Nutritional support and growth in thalassaemia major

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Abstract

Twelve thalassaemic children under 3 years of age received intensive nutritional support for one month and were discharged on a prescribed diet of locally available foods. Anthropometry, bioelectrical impedance analysis and dietary intake were longitudinally assessed. Mean energy intake was 20% greater than the recommended daily allowance during nutritional supplementation as compared with below the recommended daily allowance before and after the period of nutritional support. Weight, but not height, significantly increased during the support period and was due to increases in both fat free mass and fat mass. Body weight, fat free mass and fat mass declined in line with the reduced intake upon return home; however, height velocity accelerated and exceeded normal through the fourth month before resuming a below normal rate. It can be concluded that (1) nutritional stunting as the result of reduced nutrient intake is an important cause of growth failure in young children with thalassaemia and is responsive to nutritional support, (2) the deficit in height velocity was due to retarded truncal height growth, and (3) the bioelectrical impedance analysis method is suitable for body composition analysis of thalassaemic children.

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Keywords: thalassaemia; malnutrition; bioimpedance; anthropometry

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Abnormal growth resulting in stunting and delayed or absent puberty is characteristic of children with thalassaemia major.[1 2] Current transfusion regimens modify the pattern of distributed growth, especially in the early years, but full growth potential is rarely realised.[1 2] Several different causes of thalassaemia associated growth retardation have been implicated, including multiple endocrine abnormalities, the effects of deferoxamine therapy, and cellular hypoxia due to anaemia, but the results of investigations have been inconsistent or contradictory.[1 2] Various vitamin and micronutrient deficiencies have also been reported in thalassaemic children, and short term nutritional support increases plasma insulin-like growth factor-I, a major mediator of growth.[3–10] Yet, the role of general malnutrition as a cause of growth abnormalities has not been defined.

Nutritional status in terms of body composition, namely fat mass (FM), fat free mass (FFM), and total body water (TBW), to our knowledge has not been described previously in thalassaemic children. However, body segmental changes in terms of truncal height and leg height have been recently reported and show that thalassaemic children over 2 years of age are stunted truncally, which contributes to the total faltering in growth.[11] In this study, both body composition and body segmental changes as related to nutritional intake were prospectively and longitudinally investigated.

Methods

SUBJECTS

The first 12 children who met the selection criteria were enrolled from the thalassaemia clinic at the Maharaj Nakorn Hospital, Chiang Mai, Thailand. Inclusion criteria were documented homozygous β-thalassaemia, age 1 to 3 years, no prior splenectomy, HIV seronegative status, and informed agreement by the parents to comply with the demands of the study protocol. The usual treatment of these children included a chronic low transfusion regimen without chelation therapy and 5 mg per day of folic acid. The study protocol was approved by the human ethics committee of Chiang Mai University (CMU) and the Louisiana State University Medical School Institutional Review Board.

NUTRITIONAL INTERVENTION

The children were admitted to the metabolic ward of the Research Institute for Health Sciences, CMU for an intensive one month nutritional intervention programme as described previously.[10] The study diet was Enfapro liquid formula (Mead Johnson, Evansville, ID, USA) with added dextrose and corn oil (446 kJ (106 kcal) energy, 2.4 g protein/100 ml) in addition to supplemental vitamins and minerals comparable (100–250% recommended daily allowance (RDA)) with that used in our facility for the treatment of protein energy malnutrition.[12] The children were encouraged to consume a volume of the diet that would achieve an intake of approximately 630 kJ (150 kcal) and 4g protein/kg per day. Before discharge, mothers were counselled to provide a diet using locally available foods in an amount that approximated the daily energy and protein intake of the diet the children received during their stay in the metabolic ward. After discharge, each child was followed up monthly for 10 months at which time the diet recommendations were reinforced.

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Table 1 Anthropometric measurements of thalassaemic children before and after nutrition intervention. Values are mean (SD) except for the difference column in which they are mean (SE)

Characteristic	*Baseline*	*After*	*Difference*	*p Value*
Age (months)	27.9 (5)	28.8 (5)	1.0 (0.01)	—
Weight (kg)	10.9 (1.7)	12.1 (1.7)	1.2 (0.05)	0.003
Height (cm)				
Standing	84.8 (6)	85.1 (6)	0.3 (0.3)	NS
Leg	34.2 (3)	34.2 (3)	0.02 (0.2)	NS
Truncal	50.6 (2)	50.9 (3)	0.3 (0.2)	NS
Weight for height Z score	−0.94 (0.8)	0.05 (0.7)	1.0 (0.1)	0.003
Height for age Z score	−1.12 (1.0)	−1.14 (1.1)	−0.02 (0.06)	NS

NS = not significant.

ANTHROPOMETRY

Weights were obtained to the nearest 100 g using an electronic digital scale (Seca, model 770) standardised with a 1 kg standard weight before the weighing of each subject. Height measurements were made with a locally constructed instrument using the pressure technique in which a metal tape is extended between a footplate and headbar for the standing height measurements, and between the headbar and the top of the bench on which each subject sat for the sitting height measurements. Sitting truncal height was considered as the truncal height while the leg height was obtained by subtracting sitting or truncal height from the standing height. Body mass index (BMI), mid upper arm circumference (MUAC), biceps, triceps, subscapular, and suprailiac skinfold thickness (SFT) were measured. The mean of two consecutive measurements to the nearest 0.1 mm for all indices was recorded as the observed value.

Measurements were compared with the standards of the National Center for Health Statistics (NCHS) data and the percentage of median determined and categorised according to the system of Waterlow.[13 14] Height velocity was also compared with the median for Thai children which, for children aged 1 to 3 years, is nearly identical with the NCHS standard (≈ 0.78 cm per month).[15] The following formulas developed by Weststrate and Deurenberg[16] were used to calculate body density and body fat percentage of children from the sums of biceps, triceps, subscapular, and suprailiac SFT:

Body density (Bd) = $[1.1235 + (0.0016^{0.5})] - 0.0719 \log \sum SFT$

Body fat (%) = $[(584 - 4.7A^{0.5})/Bd] - (550 - 5.1A^{0.5})$

where A is age in months.

These equations have recently been validated by de Bruin *et al* and therefore were used in this study to assess body composition anthropometrically from SFT.[17]

BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

An RJL (Detroit, MI, USA) instrument (model 101) that utilises 800 μA current at 50 kHz was employed to measure resistance (R) and reactance (X) of the subjects lying in a supine position on a padded wooden table with arms and legs abducted from midline. The tetrapolar electrode system was used on the right wrist and right ankle. The wrist electrode pair was placed on the third phalangeal metacarpal joint in the middle of the dorsal side of the right hand and 1 inch superior to the first electrode, between the styloid process of the radius and ulna. Similarly, the electrode pair for the ankle was placed at the third metatarsal on the dorsal side of the right foot and 1 inch above the first electrode, between the medial and lateral malleolus of the ankle. Each child was encouraged not to make any movement for a few seconds during which the R and X values were measured. The mean of three consecutive measurements was recorded as the observed value.

TBW was assessed from R by using the following formula:

TBW = $[0.18 \times \text{height (cm)}^2/R] + [0.39 \times \text{weight (kg)}] + 0.76$

FFM and FM were computed from the following equations: FFM = TBW/0.783 and FM = BW − FFM; where BW is body weight.[18 19]

DIETARY INTAKE

Dietary intake was quantified by direct measurement during the nutritional support period and estimated by 24 hour recall for the periods immediately before entry into the study and during follow up. Energy intakes were compared with the Thai reference standard.[20]

STATISTICAL ANALYSIS

Group comparisons in measurements before and after nutritional intervention were made by paired *t* test; χ^2 tests of independence or Fisher's exact test were used to examine differences in proportions. Group comparisons of continuous data were made by Student's *t* test or Mann-Whitney U test, and difference in measurements before and after nutritional intervention from individual children were compared by Wilcoxon ranked sums. A moving average using three consecutive median measurements was determined to express growth velocity. Regression analysis was used to investigate relationships between dependent and one or more independent variables. Data are expressed as mean (SD) for ease of interpretation except where otherwise indicated, and statistical significance is defined as $p<0.05$.

Results

Seven girls and five boys with an age range of 20 to 36 months (mean 28 months) were enrolled into the protocol. Nine were above and three were below 2 SD height for age, and mean haemoglobin was 76 g/l (median 78, (SD 20). Weight gain was significant during the support period (table 1). Mean height also increased, principally because of gains in truncal height, but the increase was not significant ($p = 0.213$). Body composition changed in response to the nutritional support with a proportionally greater accrual of FM than FFM (table 2).

During the nutritional support period, energy intakes achieved a mean of 498 kJ/kg per day (median 499, (84). Energy intake was, however, lower than the RDA (420 kJ/kg per day) in most children both before and afterwards (fig 1). The carers of all the children reported that, while at home, the children were

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Table 2 Body composition of thalassaemic children before and after nutrition intervention. Values are mean (SD) except for the difference column in which they are mean (SE)

Characteristic	*Baseline*	*After*	*Difference*	*p Value*
BMI (kg/m^2)	15.1 (1)	16.7 (2)	1.6 (0.2)	0.003
MUAC (cm)	13.9 (1.0)	15.1 (0.9)	1.1 (0.1)	< 0.0001
FFM (kg)				
BIA	8.3 (1.2)	9.0 (1.2)	0.8 (0.05)	< 0.0001
SFT	8.8 (1.3)	9.6 (1.2)	0.8 (0.07)	< 0.0001
%FFM				
BIA	76.2 (2)	74.5 (1)	−1.7 (0.3)	0.015
SFT	81.0 (3)	77.4 (3)	−3.6 (0.5)	0.002
FM (kg)				
BIA	2.7 (0.5)	3.1 (0.5)	0.5 (0.04)	< 0.0001
SFT	2.1 (0.5)	2.5 (0.6)	0.4 (0.06)	< 0.0001
%FM				
BIA	23.8 (2)	25.5 (1)	1.7 (0.3)	0.015
SFT	19.0 (3)	22.6 (3)	3.6 (0.5)	0.002

BMI = body mass index; MUAC = mid upper arm circumference; FFM = fat free mass; FM = fat mass; BIA = bioelectrical impedance analysis; SFT = skinfold thickness.

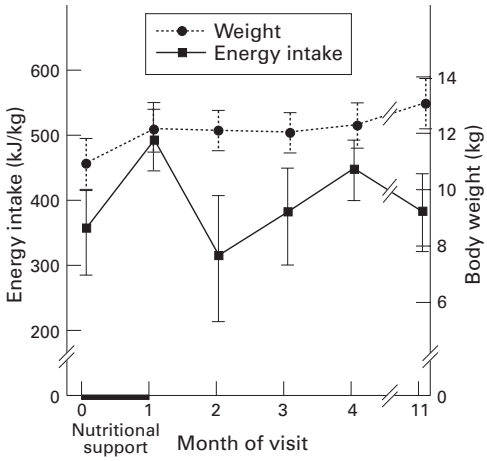

Figure 1 Mean body weight and energy intake in relation to nutritional support and subsequent diet at home of children with thalassaemia major. Conversion factor: 1 kJ = 0.239 kcal.

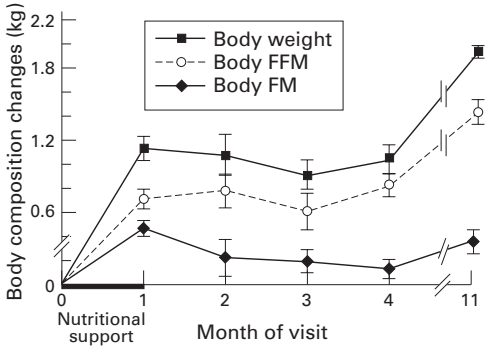

Figure 2 Changes in weight and body composition in relation to nutritional support and subsequent diet at home of children with thalassaemia major. FFM, fat free mass; FM, fat mass.

unable to consistently consume the prescribed amount of the food. In contrast with the rapid accrual of weight during the support period, the mean daily weight gain during the 10 months after the return home was approximately 2.4 g/day (median 2.7, SD (1), one third of the expected/normal weight velocity (fig 2). FFM and FM both increased as a result of the nutritional support. Both decreased upon resumption of the home diet, but FM decreased at a faster rate than FFM.

Although weight velocity began to decrease immediately after discharge commensurate

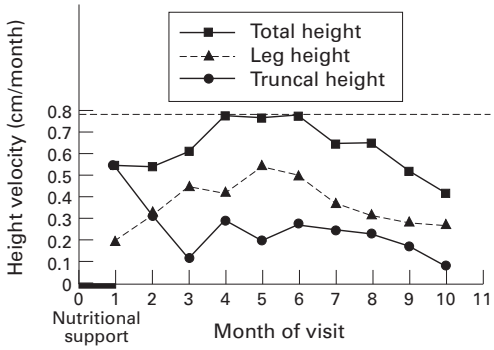

Figure 3 Changes in total height and truncal and leg lengths in relation to nutritional support and subsequent diet at home of children with thalassaemia major. Values are moving averages. Dashed line represents age matched NCHS median for total height velocity approximated for girls and boys.

with reduced food intake, height velocity continued to increase and accelerated (fig 3). The mean change in height for the first four months was significantly greater than months five to 11 of the study ($p<0.03$). After attaining a peak by the end of the fourth month greater than the median NCHS (mean 1.1, median 1.1, SD 0.4 cm/month), mean height velocity assumed a rate below the median reference standard. The changes in height were due to increases in leg length rather than to truncal length.

Discussion

These results demonstrate that undernutrition due to inadequate nutrient intake contributes to stunting of children with thalassaemia major. The children in our study demonstrated the capacity to gain weight commensurate with their nutrient intake during the support period and had a below normal growth rate upon return home to the home based diet. It is important to note that the children were vigorously offered and encouraged to consume the formula diet during the supervised one month intensive feeding period compared with the less intensive feeding of the prescribed diet on return home. We interpret this observation to indicate that these children were relatively anorexic, and that the structured feeding of the support period was able to override their usual appetite.

Linear growth was accelerated by the short term intensive nutritional support and ultimately attained a rate normal for age. Of note, there was a lag effect in which no significant improvement in height velocity occurred during the nutritional support period, and the maximum effect appeared approximately four months after the intervention, a temporal pattern also observed in a population based study in conjunction with seasonal variation in intake.[21]

In our subjects, marked increases in the body composition parameters BMI, MUAC, FFM, and FM were observed during the nutritional intervention. Although the bioeletrical impedance (BIA) and SFT measures gave different values for %FFM and %FM, they followed a similar pattern in gain. A 25.5% FM as meas-

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ured by BIA is usually considered appropriate for this age group of children.[21] Of the total weight gain of 1.2 kg over the one month intensive nutritional support period, 0.7 and 0.5 kg was due to accrual of FFM and FM respectively, according to BIA. This indicates a 41% increase in FM which agrees with previous catch-up growth studies of malnourished children.[22 23] Similar analysis of SFT data indicated a 55% FM gain, which is higher than expected on the basis of these published reports.

Changes in body composition occurred over the entire period of study with regard to weight gain velocity when measured as FFM and FM by BIA and SFT, although BIA measurements coincided more closely with body weight changes than did SFT derived values. The increment in FM at the end of the one month support period is notable along with its counterpart, FFM. A considerable downward change in both FM and body weight was observed when the children resumed their usual diet at home despite guidance to maintain an intake equivalent to that during the stay on the metabolic ward. On the second visit after discharge—that is at 90 days—weight gain velocity of the children was at a minimum (see fig 2). Accrual of weight with concordant increases in other body compartments, namely FFM and FM, was therefore achieved by the nutritional intervention, yet declined to below normal levels in line with the lower energy intake at home. In summary, the overall pattern of changes in weight, length, and body compartments during the nutritional support period and the subsequent follow up period is consistent with the pattern of recovery from undernutrition and fasting respectively.

Of interest, the leg length velocity changed commensurate with the standing height velocity, while truncal segmental change was not appreciable. This observation agrees with earlier reports that indicate that the growth stunting associated with thalassaemia major is principally due to retarded truncal height.[11 24]

The children in our study were young, most did not have manifestations of severe disease and had a height for age greater than 2 SD, and were not participating in a hypertransfusion regimen. Their response to the intervention indicates that nutritional stunting contributes to growth failure in thalassaemia, at least in the earlier years of life. Although the intensive feeding regimen of our study protocol would in practice be difficult to implement as a standard regimen, periodic intensive feeding, perhaps delivered at night via nasogastric or gastrostomy tubes, might improve nutritional status and linear growth. These results also suggest that the enhancement of growth associated with blood transfusion that occurs in some young thalassaemic children is perhaps a reflection of improved nutrition mediated by improved appetite and subsequent increased dietary intake. It is worth emphasising that in addition to the implications for growth, nutritional stunting is associated with impaired mental development.[25] Early and aggressive nutritional support should, as a minimum, be considered as adjunctive to transfusion therapy in the treatment of growth failure.

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