73:438-444, 1979

54. Reaven EP, Reaven GM: Mechanism for development of diabetic hypertriglyceridemia in streptozotocin treated rats: Effect of diet and duration of insulin deficiency. J Clin Invest 54:167-178, 1974

55. Sherlock S: Nutritional and metabolic liver diseases, in Sherlock S (ed): Diseases of the Liver and Biliary System (ed 8). Oxford, UK, Blackwell Scientific, 1989, pp 470-480