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Effect of Severe Protein-Energy Malnutrition on Circulating Thyroid Hormones

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Abstract
Protein energy malnutrition (PEM) is one of the most common health problems among Bangladeshi children. PEM is known to induce a wide variety of metabolic disorders and some of which may be mediated through alteration of endocrine functions. Both short-term and long-term alterations in nutritional state affect various aspects of thyroid hormone economy, especially peripheral hormone metabolism. Chronic malnutrition is associated with a decreased serum T_3 concentration. Serum T_4 levels also tend to be slightly decreased because of a modest decrease in iodothyronine binding protein. TSH concentrations and their response to exogenous TRH are usually normal. To identify the effects of severe protein energy malnutrition on circulating iodothyronines especially circulating T_3 & T_4 and to determine the level of TSH in severe PEM. To compare the levels of thyroid hormones before and after recovery from severe PEM and to identify any correlation with mortality and morbidity. A prospective cross-sectional comparative study was performed in Nutrition block, Department of Pediatrics, Chittagong Medical College Hospital from 01 Dec 2007 to 30 Nov 2008. Patient admitted to nutrition block with severe PEM were included in the study. The levels of T_4, T_3 and TSH measured by radioimmunoassay (RIA) method. TSH was measured by using Immunoradiometric Assay Kit, IMK-432 produced by Beijing Atom Hitech Co. Ltd, China. T_3 and T_4 were measured by using Radioimmunoassay Kit (PR), IMK-422 and IMK-419 respectively produced by Beijing Atom Hitech Co. Ltd, China. Data were presented as the percentage of total number of observation. SPSS-Version 15.0 was used for the analysis of data. Student's t-test, Z-test, χ-square test and Pearson's correlation test were used for statistical significance. 'p' value of < 0.05 were used as the minimum level of significance. The effect of protein energy malnutrition (PEM) in the children on serum levels of total thyroxine (TT_4), total triiodothyronine (TT_3) and thyrotropin (TSH) were evaluated. There were 50 children aged 6 to 60 months in the malnutrition group and 22 healthy age and sex matched controls. Serum TT_4 and TT_3 were all reduced in the malnutrition group. This decrease in TT_3 was more significant ($p<0.001$) in severe malnutrition than in mild PEM. Serum TSH levels in the malnutrition and control groups were similar. These results suggest that the children remained euthyroid and represent an adaptive response to protein energy malnutrition. The results of the above mentioned studies clearly demonstrate that thyroid functions are adversely affected in severe PEM. This was evidenced by reductions in T_3 & T_4 levels in comparison to control group.

Keywords: Protein Energy Malnutrition; Thyroxine; Triiodothyronine; Thyrotropin.

1. Introduction
Severe protein energy malnutrition is one of the most common causes of morbidity and mortality among children throughout the world, especially in most of the developing countries. It is one of the

leading causes of morbidity and mortality among children in Bangladesh [1]. Protein energy malnutrition is known to induce a wide variety of metabolic disorders and some of which may be mediated through alteration of endocrine functions [2,3]. A number of changes may take place in thyroid function during nutritional deprivation or illness; many of the changes involve alterations in thyroid hormone metabolism [4]. Both short-term and long-term alterations in nutritional state affect various aspects of thyroid hormone economy, especially peripheral hormone metabolism. Chronic malnutrition is associated with a decreased serum T_3 concentration. Serum T_4 levels also tend to slightly decrease because of a modest decrease in iodothyronine binding protein. TSH concentrations and their response to exogenous TRH are usually normal [5]. The thyroid gland is the sole source of T_4, but only 20% of the T_3 in blood is derived from the thyroid gland and remaining 80% come from the peripheral conversion of T_4 by 5′-deiodinase. Both T_3 & T_4 are associated with plasma protein. The binding protein normally includes thyroid-binding globulin (TBG), thyroid binding pre albumin (TBPA), and albumin. The most important thyroid-binding protein is TBG, which binds about 75 percent of T_4 and T_3 [5-7]. In children with PEM, there is a gradual drop of concentrations of all three thyroid hormone binding proteins, and the serum T_4 & T_3 levels decline gradually, often into clearly hypothyroid range, allowing the rise of FT_4 levels in the opposite direction. However, serum TSH level remains unchanged. These peripheral adaptive mechanisms are clearly unsuitable in long-term disease, leading to a subsequent reduction of FT_4 plasma value [8]. This study was conducted to study the effects of malnutrition on thyroid function, as assessed by T_3, T_4 and TSH levels.

2. Methodology

This study was done among the patients suffering from severe protein energy malnutrition admitted in Pediatrics Ward of Chittagong Medical College Hospital (CMCH). Age and sex matched controls were also included in the study. Fifty children with severe PEM (19 boys and 31 girls), and 22 healthy children (13 boys and 9 girls), aged 6 to 60 months admitted in our hospital during the study period were included. None of the malnourished patients had known history of endocrine or metabolic disorders and congenital anomalies. The degrees of malnutrition were determined according to WHO criteria [9] with presence of any of the following findings-

a) Bilateral symmetrical pedal oedema
b) Weight-for-age: < 60% (severe underweight)
c) Weight-for-height: <70% (severe wasting)
d) Height-for-age: <85% (severe stunting)

Blood samples were obtained from peripheral veins on Day 2-4 of admission and on Day 14-21 days, after clinical recovery. Samples were sent immediately to laboratory for measurement. Laboratory support of Nuclear Medicine Centre, CMCH was taken. The levels of T_4, T_3 and TSH were measured by radioimmunoassay (RIA) method. TSH was measured by using Immunoradiometric Assay Kit, IMK-432 produced by Beijing Atom Hitech Co. Ltd, China. T_3 and T_4 were measured by using Radioimmunoassay Kit (PR), IMK-422 and IMK-419 respectively produced by Beijing Atom Hitech Co. Ltd, China. Data were presented as the percentage of total number of observation. SPSS version 15.0 was used for the analysis of data. Student's t-test, Z-test, χ-square test and Pearson's correlation test were used for statistical significance. 'p' value of < 0.05 were used as the minimum level of significance.

3. Results

A total of 50 children were enrolled in study who meet the inclusion criteria and 22 children were selected as age and sex matched control.

Table 1. Grade of malnutrition and age profile of patients

		N=72	Observed	Percentage	Range	Z- score	P value
Weight(kg)	Case	50	6.28 ± 1.91	53.12±9.36	3.6-10.30	-4.43±0.96	<0.001
	Control	22	10.77± 2.65	81.33±8.94	6.0-15.00	-1.76±0.81	
Height(cm)	Case	50	71.87± 11.32	85.51±6.48	54.0-99.0	-3.80±1.55	<0.001
	Control	22	84.48±9.82	94.10±2.56	67.0-104.0	-1.51±0.64	
Wt/Ht	Case	50	6.281.91	73.0611.77	51-105	-2.981.37	<0.001
	Control	22	10.772.65	90.4110.33	74-110	1.310.82	

Table 1 shows the various anthropometric measurements of both cases and controls. On admission observed weight was significantly low in severe PEM cases than that of controls who were suffering from diseases other than severe malnutrition. Same differences were also observed in their height and weight-for-height, which were highly significant.

Table 2. Thyroid function tests statistics (before treatment) among study groups (p value from student's t – test).

Thyroid function tests		N	Mean	± SD	Median	Range	'P' value
Serum T_3 level (nmol/L)	Case	50	1.13	0.82	0.875	0.12 – 3.45	P < 0.001
	Control	22	2.19	0.79	2.15	0.51 – 3.55	
	Total	72	1.46	0.94	1.43	0.12 – 3.55	
Serum T_4 level (nmol/L)	Case	50	72.80	36.18	73.00	13 – 154	P < 0.001
	Control	22	120.77	35.09	122.50	56 – 206	
	Total	72	87.46	41.99	90.00	13 – 206	
Serum TSH level(mIU/L)	Case	50	4.55	3.50	3.695	0.44 – 14.87	P < 0.01
	Control	22	2.51	1.58	2.30	0.26 – 6.75	
	Total	72	3.93	3.18	3.07	0.26 – 14.87	

Serum thyroid hormone levels (T_3, T_4, TSH) are shown in Table 2, among cases and controls. The mean serum T_3 level in control & severe PEM groups were 2.19 ± 0.79 nmol/L and 1.13 ± 0.82 nmol/L respectively. The reduction in serum T_3 level in severe PEM group was highly significant. Serum T_4 level in control and severe PEM groups were 120.77 ± 35.09 nmol/L and 72.80 ± 36.18 nmol /L respectively. This difference was also highly significant. Serum TSH level in control and severe PEM groups were 2.51 ± 1.58 mIu/L and 4.55 ± 3.50 mIu/L respectively. The difference is also significant.

Table 3. Statistics of *thyroid function test* among cases before and after treatment (with t – test significance).

Thyroid function tests	Before treatment	After treatment	'P' value
Serum T_3 level (nmol/L)	1.13±0.82	1.87±0.67	P < 0.001
Serum T_4 level (nmol/L)	72.80±36.18	93.67±32.98	P < 0.001
Serum TSH level (mIU/L)	4.55±3.50	4.37±2.71	P < 0.01

Serum thyroid hormone levels (T_3, T_4, TSH) are shown in Table 3, among cases and controls. The mean serum T_3 level in control & severe PEM groups were 2.19 ± 0.79 nmol/L and 1.13±0.82 nmol/L respectively. The reduction in serum T_3 level in severe PEM group was highly significant. Serum T_4 level in control and severe PEM groups were 120.77 ± 35.09 nmol/L and 72.80 ± 36.18 nmol/L respectively. This difference was also highly significant. Serum TSH level in control and severe PEM groups were 2.51 ± 1.58 mlu/L and 4.55 ± 3.50 mIu/L respectively. Change in thyroid status is very highly significant after treatment in cases of T_3 & T_4 level but it is not significant in case of TSH level.

Table 4. Comparison of thyroid function tests before and after treatment among cases (n=12) (Paired t-test).

Thyroid function tests	Before treatment Mean SD	After treatment Mean SD	'P' value	Significance
Serum T3 level	0.56 ± 0.27	1.87 ± 0.67	0.000	P<0.001
Serum T4 level	49.83 ± 19.71	93.67 ± 32.98	0.000	P<0.001
Serum TSH level	6.34 ± 3.87	4.37 ± 2.71	0.222	P>0.05

Table 4 shows the changes of thyroid status after treatment among the cases who showed significant low level of T_3 & T_4 level initially. Change in thyroid status is very highly significant after treatment in cases of T_3 & T_4 level but it is not significant in case of TSH level.

Table 5. Statistics of *thyroid function tests* among cases in relation to outcome (with t – test significance).

Thyroid function tests(before treatment)	Mean	± SD	Outcome	N	Sign.
Serum T_3 level (nmol/L)	1.21	0.83	Alive	43	P > 0.05
	0.68	0.61	Dead	07	NS
Serum T_4 level (nmol/L)	77.46	35.16	Alive	43	P < 0.05
	44.14	30.39	Dead	07	S
Serum TSH level (mIU/L)	4-20	3.41	Alive	43	P > 0.05
	6.70	3.52	Dead	07	NS

Table 5 shows the statistics of thyroid function tests among cases in relation to outcome. Total 7 cases (14%) died due to various complications along with severe PEM during management. All the death cases suffered from severe PEM, and mean T_4 levels were significantly decreased among death cases.

4. Discussion

Control of metabolic rate has been considered as one of the major functions of thyroid gland. The adaptive role and metabolism of thyroid hormones in various grades of PEM and other nonthyroidal illnesses had been investigated widely throughout the world. The present study has been undertaken to estimate the T_3, T_4 and TSH concentration in children suffering from severe protein energy malnutrition (PEM). Attempts were also made to study changes in thyroid hormone status after nutritional rehabilitation during hospital stay and also to identify any correlation of thyroid hormone level with mortality & morbidity.

The results of these studies clearly demonstrate that thyroid functions are adversely affected in severe PEM. These were evidenced by reductions in T_3 & T_4 levels in comparison to control group. The concentrations of circulating thyroid hormones in our children with severe PEM are similar to previous studies [2, 6, 7, 8, 10, 15].

The thyroid status of these children with severe PEM in our study is fairly typical of children with severe PEM both before and after dietary treatment. These changes in thyroid function appear to be

secondary to, and provide adaptation for, the reduced energy and protein intake characteristic of children with PEM. It has been suggested that reduction in T_3 and T_4 in such children may be attributed to a number of variables, including impaired thyroidal secretion rate, low levels of thyroid binding protein [5, 11, 13, 14] and iodide deficiency associated with high faecal loss and malabsorption of iodine [19]. The reduced levels of thyroid proteins, that is, TBG, TBPA, prealbumin, and albumin are secondary to reduction in protein intake and subsequent failure of hepatic biosynthesis of these proteins which is more marked in oedematous malnutrition (kwashiorkor). The deficiency of binding proteins reduces proportionately the amounts of T_3 and T_4 while they are transported.

Low serum T_3 concentrations may also suggest impaired peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), the latter being the most active hormone. Usually approximately 40 percent of T_4 secreted by the thyroid is monodeiodinated by the enzyme 5- deiodinase and converted to T_3, which accounts for 80-90 percent of the circulating T_3. The remaining 10-20 percent is derived from direct thyroid T_3 secretion [3,5,8]. Impaired monodeiodination of T_4 in the liver has been suggested as a contributory factor to the reduced T_3 levels in PEM. In our study possibility of impaired peripheral conversion of T_4 to T_3 has been investigated by examination of T_3/T_4 ratios (normally 1:50). Our results indicated that T_3/T_4 ratios are low in PEM in comparison to control group (1:64 in cases & 1:55 in controls), suggesting impaired peripheral conversion of T_4 to T_3. Peripheral conversion of T_4 to T_3 is closely related to energy intake, in that energy restriction induces the accumulation of rT_3, the inactive form of T_3, resulting in low serum T_3 [16, 17, 20, 21]. During PEM energy intake is restricted and this may contribute to low T_3 levels.

Now it is essential to distinguish the patients with the low T_3 and T_4 status and the true hypothyroidism. There was no significant difference between serum TSH concentrations in our children with PEM and the controls. This result accords with previously reported data.

Since T_3 is the major active thyroid hormone, it is surprising that patients with decreased serum T_3 do not appear hypothyroid. Low serum T_3 is probably an adaptive change to PEM, which at least enables the sick patient to conserve protein. Because the changes in thyroid hormone metabolism that occur in PEM probably represent adaptive changes to the illness, treatment with 1-thyroxine to restore serum thyroid concentrations to the normal range is not indicated.

The apparent dissociation between serum thyroid hormone concentrations and euthyroid clinical states has raised a question of the ambiguity of thyroid hormone action at which minimum threshold is essential to appropriately maintain the thyroid hormone homeostasis in an individual, or other characteristics of an individual may have influence to adapt oneself to this low T_3 and T_4 status. Otherwise, thyroid hormone treatment is necessary to restore the hormone levels to the normal range. But it is clearly evidenced from our study and also from previous studies [3,7,10,12,14,22] that only nutritional rehabilitation alone is sufficient to restore thyroid function level to normal or near normal level within 2-3 week.

5. Recommendations

Severe PEM with hypothyroidism in children is very important. If it persists for a long period, there may be delay in both physical and mental growth and increase the risk of mortality. This can be prevented by early diagnosis and introducing appropriate nutritional therapy. Thyroid hormone replacement therapy is not usually necessary.

6. Limitations of the Study

Single centre study with a small sample size so that the study findings may not be generalizable, other biochemical changes which usually are accompanied by thyroidal dysfunction like disturbances in rT_3, FT_4, FT_3 and TBG level should be done along with thyroid antimicrosomal antibodies and TRH stimulation tests which may provide conclusive results regarding the presence of hypothyroidism as well as its probable mechanisms in these patients.

7. Conclusion

In context of the overall study, it can be asserted that thyroid function is adversely affected in severe protein-energy malnutrition. This is an adaptive response to chronic nutritional deprivation. Severe PEM with low thyroxine level is associated with increased mortality. Early provision of a balanced diet with essential nutrient supplements and improvement of caring practices are necessary to overcome the problem.

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