Serum Insulin-Like Growth Factors I and II Concentrations and Growth Hormone and Insulin Responses to Arginine Infusion in Children with Protein-Energy Malnutrition before and after Nutritional Rehabilitation

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ABSTRACT. Serum insulin, growth hormone (GH), insulin-like growth factors (IGFs) I and II, cortisol, and albumin concentrations were measured in 15 children with kwashiorkor, 15 with marasmic-kwashiorkor, and 21 with marasmus, before and in the survivors, after nutritional rehabilitation, as well as in 10 underweight and eight normal Egyptian children. We also evaluated arginine-induced insulin and GH secretion. IGF-I concentrations were reduced in the three severely malnourished groups (0.07 ± 0.03, 0.05 ± 0.03, and 0.09 ± 0.09 U/ml, respectively) but returned to normal after refeeding. IGF-II concentrations were low in the kwashiorkor (175 ± 79 ng/ml), marasmic-kwashiorkor (111 ± 57 ng/ml), and marasmic children (128 ± 70.9 ng/ml) and returned to normal after nutritional rehabilitation. Basal GH levels were high in the three severely malnourished groups (21.9, 28.8, and 16.6 ng/ml, respectively) and returned to normal after refeeding (8.1, 6.5, and 6.0 ng/ml, respectively). GH responses to arginine were depressed in the three malnourished groups and improved significantly in marasmic-kwashiorkor and marasmic children after nutritional rehabilitation. Insulin responses to arginine were impaired in kwashiorkor, and marasmic-kwashiorkor children and improved significantly after refeeding. IGF-I levels correlated significantly with percent of expected weight ($r = 0.52$, $p < 0.001$), percent of expected height ($r = 0.42$, $p < 0.001$), and weight/(height)^2 index ($r = 0.34$, $p < 0.01$). IGF-I levels correlated positively with insulin levels ($r = 0.421$, $p < 0.001$) and negatively with cortisol concentrations ($r = -0.400$, $p < 0.001$). It is suggested that effective lipolysis mediated by high GH and possibly low IGF levels, is an important adaptive mechanism to assure fuel (fatty acids) supply for metabolism of brain and peripheral tissues during nutritional deprivation. (Pediatr Res 20: 1122–1130, 1986)

Abbreviations

IGFs, insulin-like growth factors
PEM, protein-energy malnutrition
GH, growth hormone
BMI, body mass index

IGFs or somatomedins are essential anabolic hormones that direct a broad range of biological activities. Their actions are not restricted to the regulation of growth, but subserve the maintenance of mature cells (1). Recent data from in vivo studies support the concept that IGF-I/somatomedin-C (IGF-I) is the major anabolic hormone responsible for long-term effects on tissue growth (2).

Growth failure in patients with PEM has been attributed to a deficiency in the generation of the somatomedins (3, 4). Thus, measurements of somatomedin concentration may be an accurate index of nitrogen balance (flux) in such patients (5). Although there is general agreement that serum IGF-I concentrations are low in patients with kwashiorkor (3, 4, 6), there is still controversy concerning the circulating IGF-I levels (or activity) in marasmic (6, 7) individuals.

Somatomedin production and activities are influenced by many factors including growth hormone (GH) (8–10), insulin (11–13), prolactin (14, 15), and cortisol (16, 17), in addition to an important effect of nutritional balance (18–21). Since nutritional status influences secretion of these several hormones, one should consider that the observed changes in IGF-I concentrations might reflect alterations in the levels of these hormones (6, 18, 22). Thus, their effects upon skeletal growth may be mediated through their effects upon IGF generation.

Basal GH levels in PEM have been studied extensively (6, 23–26). There is a general agreement that despite impaired growth rates in children with kwashiorkor, GH concentrations are elevated. In marasmic children the results are conflicting with reports of low (27), normal (28, 29), and high GH levels (6, 30, 31). In addition, there remains disagreement regarding pituitary reserve in children with PEM. Statistically significant responses to arginine hydrochloride in patients with marasmus (27, 30, 32) and kwashiorkor (27, 33) have been reported in some, but not all, studies.

Measurements of basal insulin levels in children with kwashiorkor have yielded inconsistent results: high (34), low (6, 35, 36), and normal (37) values have been reported. In marasmic children insulin levels have been reported to be normal (38) or low (6, 39). Moreover, there is no general consensus concerning insulin reserve in children with PEM as measured by applying various stimuli-including glucose, glucagon, and arginine hydrochloride. Satisfactory and poor responses have been obtained both in children with marasmus (32, 40, 41) and kwashiorkor (41–43). In addition to a direct action on skeletal growth, it has also been proposed that insulin influences growth via stimulation of IGF-I synthesis and/or affecting somatotropic tissue receptors (44, 45).

To attempt to clarify these controversies, the present study was designed to determine: 1) the basal serum levels of IGF-I and IGF-II, GH, insulin, and cortisol in the different types of PEM before and after nutritional rehabilitation; 2) the responses of circulating GH and insulin to stimulation with an infusion of arginine hydrochloride before and after nutritional rehabilitation; and 3) the relationship among sérum GH, insulin, cortisol, albumin, and IGF-I and IGF-II concentrations in the different types of PEM.

PATIENTS AND METHODS

Sixty-one patients between the ages of 3 and 36 months with PEM were the subjects of this study. They were admitted to the Nutritional Ward of Alexandria University Children's Hospital, Alexandria, Egypt for clinical management and nutritional rehabilitation. All were examined thoroughly with special emphasis on nutritional history, weight, age, height, head and mid-arm circumferences; biceps, triceps, and subscapular skinfold thicknesses, muscle diameters, and arm cross-sectional fat (46); and clinical signs of malnutrition including: edema, hair and skin changes, mental changes, and hepatomegaly. The children were divided into four groups: 15 patients with kwashiorkor, 15 with marasmic-kwashiorkor, 21 with marasmus, and 10 underweight for age according to the differences in body weight for age and presence or absence of edema as judged by Wellcome Trust Working Party (47). Eight age-matched normal children (height and weight within the 95% confidence limits for Egyptian children) served as controls. Informed consent for the testing procedure was obtained from the parents of all children.

On the day of admission to the hospital the children were fed diets similar to those that they had consumed at home. All patients were treated with antibiotics, vitamins, and when indicated, intravenous fluids. After an overnight fast and prior to the initiation of protein feedings, a fasting venous blood sample was withdrawn through a polyethylene catheter inserted in a forearm vein. The serum was separated from the formed elements by centrifugation and kept frozen at $-20°$ C until analyzed for GH (48), insulin (49), IGF-I and IGF-II (50, 51) by radioimmunoassay, albumin by a bromocresyl green method, and glucose by a glucose oxidase method. Intraassay coefficients of variation averaged 8% in the range of insulin values detected and 7% in the range of GH measured. The intraassay CV for the IGF-I assay was 8% in the usual range but 16% for values less than 0.3 U/ml. Those for the IGF-II assay were 7% in the normal range and 15% for values below 100 ng/ml. One unit of somatomedin C is equivalent to 180 ng. The data are presented in U/ml since this is the more common notation.

After withdrawal of the fasting sample, 10% (w/v) arginine hydrochloride (0.5 g/kg) was infused intravenously for 30 min and blood samples were obtained at 0, 30, 45, and 60 min after the end of the infusion for the determination of GH, insulin, and glucose concentrations. After 4 to 8 wk of nutritional rehabilitation with a diet containing 100–150 kcal/kg/day and 4 g protein/kg/day (depending on the time necessary to bring them to a "normal" state) all the previous anthropometric measurements were repeated and the laboratory tests redone on the

available (living) children (nine of 15 from the kwashiorkor group, 10 of 15 from the marasmic-kwashiorkor group, and nine of 15 from the marasmic group as shown in Appendix Table 1).

Data are presented as means ± SD. Statistical analyses were done using the paired t test before and after treatment, when normally distributed, and paired Wilcoxon test when they were not normally distributed. Unpaired t test with Bonferonni's correction was used for the comparison of the malnourished groups to the control group, when the data were normally distributed and the Wilcoxon test when they were not.

RESULTS

Anthropometric data for the malnourished and control children are presented by diagnostic category in Table 1. The BMI [weight/(height)^2] increased significantly after nutritional rehabilitation in children with kwashiorkor ($p = 0.02$), marasmic-kwashiorkor ($p = 0.005$), and marasmus ($p = 0.01$).

Table 2 shows the albumin and hormonal data. Before nutritional rehabilitation serum albumin levels were significantly lower in the kwashiorkor (2.3 ± 0.8 g/dl, mean ± SD), and marasmic-kwashiorkor groups (2.3 ± 0.9 g/dl) than the control group (3.1 ± 0.5 g/dl; $p = 0.003$ and 0.006, respectively); however, the differences did not reach significance between the marasmic (3.5 ± 1.2 g/dl) or the underweight (3.8 ± 0.6 g/dl) groups and the control group. After refeeding, albumin levels increased significantly in those children with kwashiorkor (3.7 ± 0.8 g/dl; $p = 0.003$) and marasmic-kwashiorkor (3.7 ± 0.8 g/dl; $p = 0.002$).

Mean levels of serum IGF-I before refeeding were significantly decreased in the kwashiorkor [0.07 ± 0.03 U/ml (U = 180 ng)], marasmic-kwashiorkor (0.05 ± 0.03 U/ml), and marasmic (0.09 ± 0.09 U/ml) groups when compared to the control children (0.20 ± 0.10 U/ml; $p = 0.009$, 0.004, and 0.020, respectively). No significant differences were detected among children in any of the three malnourished groups before nutritional rehabilitation. After refeeding, IGF-I levels increased significantly in the three malnourished groups (0.21 ± 0.15, 0.15 ± 0.13, and 0.25 ± 0.16 U/ml, respectively) ($p = 0.01, 0.02,$ and 0.02, respectively) to become indistinguishable from the levels in the control children. The IGF-I levels in the underweight group (0.19 U/ml) did not differ from those for the control group. There were no significant differences in the IGF-I levels between the children who lived and those who died in the kwashiorkor ($p = 0.89$), marasmic-kwashiorkor ($p = 0.75$) or marasmic ($p = 0.15$) groups. Statistically significantly lower basal IGF-I and IGF-II levels were found in the malnourished children even after the children who died were deleted from the analysis.

Before nutritional rehabilitation the levels of IGF-II in children with marasmic-kwashiorkor (111 ± 58 ng/ml) and marasmus (128 ± 71 ng/ml) were significantly lower than the levels for the control children (224 ± 75 ng/ml; $p = 0.002$ and 0.008, respectively), but the differences were not significant between the kwashiorkor (175 ± 75 ng/ml) or the underweight (165 ± 62 ng/ml) groups and the control group. After refeeding, IGF-II levels increased significantly in the kwashiorkor (230 ± 88 ng/ml; $p = 0.007$), marasmic-kwashiorkor (195 ± 79 ng/ml; $p = 0.032$), and marasmic (287 ± 112 ng/ml; $p = 0.01$) groups.

The basal GH concentrations were significantly higher before treatment in the kwashiorkor (21.9 ± 10.0 ng/ml), marasmic-kwashiorkor (28.8 ± 5.9 ng/ml), and marasmic (16.6 ± 5.9 ng/ml) groups than those for the control group (5.9 ± 2.3 ng/ml; $p < 0.001, <0.001,$ and 0.003, respectively). No significant difference was found between the underweight (6.5 ± 5.1 ng/ml) and control groups. After refeeding, the basal GH levels decreased significantly in the kwashiorkor (8.1 ± 3.7 ng/ml; $p = 0.007$), marasmic-kwashiorkor (6.5 ± 3.0 ng/ml; $p = 0.002$), and marasmic (6.0 ± 5.1 ng/ml; $p < 0.001$) groups to become indistinguishable from the levels in the control group.

Table 1. *Anthropometric data for the malnourished and control children*

	Age (mo)	Wt (kg)	% of average wt	Ht (cm)	% of average ht	Mid-arm circumference (cm)	% of average mid-arm circumference	Muscle diameter (mm)	Wt/(ht)^2 × (10)^3
Kwashiorkor*									
Mean	13.43	6.38	71.74	65.85	89.55	10.5	68.32	27.06	1.5
SD	8.36	1.64	6.22	8.7	6.18	1.8	10.06	4.9	0.2
Kwashiorkor†									
Mean	14.83	7.5	81.43	67.76	92.18	12.06	76.93	31.0	1.6
SD	6.65	1.73	7.86	7.77	4.16	2.0	11.04	5.63	0.15
p value		0.18		0.62		0.10		0.17	0.03‡
Marasmic-kwashiorkor*									
Mean	12.00	4.75	55.49	64.68	92.44	8.76	59.54	25.16	1.14
SD	8.64	1.43	5.22	8.7	6.94	1.74	10.1	3.74	0.14
Marasmic-kwashiorkor†									
Mean	13.6	6.25	62.4	67.07	95.2	10.39	61.45	27.75	1.3
SD	6.1	1.41	21.28	6.13	12.17	1.64	19.99	4.3	0.2
p value		<0.01		0.41		0.04		0.06	<0.01‡
Marasmus*									
Mean	10.81	4.61	56.77	62.14	90.18	8.5	56.67	22.69	1.0
SD	8.69	1.57	5.88	8.5	4.39	1.32	8.08	5.45	0.25
Marasmus†									
Mean	16.44	6.74	71.77	67.01	90.18	11.33	72.6	30.33	1.48
SD	11.22	2.08	7.23	10.41	4.35	2.02	10.27	5.47	0.18
p value		0.15		0.66		0.01		0.03	0.01‡
Underweight									
Mean	23.1	7.78	71.51	77.08	96.17	12.64	78.06	32.86	1.3
SD	8.88	1.35	2.5	8.05	3.51	1.37	7.27	3.64	0.01
Controls									
Mean	8.9	8.36	110.29	68.26	101.42	12.66	85.21	33.12	1.7
SD	6.5	2.5	10.09	10.61	5.79	1.98	9.53	5.97	0.01
p value		0.56		0.07		0.97		0.91	0.001‡

* Before nutritional rehabilitation.
† After nutritional rehabilitation.
‡ Significant.

The GH responses to arginine infusion before and after nutritional rehabilitation are shown in Figure 1 *A* and *B*. Before refeeding the maximal percent increase in GH concentration above the basal levels was significantly lower in the kwashiorkor (40 ± 74%), marasmic-kwashiorkor (2.8 ± 44%), and marasmic groups (57 ± 85%) than in the control children (211 ± 270%; *p* = 0.008, <0.001, and 0.015, respectively). After nutritional rehabilitation the responses did not differ between the marasmic-kwashiorkor (191 ± 196%) or marasmic children (95 ± 100%) and the normal children, but were still significantly below normal for the children in the kwashiorkor group (26 ± 48%; *p* = 0.004).

The fasting insulin levels in the marasmic-kwashiorkor (7.3 ± 5.8 μU/ml) and marasmic groups (10.3 ± 13.2 μU/ml) did not differ significantly from the levels of the control children (13.2 ± 10.4 μU/ml) before refeeding, but they were marginally lower than normal in children with kwashiorkor (7.0 ± 5/2 μU/ml; *p* = 0.035, Table 2). After nutritional rehabilitation, no significant differences in fasting insulin levels between the three severely malnourished groups (10.3 ± 12.2, 18.9 ± 15.4, 17.4 ± 14.1 μU/ml) and the control group were noted.

The insulin responses to arginine infusion before and after nutritional rehabilitation are shown in Figure 2 *A* and *B*. Before nutritional rehabilitation, the insulin responses to arginine infusion, as measured by the percent increase of the peak levels above the basal levels, were significantly lower in the kwashiorkor (115

± 226%) and marasmic-kwashiorkor (144 ± 350%) groups than in the control group (577 ± 423%; *p* = 0.004 and 0.010, respectively). The insulin responses in marasmic children (292 ± 301%) were significantly higher than those for the kwashiorkor and marasmic-kwashiorkor children (*p* = 0.018 and 0.011, respectively), but did not differ from the control group (*p* = 0.079). After nutritional rehabilitation there were no differences between the insulin responses of the kwashiorkor (205 ± 224%), or the marasmic-kwashiorkor (266 ± 175%) groups and the response of the control children (*p* = 0.09 and 0.08, respectively).

Before treatment there were no significant differences in the fasting glucose concentrations between any of the malnourished groups and the control group. The peak responses after arginine infusion were significantly greater than the basal levels in all the studied groups (data not shown).

In all the children before refeeding IGF-I and IGF-II levels correlated significantly with the percent of expected weight for age (*r* = 0.52 and 0.50; *p* < 0.001), and the weight/(height)^2 ratio (*r* = 0.34 and 0.50; *p* < 0.001) (Fig. 3 *A* and *B*). IGF levels correlated significantly with the percent of height deficit (*r* = −0.42, *p* < 0.001). Insulin levels correlated significantly with IGF-I (*r* = 0.46, *p* < 0.001), albumin concentration (*r* = 0.49, *p* < 0.001), and arm muscle diameter (*r* = 0.28, *p* < 0.001).

GH levels correlated inversely with IGF-I concentrations (*r* = −0.50, *p* < 0.001) and with the calculated arm cross-sectional fat

Table 2. *Hormonal data (means) for the malnourished and control children before and after nutritional rehabilitation*

Groups	IGF-I (U/ml)	IGF-II (ng/ml)	GH (ng/ml)	GH Peak (ng/ml)	Insulin (μU/ml)	Insulin peak (μU/ml)	Cortisol (μg/ml)	Albumin (g/dl)
Kwashiorkor (n = 15) ‖	0.072 ±0.034	174.7 ±79.3	21.91 ±10.0	29.5 ±18.0	7.01 ± 5.2	14.8 ±17.5	27.11 ±22.7	2.31 ±0.8
Kwashiorkor (n = 9)¶	0.212* ±0.154	232.3* ±87.5	8.1† ± 3.7	10.7 ±7.3	10.3* ±12.2	31.0 ±40.4	14.8* ± 3.7	3.7* ±0.79
Marasmic-kwashiorkor (n = 15)	0.051‡ ±0.030	111.3‡ ±57.8	28.8§ ± 5.9	27.3 ±16.0	7.3 ± 5.8	14.30 ±18.0	31.9‡ ±24.1	2.3‡ ±0.9
Marasmic-kwashiorkor (n = 10)	0.153* ±0.126	194.7* 79.4	6.5* 3.0	15.8 ±6.6	18.9* ±15.4	56.4 ±39.9	13.9* ± 5.6	3.7* ±0.76
Marasmus (n = 21)	0.088‡ ±0.092	128.0 70.9	16.6‡ ± 5.9	25.0 ±28.6	10.3 ±13.2	37.7 ±42.0	24.8‡ ±15.6	3.5 ±1.2
Marasmus (n = 9)	0.252* ±0.162	287.0 ±111.8	6.0† ± 5.1	11.6 ±12.2	17.4 ±14.1	40.8 ±37.3	14.2* ± 4.6	3.8 ±0.6
Underweight (n = 10)	0.187 ±0.09	165.1 ±61.5	6.5 ± 5.1	16.6 ±12.1	16.2 ±13.0	69.4 ±57.9	11.4 ± 4.9	3.8 ±1.3
Control (n = 8)	0.197 ±0.102	224.0 ±75.8	5.9 ± 2.3	14.3 ±5.4	13.2 ±10.4	63.4 38.7	11.1 ± 7.0	3.13 ±0.50

Before treatment vs after treatment * $p < 0.05$, † $p < 0.01$.
Normal vs children with PEM ‡$p < 0.01$, §$p < 0.001$.
‖ Before nutritional rehabilitation.
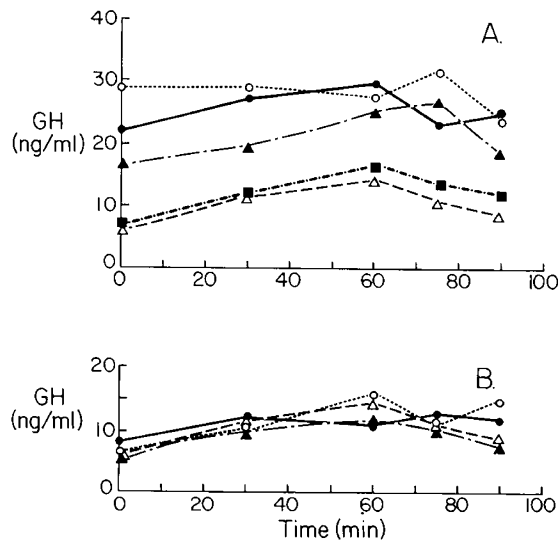¶ After nutritional rehabilitation.

Fig. 1. Serum GH concentrations during and after an intravenous infusion of L-arginine hydrochloride 0.5 g/kg from 0 to 30 min. *A* before and *B* after nutritional rehabilitation. Fifteen children with kwashiorkor ●——●; 15 with marasmic-kwashiorkor O————O; 21 with marasmus ▲————▲; 10 underweight ■-•-•-■; and eight control children △—— △. For *B* the number of children are nine with kwashiorkor, 10 with marasmic kwashiorkor, and nine with marasmus.
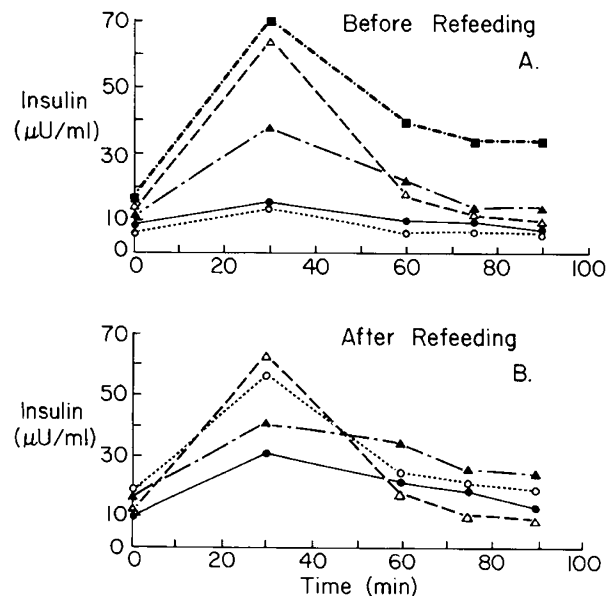

Fig. 2. Serum insulin concentrations during and after an intravenous infusion of L-arginine hydrochloride, 0.5 g/kg from 0 to 30 min. *A* before and *B* after nutritional rehabilitation. The *symbols* are the same as in Figure 1.

($r = -0.27, p = 0.028$). IGF-I levels correlated inversely with the cortisol levels ($r = -0.40, p < 0.001$), and positively with the calculated muscle diameter ($r = 0.46, p < 0.001$), and the arm cross-sectional fat ($r = 0.46, p < 0.001$). Cortisol concentrations correlated inversely with the arm muscle diameter ($r = -0.32, p < 0.001$); however, no significant correlation was detected be-

tween cortisol levels and the percent height deficit ($r = 0.22, p = 0.07$).

The insulin/cortisol ratio correlated significantly with IGF-I concentrations ($r = 0.64, p < 0.001$, Fig. 4), and with the percent weight deficit ($r = 0.42, p < 0.001$, data not shown). A significant positive correlation with refeeding was detected between increments in insulin levels and muscle diameters ($r = 0.46, p = 0.01$).
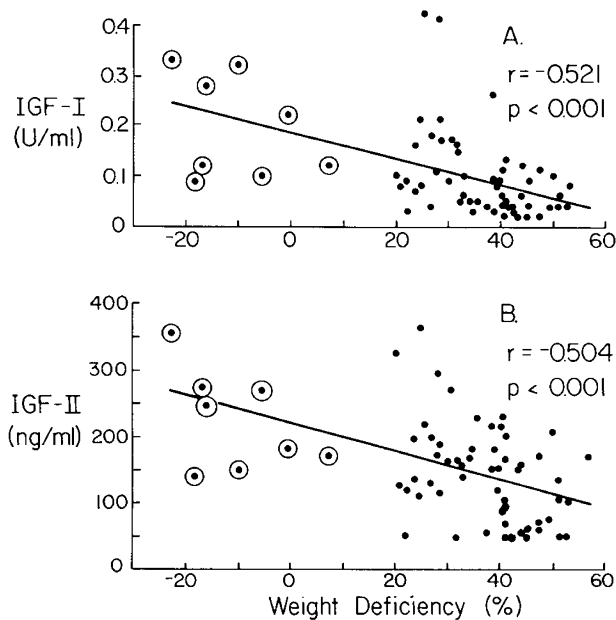
Fig. 3. Correlation of serum IGF concentrations and percent weight deficit in malnourished (●) and control children (○) before IGF-I nutritional rehabilitation. *A*, IGF-I; 1 U equals 180 ng. *B*, IGF-II.
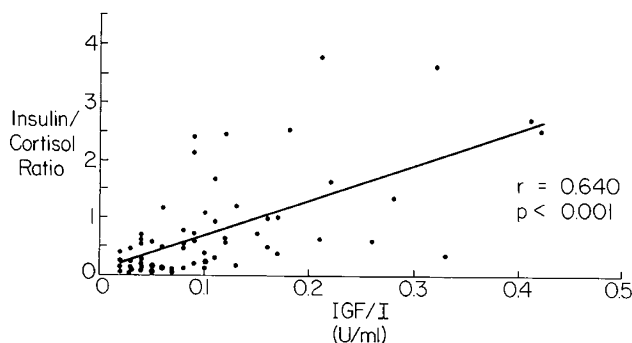

Fig. 4. Correlation of the insulin to cortisol ratio and IGF-I concentration in malnourished and control children before nutritional rehabilitation. One U IGF-I equals 180 ng.

DISCUSSION

We have shown that circulating IGF-I levels are lower than control values in children who have any of the three types of severe PEM: kwashiorkor, marasmic-kwashiorkor, and marasmus, and rise to normal with nutritional rehabilitation. IGF-II levels were also decreased compared to control children and increased significantly in the three severely malnourished groups after refeeding. IGF-I and IGF-II levels correlated significantly with the percent of expected weight for age and the weight/(height)^2 ratio. Thus, measurement of IGF-I concentration is a more sensitive indicator of the nutritional status of children than are serum albumin levels, since the latter do not correlate with either percent of expected weight or weight/(height)^2 ratios in malnourished children (data not shown), and were normal in our marasmic patients. Moreover, the presence of normal serum albumin concentrations with low IGF-I levels in the marasmic group implies that the decrement in IGF-I is not a part of a generalized decrease in hepatic protein synthesis as suggested by other investigators (7, 52). The insignificant differences in the IGF-I concentrations between the children who lived and those who died in each of the severely malnourished groups suggested that reasons other than the severity of malnutrition per se were the cause of death in the decedents.

The low serum albumin levels in kwashiorkor and marasmic-kwashiorkor can be explained by the adequate energy, but protein-deficient diets. Such diets have been shown in experimental animals to cause hypoalbuminemia, whereas the energy- and protein-deficient diets, similar to those consumed by the marasmic children, did not lead to hypoalbuminemia (53).

The fasting insulin levels were normal in the marasmic and marasmic-kwashiorkor children and only marginally lower in children with kwashiorkor when compared to normal children. The biological significance of this small difference is unclear. The insulin secretory responses to arginine infusion as measured by the percent increase of the peak value above basal level were impaired in kwashiorkor and marasmic-kwashiorkor groups when compared to the control group. There was no significant difference in insulin responses between the marasmic and normal children. After refeeding, the insulin responses did not differ in kwashiorkor and marasmic-kwashiorkor children from those in the control group. The insulin responses before nutritional rehabilitation were significantly higher in marasmic children than in those in the kwashiorkor and marasmic-kwashiorkor groups. The low basal insulin levels in kwashiorkor, and the impaired insulin reserve in kwashiorkor and marasmic-kwashiorkor patients can be attributed to the effect of their unbalanced high energy-low protein diet. In support of this view, in experimental animals maintained on low protein diets where the carbohydrate content is necessarily high, plasma insulin levels are consistently low (54, 55).

Insulin levels correlated significantly with IGF-I concentrations in all the children before refeeding ($r = 0.42$, $p < 0.001$). This may reflect a causal relationship between insulin and IGF-I secretion (13). In addition, the positive correlation between insulin and albumin concentrations in these children ($r = 0.52$, $p < 0.001$) may reflect an important role played by insulin to support hepatic protein synthesis.

Fasting serum GH values were significantly higher in the three severely malnourished groups, with no significant differences among them, and returned to normal with nutritional rehabilitation. These findings are in contrast to those of Mohan *et al.* (7) who have reported normal GH and somatomedin activity in marasmic children. The impaired release of GH after arginine stimulation in children in the three severely malnourished groups in the presence of the high basal GH levels may indicate that their pituitaries may be near maximally stimulated in the basal state. After refeeding, the response of GH to arginine infusion improved in all the malnourished groups to become indistinguishable from that of the normal children. The significantly negative correlation between GH and IGF-I suggests an intact negative feedback effect IGF-I concentrations on the hypothalamic-pituitary release of GH, but the reasons why the high levels of GH do not stimulate IGF-I synthesis are not clear. However, the highly significant correlation between the IGF-I levels on the one hand and the insulin and cortisol levels on the other hand indicate that the impaired insulin secretion and the elevated cortisol levels in malnourished children in addition to the deficient diet, may override the effect of high GH levels on IGF-I and IGF-II production during nutritional deprivation.

The insulin/cortisol ratio correlated well with the IGF-I concentration as well as with the percent of expected weight, suggesting that insulin and cortisol may exert their actions on nitrogen balance, at least partially, through their effect on IGF-I synthesis.

The significant positive correlation between IGF-I levels and the calculated arm cross-sectional fat as well as the negative correlation between GH and cross-sectional fat are in agreement with the hypothesis that high GH levels in the presence of low somatomedin concentrations is an important adaptive mechanism to provide the organism with fuel (fatty acids), through lipolysis, during nutritional deprivation (56).

IGF-I, cortisol (negatively), and insulin levels correlated significantly with the calculated arm muscle diameter in all the

children before refeeding. In addition, there is a significant correlation between the increments in insulin levels and muscle diameters with refeeding. These findings suggest that the increased catabolic action mediated by the high cortisol levels in addition to the low anabolic activities due to low IGF and insulin levels during nutritional deprivation allow proper breakdown of muscle protein necessary to provide the liver with the amino acids for gluconeogenesis and protein synthesis.

Although physiologically high levels of circulating cortisol have been shown to inhibit the stimulatory action of IGF-I on epiphyseal cartilage (56–58), we have found a significant negative correlation between IGF-I levels and the percent height deficit, but no significant correlation has been detected between cortisol levels and the percent height deficit. This finding may indicate a more important role of low IGF-I levels than of excessive cortisol levels on the impairment of growth of epiphyseal cartilage during periods of malnutrition.

In summary, various alterations in hormonal levels and their responsiveness to secretagogues act to defend the body against PEM. The elevated GH levels stimulate lipolysis, whereas the low IGF-I concentrations and impaired insulin secretion inhibit lipogenesis. Both processes assure fuel supply (fatty acids) to the brain and peripheral tissues through effective breakdown of adipose tissue. Moreover, the increased muscle protein catabolism mediated by elevated basal cortisol levels and depressed anabolic activity due to the selective decrease in somatomedin levels assure an adequate supply of amino acids to the liver. This metabolic intermediate allows gluconeogenesis and protein synthesis to proceed and guards against the development of hypoglycemia and hypoalbuminemia in children with PEM. Thus, there is coordinated regulation of metabolism in PEM to defend the organism against hypoglycemia and to provide alternate substrates to subserve the essential energy and biosynthetic requirements.

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Appendix Table 1. *Anthropometric data for the malnourished and control children*

	Age (mo)	Wt (kg)	% of exp. wt	Ht (cm)	% of exp. ht	Mid-arm circumference (cm)	% of exp. mid-arm circumference	Muscle diameter	Wt/(ht)^2 × (10)^3
Kwashiorkor (before)									
1	19	7.8	76.4	70.5	91.3	11.5	70.9	32.4	1.5
2	7	4.5	61.6	56	84.7	9	59.2	22.4	1.4
3	14	7.2	79.1	70.2	95.7	11.5	73.2	26.3	1.4
4	3	3.6	65.4	49.5	83.2	7.2	55.3	19.1	1.4
5	8	5.6	73.4	61.5	91.4	12.2	81.3	33.0	1.4
6	15	7.2	77.8	66.1	89.1	9.4	58.3	24.1	1.6
7	18	7.5	76.3	74.8	97.9	11.7	73.5	30.8	1.3
8	11.5	5.6	65.8	68.5	96.0	9.3	59.8	23.2	1.1
9	24	8.5	77.9	75.6	93.7	12.7	78.8	34.0	1.4
10	14	7	75.2	64.5	87.9	9.6	59.6	24.3	1.6
11	9	5.5	67.9	50	73.1	9.5	62.5	25.6	2.2
12	7	6	80	61	92.4	13.3	89.8	31.5	1.6
13	8	5.3	67	58	86.2	9.1	60.6	20.5	1.5
14	8	5.1	64.5	59.5	88.4	10.2	68	25.6	1.4
15	36	9.2	67.1	83.2	91.4	12.1	73.3	32.7	1.3
Mean	13.43	6.38	71.74	64.59	89.55	10.55	68.32	27.06	1.52
SD	8.36	1.64	6.22	9.49	6.18	1.71	10.06	4.93	0.22
Marasmic-kwashiorkor (before)									
1	12	5	56.8	62.5	86.9	7.8	50	21.6	1.2
2	20	5	47.6	70.5	90.2	7	42.9	20	1.0
3	24	6.6	60	76.5	94.8	11	67.0	30.4	1.1
4	4	3	52.6	62	100.8	6.6	46.8	18	0.7
5	10	3.6	43.3	56	80.5	7.5	48.7	19.6	1.1
6	14	5.1	54.8	66.5	90.7	8.5	54.1	23.6	1.1
7	7	3.9	52.8	58	87.8	9	60.8	21.4	2.2
8	12	5.1	59.7	69.3	96.3	11	70.5	30.4	1.0
9	7	3.7	50.6	57.5	87.1	8.7	57.2	22.4	1.1
10	10	6.5	59.0	68	96.1	10.5	66.8	29.1	1.4
11	7	4.3	58.9	60	90.8	10.3	69.5	25.9	1.1
12	36	8.5	62.5	88.2	96.9	12.4	75.1	33.6	1.0
13	18	5.7	58.1	71.2	93.2	8.1	50.9	22.5	1.1
14	18	5.5	56.1	65.1	85.2	10.2	64.1	27.2	1.2
15	25	6.5	59.0	76.9	108.6	11.2	68.2	31.0	1.0
Mean	12	4.75	55.4	67.2	92.4	9.32	59.54	25.16	1.13
SD	8.64	1.43	5.22	8.71	6.93	1.74	10.10	3.74	0.14
Marasmus (before)									
1	20	6.1	59.2	72.9	93.3	9.5	59.3	26.0	1.1
2	4	3.7	60.7	55.5	90.2	7.2	51.0	19.3	1.2
3	5	3.6	54.6	56	88.7	8.2	56.5	23.1	1.1
4	18	5.8	59.0	69.2	90.6	9.7	59.8	27.4	1.2
5	4	3.1	50.2	51.2	83.2	7.5	54.7	21.4	1.1

Appendix Table 1.—*continued*

	Age (mo)	Wt (kg)	% of exp. wt	Ht (cm)	% of exp. ht	Mid-arm circumference (cm)	% of exp. mid-arm circumference	Muscle diameter	Wt/(ht)² × (10)³
6	8	4.4	57.7	61.5	91.4	8.5	55.9	23.6	1.1
7	26	8.2	71.9	77.5	94.4	11.2	69.1	31.2	1.3
8	36	8.5	61.6	81.2	89.2	10.2	62.1	27.4	1.2
9	12	4.5	52.6	58.1	80.7	9.2	57.8	4.8	
10	4	3	48.6	53.8	90.5	7.7	56.2	20.1	1.0
11	4	3.4	55.1	54.1	87.9	8.2	59.8	22.3	1.1
12	6	4.2	59.4	61.5	95.3	7.5	50.3	21.6	1.1
13	12	5.1	59.7	62	86.2	11	69.1	31.8	1.3
14	12	5.2	60.8	71.5	99.4	9.1	57.2	24.1	1.0
15	8	5.5	56.0	66.2	86.7	7	45.4	19.6	1.2
16	3	4.8	58.8	67	96.3	8	59.2	23.2	1.0
17	5	2.7	48.9	53	89.1	7.1	48.9	20.4	0.9
18	3	3.9	59.1	56	88.8	9.9	76.1	26.3	1.2
19	12	2.6	47.1	53.2	89.5	7.4	46.5	21.3	0.9
20	6	4.2	49.1	62.5	86.9	7.2	48.3	20.7	1.0
21	19	4.3	61.2	61.1	94.6	7.3	45.9	20.0	1.1
Mean	10.81	4.61	56.77	62.14	90.17	8.50	56.67	22.6	1.10
SD	8.69	1.57	5.88	8.50	4.39	1.32	8.08	5.45	0.24
Underweight									
1	21	7.5	74.8	75.3	97.6	12.2	75.3	30.7	1.3
2	21	7.5	71.0	76.1	96.6	14.5	88.9	37.1	1.2
3	18	7.2	73.3	74.2	97.1	12.5	77.1	31.5	1.3
4	36	9.3	68.4	89.8	98.7	13.3	80.6	34.7	1.1
5	30	9.1	75.4	87.5	103.1	14	84.8	38.7	1.1
6	24	7.8	71.5	77.1	95.6	13.1	81.3	34.2	1.3
7	12	5.9	69.4	65.5	91.0	10.5	67.3	27.2	1.3
8	10	5.7	69.9	67	96.3	10.3	65.6	28.1	1.2
9	36	9.8	72.1	84.5	92.8	13.5	81.8	33.6	1.3
10	23	8	68.3	73.8	92.3	12.5	77.6	32.2	1.4
Mean	23.1	7.78	71.51	77.08	96.17	12.64	78.06	32.86	1.30
SD	8.88	1.35	2.50	8.05	3.51	1.37	7.26	3.64	0.09
Control									
1	3	5.1	92.7	54.1	91.0	10.5	80.7	29.0	1.7
2	6	7.1	100.5	64.5	99.9	11.4	76.5	29.4	1.7
3	6	8.2	116.1	67.5	104.6	13.4	89.9	36.0	1.7
4	18	11.6	118.1	81.5	106.7	15.4	96.8	40.8	1.7
5	4.5	6.6	110	59.5	95.7	10	69.9	22.6	1.8
6	10	8.6	105.5	72.5	104.2	12.5	81.1	33.1	1.6
7	4	7.2	116.6	62	100.8	13	92.1	34.3	1.8
8	20	12.5	122.5	84.5	108.1	15.1	94.3	39.4	1.7
Mean	8.9	8.36	110.29	68.26	101.41	12.66	85.21	33.13	1.76
SD	6.57	2.51	10.09	10.61	5.79	1.98	9.53	5.97	0.07
Kwashiorkor (after)									
1	20.5	8.8	83.0	71.3	90.5	13.2	80.9	36.4	1.7
2	8	5.8	76.3	57.2	85.0	9.3	62	23.4	1.7
3	15.5	8.5	91.8	72.1	97.2	12.7	80.3	29.8	1.6
4	5	4.2	63.7	55.5	87.9	9.4	66.1	24.3	1.3
5	9.5	6.6	80.9	62.5	91.4	14.2	91.6	38	1.6
6	17	8.3	85.3	68.5	90.4	10.5	64.8	26.6	1.7
7	19	8.4	84	76.1	96.6	13.5	84.9	35.1	1.4
8	13	7.1	81.6	69.5	95.8	11.3	71.9	28.7	1.4
9	26	9.8	85.9	77.2	94.3	14.5	89.5	36.5	1.6
Mean	14.83	7.5	81.43	67.76	92.18	12.06	76.93	31.00	1.61
SD	6.65	1.73	7.86	7.77	4.16	2.00	11.0	5.63	0.15
Marasmic-kwashiorkor (after)									
1	13.5	6.1	67.8	77.7	126.2	12.0	71.0	24.4	1.5
2	21.5	7.6	71.0	71.5	90.5	9.1	55.8	26.3	1.4
3	25.5	7.5	66.9	78	95.5	11.4	69.5	31.6	1.2
4	5	4.1	66.1	63	99.8	7.1	48.9	19.4	1.0
5	11	4.2	48.8	58.5	82.6	9.5	61.2	25.6	1.2
6	16	8	85.1	70.1	93.5	11.3	71.5	30.1	1.6
7	8.5	5.2	67.5	60.5	89.2	10.2	67.5	24.6	1.4

Appendix Table 1.—*continued*

	Age (mo)	Wt (kg)	% of exp. wt	Ht (cm)	% of exp. ht	Mid-arm circumference (cm)	% of exp. mid-arm circumference	Muscle diameter	Wt/(ht)^2 × (10)^3
8	14	6.2	66.6	72	98.2	11.6	73.8	30.9	1.1
9	9	6.1	77.5	62.1	90.8	12.1	77.5	32.1	1.5
10	12	7.5	66.9	69.5	85.1	12.3	77.3	32.1	1.5
Mean	13.6	6.25	62.45	61.29	95.20	9.66	61.45	27.75	1.25
SD	6.14	1.41	21.28	19.77	12.17	3.13	19.99	4.30	0.43
Marasmus (after)									
1	22	7.8	72.8	76.3	95.9	12.6	78.7	33.1	1.3
2	6	5.7	77.7	60	92.9	11	73.8	27.8	1.5
3	6	4.1	58.0	57.2	88.6	8.9	59.7	25.1	1.2
4	20	6.9	67.6	71	90.9	12.1	75.6	33.1	1.3
5	6	5.2	73.6	53	82.1	7.9	54.4	20.9	1.8
6	9	5.1	64.8	62	90.7	10.1	66.4	27.0	1.3
7	27	9.6	82.7	78.1	94.4	13.1	80.8	36.4	1.5
8	38	10.2	73.3	83	90.6	14	85.3	37.5	1.4
9	14	6.1	69.6	62.5	85.2	12.3	78.3	31.7	1.5
Mean	16.44	6.74	71.17	67.01	90.18	11.33	72.60	30.33	1.48
SD	11.22	2.08	7.23	10.41	4.35	2.02	10.27	5.47	0.18