Effects of childhood malnutrition on Insulin-like Growth Factor-I (IGF-I) and IGF-Binding Protein-3 levels: a Malaysian and New Zealand analysis

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Plasma IGF-I and IGFBP-3 levels were measured in 190 clinically confirmed malnourished Malaysian children and 86 normal New Zealand children. Children were grouped into age groups of 4-10 and 11-15 years, and were classified as normal, moderate and severely stunted using WHO criteria. Plasma IGF-I levels of moderate and severely stunted children were significantly lower than age-matched normal children, in the 4-10 ($p<0.01$ and $p<0.001$ respectively) and 11-15 ($p<0.01$ and $p<0.001$ respectively) years age groups. Malnourished children of age group 4-10 years had significantly lower ($p<0.001$) IGFBP-3 levels compared to normal but in the older group, significant difference was observed only in the severely stunted children. Compared to those who were moderately stunted, IGF-I and IGFBP-3 levels of severely stunted children were significantly lower ($p<0.001$ and $p=0.03$ respectively). There was significant increase in IGF-I and IGFBP-3 levels between age groups, in normal ($p<0.001$ and $p=0.02$ respectively), moderate ($p<0.01$ for both) and severely ($p<0.001$ and $p<0.001$ respectively) stunted children. Significant correlation between IGF-I and IGFBP-3 levels was observed both in normal ($r=0.511$, $p<0.001$) and malnourished ($r=0.657$, $p<0.001$) children. Standard deviation score (SDS) of height and weight correlated significantly to the IGF-I levels, both in age group of 4-10 ($r=0.472$, $p<0.001$ and $r=0.443$, $p<0.001$ respectively) and 11-15 years ($r=0.445$, $p<0.001$ and $r=0.539$, $p<0.001$ respectively). Correlations between SDS of height and weight and IGFBP-3 levels were highly significant only in the younger children ($r=0.494$, $p<0.001$ and $r=0.489$, $p<0.001$ respectively). The study showed that nutrition exerts a greater effect on IGF-I compared to IGFBP-3, suggesting that its significance is in determining the linear growth of malnourished children.

Key words: malnutrition, childhood, Malaysia, New Zealand, growth, height, weight, Insulin-like Growth Factor-I (IGF-I), IGF-Binding Protein-3

Introduction

Nutrition is an important determining factor for optimal growth and development in children. Studies conducted under the Nutrition Collaborative Research Support Program showed that mild to moderate malnutrition leads to stunting of growth and by the age of 3 to 4 months, children suffer permanent losses in their ability to grow and develop normally[1].

Malnutrition induces a state of growth hormone (GH) resistance. The mechanisms involved depend on the severity, duration and time of onset, postulated to be due to down-regulation of GH-receptors or defects at the post-receptor level[2]. However, as the growth-promoting effect of GH is mediated in part by insulin-like growth factor-I (IGF-I)[3], the low levels of this growth factor and its carrier protein, IGF binding protein-3 (IGFBP-3), during nutritional deprivation[2,4,5] have also been implicated as contributing factors for GH insensitivity. To further understand the possible alterations and derangement involved, we undertook this study to evaluate the effect of childhood malnutrition on IGF-I and IGFBP-3 levels and their associations to height attainment, in comparison with age-matched apparently healthy children.

Methods

This is a collaborative study between 3 centres; 190 mild to moderately malnourished children were recruited from 3 Malaysian villages of low socioeconomic status, while, for comparison purposes, 86 healthy children, without limitation in food intake, were recruited by the Christchurch Hospital, New Zealand. The children were between 4 and 15 years old, thoroughly examined and malnutrition confirmed clinically by the Paediatric Endocrinologist involved in the study. Blood was collected from the forearm vein and plasma aliquots were immediately stored at -40°C until assayed for IGF-I and IGFBP-3. Parents gave informed consent prior to the study and the protocol was approved by the Ethics Committee of the Medical Faculty, Universiti Kebangsaan Malaysia and the Southern Regional Health Area Ethics Committee, New Zealand. Standard deviation scores (SDS) for weight and height for chronological age were calculated using CDC Anthropometric Software Package.

Plasma IGF-I and IGFBP-3 were quantitated by RIA

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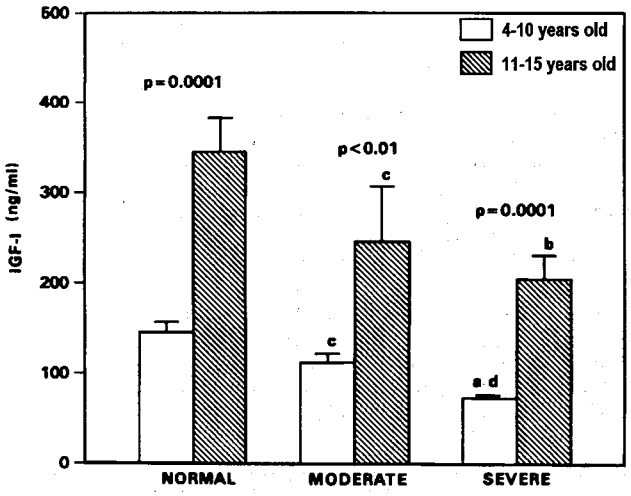
using kits purchased from Nichols Institute Diagnostics (San Juan Capistrano, CA). An acid-ethanol extraction procedure was used for the IGF-I assay. Intra- and inter-assay coefficients of variations were 5.8 and 9.1% respectively for IGF-I and 4.9 and 8.4% respectively for IGFBP-3. Assay sensitivity was 20ng/ml for IGF-I and 0.13μg/ml for IGFBP-3.

Statistics

Data were analysed according to 2 age-groups: 4-10 and 11-15 years. Differences between normal and malnourished, and between age groups were analysed by the non-parametric Wilcoxon test. Associations between IGF-I or IGFBP-3 and weight or height SDS were determined by Spearman correlation. Results are expressed as mean ± SEM.

Figure 1. Plasma IGF-I levels (mean ± SEM) in normal, moderate and severely stunted children of 4-10 and 11-15 years age group.

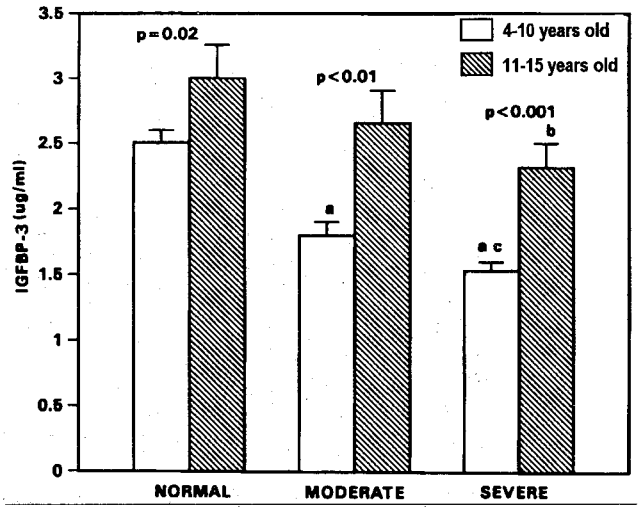


Significance of difference between age groups is shown by p value above each histogram pair for level of severity of stunting.
[a]p=0.0001, [b]p<0.001, [c]p<0.01 compared to age-matched normal children. [d]p<0.001 compared to age-matched moderately stunted children.

Results

Based on WHO definition[1,6], the malnourished children were classified as *moderate stunting* when their computed height SDS values were between 2 and 3 SD below the reference median, and as *severe stunting* when the height SDS values were more than 3 SD below the reference median. The median and 95% range for height and weight SDS of both the malnourished and normal statured children are presented in Table 1. Plasma IGF-I levels of moderate and severely stunted children were significantly lower than age-matched normal children, both in the 4-10 ($p<0.01$ and $p=0.0001$, respectively) and 11-15 ($p<0.01$ and $p=0.0001$ respectively) years age groups (Figure 1). Similarly, compared to normal, IGFBP-3 levels of the 4-10 years old moderate and severely stunted children were low ($p = 0.0001$) (Figure 2). In the older age group however, significant decrease in IGFBP-3 levels was observed only in the severely stunted group ($p<0.01$ versus age-matched normal). As shown in Figures 1 and 2, the IGF-I and IGFBP-3 levels of the 4-10 years old severely stunted children were significantly lower ($p=0.0005$ and $p=0.03$ respectively) than those who were only moderately stunted. Nevertheless, there was significant increase in IGF-I and IGFBP-3 levels with age in the moderate ($p < 0.01$ for both) and severely ($p = 0.0001$ and $p<0.001$ respectively) stunted children, comparable to that observed in normal statured children ($p=0.0001$ and $p=0.02$ respectively).

Figure 2. Plasma IGFBP-3 levels (mean + SEM) in normal, moderate and severely stunted children of 4-10 and 11-15 years age group.



Significance of difference between age groups is shown by p value above each histogram pair for level of severity of stunting.
[a]p=0.0001, [b]p<0.01 compared to age-matched normal children. [c]p=0.03 compared to age-matched moderately stunted children.

Correlation between IGF-I and IGFBP-3 levels was highly significant, both in the normal ($r=0.511$, $p=0.0001$, Figure 3) and malnourished children ($r=0.657$, $p=0.0001$, Figure 4). The associations between SDS of height, weight and IGF-I or IGFBP-3 are presented in Table 2. SDS of height and weight were significantly correlated to IGF-I levels, in the 4-10 ($r=0.472$, $p=0.0001$ and $r=0.443$, $p=0.0001$ respectively) and 11-15 years age group ($r=0.445$, $p=0.0001$ and $r=0.539$, $p=0.0001$ respectively). Similar significant correlations were also obtained between SDS of height and weight with IGFBP-3, but only amongst the younger children ($r=0.494$, $p=0.0001$ and $r=0.489$,

Table 1. Characteristics of normal, moderate and severely stunted children.

	4-10 years old			11-15 years old		
	Normal (n=56)	Moderate (n=60)	Severe (n=76)	Normal (n=30)	Moderate (n=14)	Severe (n=40)
Height SDS	-0.01 -1.2 - +2.0	-2.51 -3.0 - -2.1	-3.77 -5.7 - -3.1	+0.05 -1.7 -+2.3	-2.41 -3.0 - -2.1	-3.76 -5.1 - -3.1
Weight SDS	+0.39 -1.2 - +3.0	-2.21 -3.5 - -1.4	-3.0 -4.1 - -1.9	+0.33 -1.5 -+1.4	-2.2 -3.0 - -1.9	-2.74 -3.8 - -1.4

Values are the median and 95% range.

p=0.0001 respectively). In the older age group, correlations were weaker though still significant (IGFBP-3 vs. height SDS, r=0.296, p<0.01; IGFBP-3 vs. weight SDS, r=0.313, p<0.01).

Figure 3. Correlation between IGF-I and IGFBP-3 levels of normal children.

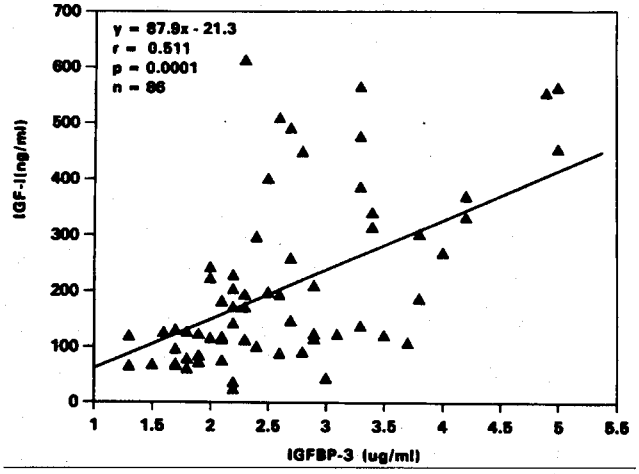


Figure 4. Correlation between IGF-I and IGFBP-3 levels of moderate and severely stunted malnourished children.

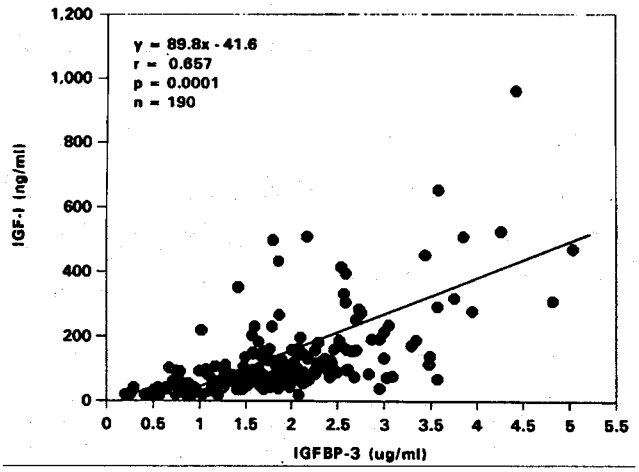


Table 2. Correlations between SDS of height, weight and plasma IGF-I or IGFBP-3 levels in study subjects.

		4-10 years old		11-15 years old	
Constant	**Variable**	**r**	**p**	**r**	**p**
Height SDS	IGF-I	0.472	0.0001	0.445	0.0001
Weight SDS	IGF-I	0.443	0.0001	0.539	0.0001
Height SDS	IGFBP-3	0.494	0.0001	0.296	<0.01
Weight SDS	IGFBP-3	0.489	0.0001	0.313	<0.01

Discussion

In underprivileged populations, poor growth in children is mostly caused by inadequate food intake and associated repeated parasitic infections. Various anthropometric indices have been used to assess growth status. These include, height for age which represents linear growth and measures long-term growth faltering, weight for height which reflects body proportion, and weight for age which is a representation of both linear growth and body proportion[7]. As shown in this study, childhood malnutrition has resulted in moderate and severe growth retardation in a group of children. The low IGF-I and IGFBP-3 levels in moderate and severely stunted children were consistent with the results of previous studies where malnutrition due to coeliac disease[8], short-term fasting[9] and anorexia nervosa[10] caused significant reduction in both IGF-I and IGFBP-3 levels. We have also reported a similar observation in our earlier study[11]. Using body mass index (BMI) to categorise our malnourished children, IGF-I of mildly (BMI=15-18 kg/m^2) and moderately (BMI <15 kg/m^2) malnourished children of age-group 4-10 years were found to be significantly lower than those with normal BMI (>18 kg/m^2). In this study, IGF-I was found to be more sensitive than IGFBP-3 to the nutritional status. All malnourished children had significantly lower IGF-I levels compared to normal children. On the other hand, IGFBP-3 levels were significantly lower than normal children only in the younger age group. This binding protein normalised in the older children, and the difference was significant only in the severely stunted children. The explanation for this observation is possibly related to the pubertal increase in sex steroids and growth hormone[12-14] which in this case, resulted in normalisation of IGFBP-3 but not IGF-I, which remained significantly low.

As reported by others[15,16], IGF-I and IGFBP-3 levels of the normal children were significantly correlated. Malnutrition has been known to cause derangement in the GH/IGF-I axis, resulting in elevated GH and low IGF-I levels[2,5,9,10]. In this study, however, IGF-I levels of the malnourished children were found to be positively and highly significantly correlated to IGFBP-3 levels, indicating that both IGF-I and IGFBP-3 were equally affected in mild to moderate malnutrition. In addition, we have also observed that in spite of the malnutrition and impaired growth, there was still significant age-related increase in IGF-I and IGFBP-3 levels, similar to that seen in the normal children.

A number of previous studies have shown that IGF-I SDS correlated positively and significantly with height SDS of only prepubertal, but not pubertal subjects[16,17]. In this study, however, IGF-I levels of all children were found to correlate significantly with the SDS of height and weight, while association between IGFBP-3 and SDS of height or weight was observed only amongst the older children. Thus, our results showed that nutrition exerts a greater effect on IGF-I compared to IGFBP-3, suggesting that this growth factor plays a more important role in determining the linear growth of nutritionally deprived children.

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兒童營養不良對似胰島素生長因素-Ⅰ（IGF-I）與其結合蛋白質-3（IGF-BP-3）的血漿水平的影響

摘要

作者測量了 190 位馬來西亞營養不良與 86 位紐西蘭正常兒童的 IGF-I 和 IGF-BP-3 的血漿水平。這些兒童被分爲 4-10 歲與 10-15 歲的組合，以及發育正常、矮小、嚴重矮小的組合（根據 WHO 標準）。矮小兒童的血漿 IGF-I 和 IGF-BP-3 的水平比正常兒童的水平低：4-10 歲（各爲 $p<0.01$ 與 $p<0.001$）；11-15 歲（各爲 $p<0.01$ 與 $p<0.001$）。4-10 歲組合營養不良兒童 IGF-BP-3 的血漿水平比正常的兒童低。但是較低的 IGF-BP-3 水平只見於嚴重矮小的兒童。嚴重矮小兒童血漿 IGF-I 與 IGF-BP-3 的水平是比矮小兒童低（$p<0.001$ 與 $p=0.03$）。IGF-I 與 IGF-BP-3 血漿水平都因更高的歲數組合而增加。這見証於正常兒童（$p<0.001$ 與 $p=0.02$）；矮小兒童（$p<0.01$ 與 $p<0.01$）；嚴重矮小（$p<0.001$ 與 $p<0.001$）。IGF-I 與 IGF-BP-3 兩者的相關係數在正常兒童是 $r=0.511$，$p<0.001$；而營養不良兒童是 $r=0.657$，$p<0.001$。高度與體重的 SDS (Standard Deviation Score) 與 IGF-I 有相互關係：於 4-10 歲（$r=0.472$，$p<0.001$；$r=0.443$，$p<0.001$）；於 11-15 歲（$r=0.445$，$p<0.001$；$r=0.539$，$p<0.001$）。高度與體重的 SDS 與 IGF-BP-3 的相關係數只見於 4-10 歲的組合（$r=0.494$，$p<0.001$；$r=0.489$，$p<0.001$）。這個研究說明營養對血漿 IGF-I 水平的影響是比 IGF-BP-3 爲大，並提出它可能主宰營養不良兒童的直線發育。

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