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Effects of a Protein-Rich Diet during Convalescence from Shigellosis on Catch-up Growth, Serum Proteins, and Insulin-Like Growth Factor-I

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ABSTRACT. Shigellosis in children can cause growth retardation, worsening of malnutrition, and hypoproteinemia. To assess the effects of ingestion of a protein-rich diet during convalescence, 22 children aged 2 to 4 y with culture-proven shigellosis were randomly assigned after 5 d of antibiotic treatment to 21-d feeding regimens of either a 150 kcal/kg/d high-protein diet with 15% of calories as protein or an isocaloric control diet with 6% of calories as protein. At the start and end of dietary treatment, weight, height, mid-arm circumference, skinfold thickness, serum protein concentrations, and serum IGF-I were measured. Means of weight gain and increases in mid-arm circumference were greater in children fed high-protein diets than those fed control diets (1.23 *versus* 0.76 kg; 1.40 *versus* 0.96 cm; $p < 0.05$). Mean increase in height in children fed high-protein diets (0.83 cm) was not significantly greater than with control diets (0.74 cm). Mean increases in serum concentrations of total protein, prealbumin, and retinol-binding protein were greater in the high-protein group than in controls ($p < 0.05$). Mean serum concentrations of IGF-I were low in both groups before treatment [4.2 ± 2.6 nmol/L (31.9 ± 19.6 ng/mL) in controls; 3.1 ± 3.4 nmol/L (24.0 ± 26.3 ng/mL) in the high-protein group] but increased more in the high-protein group [39.0 ± 16.2 nmol/L (298 ± 124 ng/mL)] than in the control group [16.7 ± 9.2 nmol/L (128 ± 70 ng/mL), $p < 0.01$]. These results suggest that high dietary protein is more effective than a normal protein intake in repleting body proteins and in stimulating growth after shigellosis in children. A possible mechanism for this stimulatory effect on growth may be through the restoration of IGF-I. (*Pediatr Res* 32: 689–692, 1992)

Abbreviations

IGFBP, insulin-like growth factor binding protein

Children in developing countries have slower growth rates than children in developed countries, and many are stunted when they reach adulthood. A large part of this growth retardation is caused by malnutrition due to decreased intake of food during infectious diseases. Scrimshaw (1) attributed the decreased intake/use of calories during infection to a combination of anorexia, fever, withdrawal of solid food by parents, impaired intestinal absorption, and nutrient losses in body fluids. From a prospective study of the effects of diarrheal infections on growth of children in Bangladesh, Black *et al.* (2) concluded that shigellosis caused significant retardation of linear growth, and diarrhea due to *Escherichia coli* caused retardation of weight gain.

The World Health Organization advised continued breastfeeding and feeding of weaning diets during diarrhea (3). These recommendations apply mainly to watery diarrheas affecting the small intestine, and less attention has been given to shigellosis and other infections affecting the colon (4). Furthermore, no recommendations are available regarding feeding during the recovery period.

Catch-up of lost growth is desirable during and after acute infections. Whitehead (5) calculated that a 7-kg child needs 25% more calories for catch-up growth than for normal growth (about 150 kcal/kg/d), and the percentage of calories supplied as protein needs to be nearly doubled (to more than 11%). The duration of intensive feeding needed for growth catch-up was estimated to be about three times longer than the preceding acute disease, because the anabolic phase of recovery is assumed to last three times longer than the catabolic phase of disease (1).

In addition to growth impairment, infections and malnutrition lead to reductions in serum protein concentration. In Bangladesh, serum protein concentrations in children with severe shigellosis are about half of the normal values (6). Diets with higher protein content may have a beneficial effect to increase the rate of albumin synthesis, thus raising the serum albumin and protecting children against symptoms of malnutrition (7).

In the following study, children recovering from acute shigellosis were fed a high-protein diet and were compared with a control group fed an isocaloric diet with less protein. The role of hormonal control of catch-up growth was examined by measuring serum IGF-I, which is a mediator of growth hormone and known to rise in patients after dietary repletion with calories and protein (8).

MATERIALS AND METHODS

Patient selection and management. Twenty-two children between 2 and 4 y of age with culture-proven *Shigella* dysentery were the subjects of this study. To be eligible, the patients' respective parents or guardians had to give consent for the patient to remain in the hospital for 26 d and agree to receive one of the two study diets by randomization. Patients were excluded if they had 3rd-degree malnutrition [body weights less than 60% of the Harvard Standard of weight for age (9)], nutritional edema, or

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other signs of kwashiorkor. Each patient was treated for 5 d with nalidixic acid or another antimicrobial chosen on the basis of *in vitro* sensitivity testing of their *Shigella* isolates. The standard hospital diet was provided during these 5 d of treatment.

Randomization and dietary treatments. At the end of the 5 d of treatment, patients were randomly assigned either to the control or the high-protein diet, using sealed envelopes that contained cards designating diets in an order obtained from a table of random numbers. Both diets were isocaloric and provided a caloric intake of 150 kcal/kg body weight/d. The control diet contained approximately 6% of total calories as protein, whereas the high-protein diet contained 15% as protein. The bulk of calories in both diet groups was derived from rice and bread. The protein sources consisted mainly of eggs, chicken, and dried skimmed milk. In sample diets, caloric value was determined by Idiabetic bomb calorimetry (Gallenkamp, United Kingdom) and protein content from measurement of nitrogen content by the Kjeldahl method (10). The diets were given in the hospital for 21 d. Nurses recorded portions of food vomited or not eaten.

Protein measurements and data analysis. Before the start of the diets, patients were weighed to the nearest g, and height was measured to the nearest mm on a stand-up scale. Mid-upper-arm circumference was measured with a tape, and triceps skinfold thickness with a skin caliper (John Bull, British Indicators, Ltd., United Kingdom). Blood was obtained for determination of serum proteins. The total serum protein was measured by refractometry and the albumin concentration by the biuret method (11). The serum prealbumin and retinol-binding protein were determined by radial immunodiffusion (Boehringer AG, Mannheim, Germany). Serum concentrations of IGF-I were measured by RIA, after the IGF-I had been separated from IGFBP by Sep-Pak Chromatography (Waters Associates, Milford, MA) (12). IGF-I values of Bangladeshi patients were compared with those of normal US children of similar age (13). At the end of 21 d of dietary treatment, the weight and height measurements and determinations of concentration of serum proteins and IGF-I were repeated. Means of the increments of height, weight, and serum protein concentrations between the two dietary groups were compared by a paired *t* test.

Table 1. *Characteristics of patients before treatment in groups that received control diet and high-protein diet**

	Control diet (n = 10)	High-protein diet (n = 12)
Age (mo)	31.7 ± 9.3	36.3 ± 6.7
Range	(24–48)	(24–48)
Gender (no. male/female)	7/3	10/2
Shigella species (no. with)		
Dysenteriae 1	5	8
Flexneri	5	3
Sonnei	0	1
Stool weight/24 h (g)	304 ± 196	278 ± 110
Weight (kg)	10.3 ± 2.0	10.8 ± 1.4
Height (cm)	85.0 ± 8.4	87.5 ± 5.6
Weight for age†	−2.4 ± 1.0	−2.3 ± 0.8
Weight for height†	−1.6 ± 0.6	−1.6 ± 0.7
Height for age†	−1.7 ± 1.6	−1.7 ± 1.0
Mid-upper-arm circumference (cm)	13.1 ± 0.7	13.3 ± 1.0
Triceps skinfold thickness (mm)	6.4 ± 1.2	6.4 ± 1.3
Serum concentrations‡		
Total protein (g/L)	68.8 ± 4.2	66.9 ± 4.4
Albumin (g/L)	39.6 ± 3.7	38.6 ± 4.9
Prealbumin (mg/dL)§	12.1 ± 3.4	9.3 ± 3.1
Retinol-binding protein (mg/dL)§	1.65 ± 0.62	1.08 ± 0.33
IGF-I (ng/mL)§	31.9 ± 19.6	24.0 ± 26.3

* Values are means ± SD, or as indicated.

† Values are Z-scores calculated from National Center for Health Statistics data.

‡ Normal values for total protein in children, 62–80 g/L; albumin after infancy, 35–50 g/L; prealbumin after 1 y of age, 10–40 mg/dL; and retinol-binding protein in children 2–10 y old, 2.2–4.5 mg/dL (14). Normal range of IGF-I from birth to 6 y, 30–141 ng/mL (13).

§ For conversion to SI units, multiply mg/dL values of prealbumin and retinol-binding protein by 0.01 to obtain g/L. For IGF-I, multiply ng/mL values by 0.1307 to obtain nmol/L.

RESULTS

Characteristics of children before dietary intervention. The 22 children in the two study groups were comparable in regard to male preponderance, species of *Shigella* infections, and mean weight of stool passed on the first hospital day (Table 1). There was a trend toward patients in the high-protein group being older, heavier, and taller, but these differences of means were not statistically significant ($p > 0.05$). Z-scores for weight and height indicated that ratios for both groups were lower than for National Center for Health Statistics controls. The means of serum concentrations of total protein and albumin were comparable, but there were significantly greater mean concentrations of prealbumin and retinol-binding protein in the control group than the high-protein group ($p < 0.05$). The mean values of serum IGF-I concentrations in both groups were lower than the mean value of 8.5 nmol/L (65 ng/mL) reported for normal US children of the same age (13).

During the first 5 hospital d before the start of dietary therapy, estimates of intake of calories and protein on the regular hospital diet were made. Both groups were comparable, with mean ± SD of calorie intakes in kcal/kg/d of 128 ± 16 for controls and 118 ± 15 for the high-protein group. Estimated mean ± SD of intakes of protein in g/kg/d was 2.1 ± 0.2 for controls and 2.0 ± 0.4 for the high-protein group.

Effects of dietary intervention on growth and serum proteins. All patients completed 21 d of dietary intervention except for two each in the control and the high-protein groups who completed 16 and 18 d each. The mean ± SD of estimated daily average caloric intake for the children fed the control diet was 152 ± 9 kcal/kg/d and for children fed the high-protein diet, 140 ± 6 kcal/kg/d. The mean ± SD of estimated daily average protein intake was 2.34 ± 0.23 g/kg/d for children fed the control diets and 5.47 ± 0.25 g/kg/d for children fed the high-protein diets.

Children who were fed high-protein diets showed greater mean increases in body weight and height than children fed the isocaloric control diet (Table 2), but only the difference in weight gain was statistically significant ($p < 0.025$). Greater increases in mean concentrations of serum proteins were measured in children fed high-protein diets than in children fed control diets, with statistically significant differences demonstrated for total protein, prealbumin, and retinol-binding protein ($p < 0.05$; Table 2). The increases in serum IGF-I were such that the mean increase ± SD in the control group of 16.7 ± 9.2 nmol/L (128 ± 70 ng/mL) placed this group at the upper limits of the normal range for normal US children of the same age. The mean increase in the children fed the high-protein diet of 39.0 ± 16.2 nmol/L (298 ± 124 ng/mL) placed them well above the normal range. The magnitude of the increase in IGF-I concentration was greater in the children fed the high-protein diet ($p < 0.01$; Table 2).

DISCUSSION

Children fed the high-protein diet showed significantly greater increases in weight and mid-upper-arm circumference during the feeding period than children fed the control diet. Similarly, there was a trend toward greater increases in height and skinfold thickness in the group receiving the high-protein diet. Concentrations of total serum protein, albumin, prealbumin, and retinol-

Table 2. *Increases in nutritional determinants and serum concentrations of proteins and IGF-I between pretreatment measurements and end of 21 d of dietary intervention in children who received control diets or high-protein diets**

	Control diet (n = 10)	High-protein diet (n = 12)	p value
Weight (kg)	0.76 ± 0.45	1.23 ± 0.36	<0.025
Height (cm)	0.74 ± 0.40	0.83 ± 0.42	NS
Weight for age†	0.5 ± 0.4	0.8 ± 0.2	<0.01
Weight for height†	0.5 ± 0.5	0.9 ± 0.3	<0.05
Height for age†	0.02 ± 0.1	0.04 ± 0.1	NS
Mid-upper-arm circumference (cm)	0.96 ± 0.43	1.40 ± 0.42	<0.05
Triceps skinfold thickness (mm)	1.28 ± 0.65	1.60 ± 0.82	NS
Serum concentrations			
Total protein (g/L)	3.05 ± 2.63	6.88 ± 4.35	<0.05
Albumin (g/L)	3.86 ± 3.28	5.23 ± 5.34	NS
Prealbumin (mg/dL)‡	3.80 ± 6.92	14.20 ± 6.74	<0.01
Retinol-binding protein (mg/dL)‡	1.02 ± 0.86	2.67 ± 1.37	<0.01
IGF-I (ng/mL)‡	128 ± 70	298 ± 124	<0.01

* Values are means ± SD.

† Values are Z-scores calculated from National Center for Health Statistics data.

‡ For conversion to SI units, multiply mg/dL values of prealbumin and retinol-binding protein by 0.01 to obtain g/L. For IGF-I, multiply ng/mL values by 0.1307 to obtain nmol/L.

binding protein also increased more in the children fed the high-protein diet than in those fed the control diet. These results showing beneficial effects of a diet high in both caloric value and protein content on catch-up growth and serum proteins are consistent with dietary studies of malnutrition in Thai children (15). The lesser degree of malnutrition among our patients, though they were not as severely malnourished as the Thai children, is probably more characteristic of children in developing countries. Although the high-protein diet did not produce significantly more height gain, it is possible that a longer period of dietary intervention or follow-up studies after hospital discharge would reveal significant differences.

We measured serum concentrations of IGF-I, a mediator of the growth-promoting actions of growth hormone that is responsive to repletion of calories and protein in malnourished patients (8), to determine whether this peptide might be involved in the faster growth of the children fed high-protein diets. Concentrations of IGF-I of both groups of Bangladeshi children before dietary intervention were lower than those for normal US children, indicating prior malnutrition or short-term nutrient deprivation due to their *Shigella* infection (16). IGF-I concentrations in children fed both diets rose significantly above normal values, indicating an over-response similar to that described in malnourished adults during nutritional repletion and return to positive nitrogen balance. (17). The greater increases in IGF-I observed in children fed the high-protein diet confirms that this mediator of growth hormone action is responsive to dietary protein (8, 18). The magnitude of the increase in IGF-I may also reflect the sensitivity of children to sufficiency of dietary protein, because the serum IGF-I concentration in young rats is exquisitely sensitive to dietary protein restriction (19).

The mechanisms for the dramatic rise in serum IGF-I during dietary repletion are not defined by this study. It is highly probable, however, that there is an increase in IGF-I synthesis, because diet restriction in rats reduces IGF-I mRNA (20, 23), and refeeding leads to restoration of serum IGF-I peptide concentrations in rats (24) and humans (17). The "overshoot" in serum IGF-I might indicate a measure of IGF-I resistance, as it has been shown that protein-restricted rats do not undergo somatic growth in response to administration of IGF-I or growth hormone (25). It is conceivable, therefore, that refeeding improved the synthetic capacity for IGF-I more rapidly than it improved tissue response to IGF-I. Against the possibility of IGF-I resistance, but not excluding it, is the finding that weight gain and statural growth occurred during the refeeding period. The serum concentrations of IGF-I are regulated by several binding proteins, and at least three of these peptides are modulated by nutritional status (26). IGFBP-III is a likely candidate for change relevant to the events we have observed, because IGFBP-III, the major carrier of IGF-I in serum, is reduced in diet restriction (27). A dramatic increase in this peptide during refeeding could facilitate the rise observed in IGF-I. Studies of the changes in IGFBP in our patients are in progress and will be the subject of a future report.

Increased protein in the diet of patients recovering from shigellosis may also have a beneficial effect on the repair of injured intestinal mucosa. Patients with acute shigellosis are known to have protein-losing enteropathy (28) and sometimes show extensive inflammatory destruction of intestinal mucosa (29). Studies to measure intestinal clearance of α-1-antitrypsin before and after dietary intervention will be needed to detect any improvement in the healing of the intestinal mucosa due to treatment.

On the other hand, efforts to promote protein synthesis and growth during recovery from shigellosis may be opposed by the acute phase reaction of inflammation. During acute inflammatory reactions, the liver shifts to synthesizing acute-phase reactant proteins, such as C-reactive protein, and decreases synthesis of other proteins, such as albumin and prealbumin (30). Thus, the hypoalbuminemia and impaired growth rates associated with acute infections may be, to some extent, refractory to dietary treatment that is begun while inflammation is active.

In our patients, the serum concentrations of prealbumin and retinol-binding protein were more responsive to protein in the diet than was the albumin concentration. This may be explained by the fact that the former proteins have a high turnover rate, with half-lives of 1.9 d for prealbumin and 10 h for retinol-binding protein. In contrast, albumin has a half-life of 12–21 d (31). In Egyptian children with kwashiorkor, the serum concentrations of prealbumin and retinol-binding protein also increased significantly 2–4 wk after beginning dietary treatment (32), and in premature infants the serum prealbumin was a more sensitive indicator of nutritional intake than was serum albumin (31).

These results indicate that dietary treatment of dysentery, and perhaps other infectious diseases, in growing children should include diets plentiful in protein. The quality of the protein provided in protein-restricted normal adults has been shown to regulate the serum concentrations of IGF-I (33). It is important, therefore, to determine which protein-containing foods will promote recovery most rapidly. In this study, the bulk of the excess protein was in the form of milk, eggs, and chicken. It will be useful to determine whether more readily available and economical vegetable proteins such as those derived from legumes will achieve the same effects as the animal proteins used in this study.

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