

Insulin-like growth factor I response during nutritional rehabilitation of persistent diarrhoea

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Abstract

Objective—Evaluation of nutritional recovery, intestinal permeability, and insulin-like growth factor I (IGF-I) response in malnourished children with persistent diarrhoea and their relation to concomitant systemic infection(s).

Study design—Open study of severely malnourished children (aged 6–36 months) with persistent diarrhoea (≥ 14 days) admitted for nutritional rehabilitation with a standardised rice-lentil and yogurt diet. Successful recovery was defined prospectively as overall weight gain (> 5 g/kg/day) with a reduction in stool output by day 7 of treatment. Data on coexisting infections and serum C reactive protein (CRP) were collected at admission.

Results—Of 63 children, 48 (group A) recovered within seven days of dietary treatment. These children had a significant increase in serum IGF-I (Δ IGF-I%) and, in contrast to serum prealbumin and retinol binding protein, Δ IGF-I% correlated with weight gain ($r = 0.41$). There was no correlation between the IGF-I response and intestinal permeability as assessed by urinary lactulose/rhamnose excretion. Treatment failures (group B) included more children with clinical (relative risk, 4.8; 95% confidence interval, 1.2 to 19.7) and culture proven sepsis at admission and higher concentrations of serum CRP (median (range), 36 (0–182) v 10 (0–240) mg/l) at admission. There was a negative correlation between admission CRP concentration and Δ IGF-I% ($r = -0.45$).

Conclusions—In comparison with serum albumin, prealbumin, and retinol binding protein, serum IGF-I increment is a better marker of nutritional recovery in malnourished children with persistent diarrhoea. The possible association of systemic infections, serum IGF-I response, and mucosal recovery needs evaluation in future studies.

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ated with severe malnutrition and appropriate nutritional rehabilitation is considered an important cornerstone of treatment. The objective of dietary treatment in such children is manifold and studies evaluating the response to treatment of persistent diarrhoea need to ascertain both weight gain and diarrhoeal recovery.² Despite some advances in understanding the pathogenesis of the disorder, there is sparse information on factors influencing intestinal mucosal repair and nutritional recovery in persistent diarrhoea.

There is considerable interest in the role of growth factors in postnatal intestinal growth and maturation³ and the regulation of intestinal adaptation to changes in nutritional status.⁴ Circulating insulin-like growth factor I (IGF-I) is produced mainly in the liver in response to growth hormone, but is also produced in most tissues, and the distribution of IGF-I receptors is widespread. Thus, both autocrine and paracrine functions have been ascribed to IGF-I.⁵ The intestine is considered to be one of the most responsive target organs for IGF-I,^{6,7} and some regard it as essential for intestinal repair.⁸

Previous studies have identified low concentrations of IGF-I in malnourished children,⁹ and Soliman *et al* demonstrated a rapid return to normal concentrations of IGF-I after nutritional rehabilitation.¹⁰ There is considerable interest in the regulation of IGF-I in children with chronic inflammatory states such as cystic fibrosis¹¹ and inflammatory bowel disease¹²; however, little is known about its regulation in systemic infection. Although low IGF-I concentrations have been described in children with acute shigellosis,¹³ there are few data on IGF-I status and its dynamics during recovery from persistent diarrhoea. Therefore, we prospectively studied the IGF-I response and pattern of recovery in hospitalised malnourished children with persistent diarrhoea undergoing nutritional rehabilitation with special reference to clinical and laboratory markers of infection.

Material and methods

Our study was approved by the human subjects protection committee at the Aga Khan University Medical Centre. We identified children (aged 6–36 months) with persistent diarrhoea, defined as diarrhoea lasting ≥ 14 days with growth faltering,¹ from the ambulatory care services and they were then evaluated for potential inclusion in our study. After informed consent, children were stabilised with correction of dehydration or electrolyte abnormalities. In all cases, baseline stool cultures, quantitative C reactive protein (CRP), complete

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Persistent diarrhoea is recognised as a major cause of morbidity and mortality in childhood, accounting for 3–20% of all childhood diarrhoeal episodes, with associated case fatality rates exceeding 15%.¹ It is frequently associ-

Table 1 Comparison of admission characteristics according to outcome of treatment

	Group A Treatment success	Group B Treatment failure
Number	49	14
Boys:girls	32:17	9:5
Mean age (months)	10.0 (6.0 to 24.0)	13.0 (7.0 to 30.0)
Weight for age z score	-3.4 (-5.7 to 0.6)	-3.0 (-4.9 to -1.0)
Height for age z score	-1.6 (-5.2 to 1.5)	-0.8 (-3.5 to 1.5)
Weight for height z score	-3.0 (-6.3 to 0.4)	-2.8 (-3.8 to -0.9)
Duration of diarrhoea (days)	30.0 (14.0 to 90.0)	24.0 (14.0 to 60.0)
Observed stool volume (g/kg/day)	89.8 (10.6 to 516.0)	70.2 (26.5 to 956.8)
Observed stool frequency (number/day)	9.9 (2.0 to 28.0)	8.6 (3.0 to 39.0)
Haemoglobin (g/l)	95.0 (52.0 to 134.0)	92.0 (48.0 to 126.0)
Serum albumin 1 (g/l)	35.0 (19.0 to 46.0)	35.0 (20.0 to 50.0)
Serum prealbumin 1 (mg/l)	93.0 (33.0 to 167.0)	86.5 (35.3 to 93.0)
Serum retinol binding protein (mg/l)	14.0 (8.0 to 52.0)	16.0 (8.0 to 34.0)
Serum C reactive protein (mg/l)	10.0 (0 to 240.0)	36.0 (0 to 182.0)

Data are median (range). All differences are not significant.

blood count, serum albumin, prealbumin, retinol binding protein (RBP), and IGF-I were obtained. We performed a baseline urinalysis in all cases.

We performed a dual sugar absorption test, using oral administration of an isotonic solution of lactulose (molecular weight 342; 3.5 g) and L-rhamnose (molecular weight 164; 0.5 g), followed by urine collection for six hours, at baseline and repeated it on day 7. A drop of chlorhexidine was added to the samples to prevent bacterial degradation and urine was stored at -20°C until analysis by thin layer chromatography.¹⁴

We obtained blood cultures at admission in children with fever (axillary temperature $\geq 38^\circ\text{C}$) or in those with features suggestive of sepsis. We used standardised definitions and treatment of associated infections as described previously.¹⁵ After stabilisation, we placed the children on a previously validated dietary regimen of rice-lentil (khitchri) and yogurt,¹⁶ aimed at providing at least 100 kcal/kg/day by day 3, with ad libitum feeds thereafter. The children were nursed for the duration of study in a five bed research ward with twice daily recording of clinical condition, vital signs, and hydration status. We recorded baseline anthropometric values and daily nude weight at a fixed time before the first morning feed in all children. We made urine and stool collections separately using adhesive urine bags, and estimated stool output using preweighed diapers (given the risk of perineal skin breakdown in girls, we recorded stool frequency only after 72 hours of treatment). We repeated the serum albumin, prealbumin, RBP, and IGF-I measurements at day 7. We defined a successful response to treatment as an overall weight gain of ≥ 5 g/kg/day and resolution of diarrhoea (improvement in stool consistency to semi-solid along with a reduction of stool volume to < 40 g/kg day in boys or stool frequency

< 5 /day in girls) by day 7 of treatment. We used the latter definition because of the risk of perineal skin breakdown after prolonged application of adhesive urine bags in girls. We regarded the alternative as failure of treatment.

LABORATORY ANALYSIS

We stored serum IGF-I samples at -70°C and transported them in dry ice to Stockholm for analysis. We acid/ethanol extracted the serum samples before the IGF-I radioimmunoassay (RIA) to partially separate IGFs from their binding proteins, and we used ^{125}I labelled des(1-3) IGF-I radioligand in the IGF-I RIA to avoid interference by IGF binding proteins not removed by the extraction procedure.¹⁷ The recovery of cold IGF-I was 98% and the intra-assay and interassay coefficients of variation were 7% and 9%, respectively. The lowest detectable concentration of IGF-I was 6 $\mu\text{g/l}$. We also validated the IGF-I assay from the sera of these patients in accordance with current recommendations.¹⁸ We measured prealbumin and serum RBP by radial immunodiffusion using standard human serum (Behring Diagnostics, Westwood, Massachusetts, USA). We thawed the urine samples for lactulose and rhamnose estimation and measured sugar excretion by thin layer chromatography and reflectance densitometry. We performed the sugar chromatography tests in duplicate and the mean coefficient of variation was 7%. We measured serum CRP by means of a fluorescent polarisation immunoassay system using a TdxFLx analyser (Abbott Laboratories, Chicago, Illinois, USA).

For comparison of continuous data we used the non-parametric Mann-Whitney U test and for categorical data we used estimation of relative risks (RR) and corresponding 95% confidence intervals (CI) or Fisher's exact test, as appropriate. We evaluated association of variables of interest by Spearman rank correlation (two tailed). We set significance at $p < 0.05$. We analysed all data using the statistical package for social sciences SPSS Windows version 6.1 (SPSS Inc, Chicago, Illinois, USA).

Results

Of 75 consecutive children with persistent diarrhoea admitted from outpatients to the nutrition research ward, seven could not be stabilised sufficiently within 24 hours of admission to receive the diet because of intercurrent infections (six patients) or persistent vomiting (one patient). A further four children were prematurely withdrawn by parents within 24 hours of initiation of treatment and one child developed severe dehydration and vomiting after two days of dietary treatment, necessitating intravenous treatment. Thus, a total of 63 children completed a minimum seven days of inpatient treatment with serial observations and laboratory evaluation as laid out in the protocol, and are included in the final analysis. There were no deaths in this group of children, although three developed further episodes of mild dehydration after initiation of treatment. Overall, 14 children were unable to meet criteria of successful recovery on the basis of poor weight gain and

Table 2 Comparative change in weight for age z (WAZ) score and nutritional markers of recovery over seven days of treatment

	Group A (n = 49) Treatment success	Group B (n = 14) Treatment failure
WAZ score increase (ΔWAZ score %)	11.1 (-9.8 to 49.8)	2.2 (-10.2 to 30.4)*
IGF-I increment ($\Delta\text{IGF-I}\%$)	122.7 (-61.1 to 850.0)	33.3 (-55.6 to 184.0)*
Prealbumin increment ($\Delta\text{prealbumin}\%$)	79.6 (-27.3 to 612.1)	93.1 (-15.0 to 611.0)
Retinol binding protein increment ($\Delta\text{RBP}\%$)	96.2 (0 to 453.9)	92.3 (0 to 450)

Values are median (range).

* $p < 0.05$ Mann-Whitney U test.

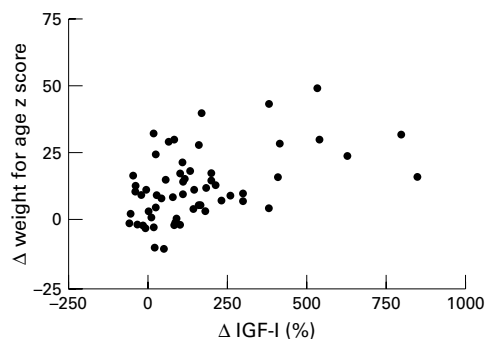


Figure 1 Correlation of overall IGF-I increment (Δ IGF-I%) and increase in weight for age score (Δ weight for age z score). Spearman rank correlation coefficient, 0.4; $p = 0.002$.

persistently high stool output (group B), whereas 49 were classified as treatment successes (group A).

We compared the admission clinical and laboratory characteristics for the two groups of children (table 1) to assess predictors of recovery. There were no significant differences between the two groups for nutritional status or severity and duration of diarrhoea, but failures had higher serum CRP concentrations at admission. Although the overall mean energy intake of the two groups was comparable (group A: mean (SD) 118.4 (35.4) v group B: 107.3 (38.0) kcal/kg/day; not significant (NS)), group B children had significantly lower mean (SD) weight gain (2.0 (2.5) v 10.3 (4.2) g/kg/day; $p < 0.01$). The mean (SD) daily stool frequency in group B children was significantly higher throughout the course of our study (12.3 (6.5) v 7.0 (3.6) each day; $p < 0.01$), as well as the mean (SD) stool volume measured among the boys in our study (159.4 (127.3) v 70.5 (54.2) g/kg/day; $p < 0.001$).

The mean (SD) increment in weight for age

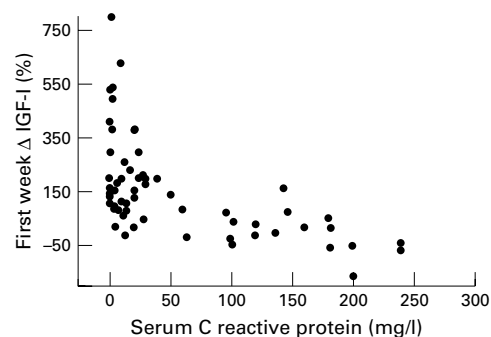


Figure 2 Correlation of serum C reactive protein (CRP) concentration at admission and overall IGF-I increment (Δ IGF-I%) for the following seven days. Spearman rank correlation coefficient, -0.45 ; $p < 0.01$.

z (WAZ) score was almost twice as high among successes as it was among failures (14.1% (12.7%) v 6.6% (11.9%); $p < 0.001$) and the corresponding increments in serum albumin, prealbumin, RBP, and IGF-I are shown in table 2. Admission values of serum IGF-I were low in all children and improved significantly in group A by day 7 of treatment. There was a significant correlation between increment in WAZ% scores and corresponding per cent increment in IGF-I concentration (Δ IGF-I%) (Spearman rank correlation coefficient, 0.4; $p = 0.002$; fig 1), whereas none was seen with the corresponding increase in serum prealbumin (Spearman rank correlation coefficient, -0.01 ; $p = 0.93$), or RBP (Spearman rank correlation coefficient, 0.06; $p = 0.65$).

Table 3 shows the corresponding urinary lactulose and rhamnose excretion for the two groups of children at baseline and day 7 of treatment. Small but opposing trends of urinary excretion of the oral lactulose dose were seen in both groups over the seven days of treatment, indicating worsening enteropathy among the failures. However, there was no correlation between any of the permeability parameters and IGF-I at either baseline or recovery.

There was a significant correlation between CRP concentrations at admission and corresponding individual Δ IGF-I% values over the ensuing seven days of treatment (Spearman rank correlation coefficient, -0.47 ; $p < 0.01$; fig 2).

Table 4 shows the associated morbidity patterns between the two groups of children. Of the 35 children screened for sepsis overall, the positivity rate for blood cultures was 17%, mostly consisting of Gram negative organisms. A significantly greater number of treatment failures had suspected and subsequently proven systemic infections at admission, which required intravenous antibiotics. There were no significant differences between the two groups for other infections such as skin infections, upper respiratory infections, associated pneumonia, or non-specific fever.

Discussion

Our data confirm previous findings¹⁶ that a traditional home available rice-lentil (khitchri) and yogurt diet can be used successfully for enteral nutritional rehabilitation in malnourished children with persistent diarrhoea and

Table 3 Comparative sequential urinary lactulose and rhamnose excretion after nutritional rehabilitation

	Group A (n = 49) Treatment success	Group B (n = 14) Treatment failure
<i>Baseline</i>		
Lactulose excretion (%)	30.4 (2.4 to 238.4)	15.2 (1.7 to 134.6)
Rhamnose excretion (%)	27.1 (1.0 to 132.9)	22.7 (13.2 to 114.1)
Lactulose:rhamnose ratio	0.12 (0.02 to 2.06)	0.09 (0.00 to 0.67)
<i>Day 7</i>		
Lactulose excretion (%)	25.9 (3.6 to 96.5)	31.7 (6.4 to 321.2)
Rhamnose excretion (%)	37.0 (1.52 to 192.3)	36.9 (6.8 to 178.5)
Lactulose:rhamnose ratio	0.11 (0.02 to 0.91)	0.10 (0.02 to 0.38)
<i>Overall change</i>		
Δ Lactulose excretion	0.1 (-0.9 to 22.2)	2.1 (0.7 to 20.2)*
Δ Rhamnose excretion	0.3 (-0.9 to 35.6)	0.4 (-0.8 to 10.9)
Δ Lactulose:rhamnose ratio	-0.25 (-0.97 to 5.28)	0.93 (-0.61 to 8.48)**

Values are median (range).

* $p < 0.05$; ** $p < 0.001$; Mann-Whitney U test.

Δ , overall increment.

Table 4 Associated morbidity patterns according to treatment response

	Group A Treatment success	Group B Treatment failure	RR	95% CI
Upper respiratory infections	19	6	1.1	0.5 to 2.9
Pneumonia	8	3	1.3	0.4 to 3.9
Skin infection	7	4	1.9	0.7 to 4.9
Suspected sepsis†	23	12	4.8	1.2 to 19.7*
Proven sepsis	2	4	3.8	1.7 to 8.4*

* $p < 0.02$; Fisher's exact test.

†Suspected clinically and put on antibiotics.

RR, relative risk; CI, confidence interval.

that this treatment leads to adequate weight gain in most patients. Our data also suggest that in contrast to serum albumin, prealbumin, and RBP, an increment in serum IGF-I levels correlates closely with weight gain and reduction in stool output. We also saw an association of delayed recovery with sepsis and raised blood CRP concentrations at admission.

A striking finding was the severely depressed baseline concentrations of IGF-I in children with persistent diarrhoea at admission, although most had a brisk response to nutritional treatment within seven days of initiation. These values are significantly lower than serum IGF-I values seen among healthy, uninfected children of comparable age in Pakistan (ZA Bhutta *et al*, unpublished observations, 1998). These values are also severalfold lower than IGF-I concentrations reported from poor children in Ecuador,¹⁹ malnourished children in Guinea-Bissau (L Smedman, personal communication), or acutely malnourished children with shigellosis in Bangladesh.¹¹ However, our values are comparable to those reported from malnourished children in Vietnam²⁰ and from critically ill adult patients.²¹ Although prealbumin measurements have been recommended for monitoring nutritional rehabilitation,²² our data confirm the findings of Clemmons *et al* in adult patients that IGF-I concentrations are more sensitive measures of nutritional repletion.²³

Several limitations should be recognised in reviewing our data. Although predefined, our criteria for defining treatment failure were somewhat arbitrary because despite continued diarrhoea in the first week, some of these children were still gaining weight by day 7, albeit slowly, and most subsequently recovered. However, the overall rate of weight gain among children considered to be treatment failures was significantly lower than other studies of nutritional rehabilitation.^{16 24 25} Despite comparable energy intakes exceeding 100 kcal/kg/day, several children failed to gain an adequate amount of weight and continued to have a high stool output, indicating the possibility of relatively poor energy and macronutrient absorption. Although we do not have objective evidence of mucosal recovery on histopathology, the urinary lactulose:rhamnose excretion ratio has been used as a marker of intestinal recovery and macronutrient absorption in malnourished children.^{26 27} The opposing trends of lactulose excretion, reflecting the passage of the sugar through the paracellular pathway in the intestinal mucosa,¹⁴ and the significantly differing change in the lactulose:rhamnose excretion ratio between the two groups, support our contention that failures had persistent mucosal injury and diarrhoea. It is possible that the low IGF response among treatment failures paralleled continued enteropathy and persisting diarrhoea.

There was a trend towards more severe illness among treatment failures and a significantly greater number of these children had evidence of serious systemic infection. The association of persistent diarrhoea with overt and silent systemic infections has been sug-

gested by several recent studies.^{15 28} Although relatively few had culture proven bacteraemia, our findings of significantly raised CRP concentrations in children with a correspondingly low IGF-I response indicate a continued inflammatory or infected state in these children. We have shown previously that concomitant bacteraemia and probable bacterial translocation may be an important risk factor for diarrhoea associated mortality,²⁹ and the possibility of this being operative in some of the treatment failures in our study cannot be discounted. The reduced serum IGF-I response in some of our patients, despite adequate nutrient and energy intake, could suggest a direct effect of intercurrent infections on IGF-I production. Severe infections have been shown to affect both the production of IGF-I³⁰ and induction of a protease for IGF binding protein 3 in the plasma.³¹

Our data provide evidence that in comparison with other markers of nutritional recovery, such as serum albumin, prealbumin, and RBP, the serum IGF-I response in recovering malnourished children with persistent diarrhoea may provide an important and sensitive measure of nutritional and diarrhoeal recovery. However, further studies are needed to evaluate factors regulating the IGF-I response in such children, especially the effect of intercurrent infections.

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