

## Research Article

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# Thyroid hormone status in children with protein energy malnutrition

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## ABSTRACT

**Background:** Protein energy malnutrition (PEM) continues to be a major public health problem throughout the developing world. PEM is associated with reduced synthesis of plasma proteins; it affects several aspects of secretion and metabolism of thyroid hormones. The present study has been conducted to study the effect of PEM on thyroid hormone, plasma protein levels and to find correlation between thyroid hormones, plasma protein levels in PEM children.

**Methods:** Present study was a cross sectional hospital based case control study. 125 children with PEM, equal number of controls of age group 1-5 years were included in the study; details were collected in predesigned proforma. Triiodothyronine ( $T_3$ ), thyroxine ( $T_4$ ), thyroid stimulating hormone (TSH), serum total protein, albumin and hemoglobin levels were estimated. The parameters were compared among cases and controls using appropriate statistical tool.

**Results:** Mean haemoglobin, serum total protein, albumin levels, A/G ratio,  $T_3$  and  $T_4$  levels were significantly low in PEM children (cases) as compared to controls. TSH levels were similar in both groups.  $T_3$  and  $T_4$  levels had a significant positive correlation with haemoglobin, serum total protein and serum albumin levels.

**Conclusions:** PEM is associated with reduction in  $T_3$  and  $T_4$  levels without any alteration in TSH levels. The altered thyroid hormone status in children with PEM is perhaps a defense mechanism against excessive metabolic stimulation and energy consumption and protects the malnourished child with low calorie reserve from an early death.

**Keywords:** Protein energy malnutrition, Thyroxine, Triiodothyronine, Serum total protein, Albumin

## INTRODUCTION

Protein Energy Malnutrition (PEM) is one of the most common nutritional problem of developing countries and an important cause of childhood mortality and morbidity leading to permanent impairment of physical and mental growth.<sup>1, 2</sup> According to estimates in the world there are about 162 million children suffering from various forms of PEM. It is estimated that PEM is the primary or associated cause of nearly half of approximately 3 million deaths in children under the age of 5 years. Three-quarters of the world's stunted children live in South Asia and Sub-Saharan Africa; India is home to nearly one-third of world's malnourished children, as per national

family health survey-3 (NFHS-3) report prevalence of underweight, stunting and wasting in India is 43%, 48% and 20% respectively.<sup>3-5</sup>

The World Health Organization (WHO) defines malnutrition as "The cellular imbalance between the supply of nutrients and energy, and the body's demand for them to ensure growth, maintenance, and specific functions". PEM initially leads to failure in maintaining adequate weight gain and growth rate in early stages, as the condition progresses there is loss of weight associated with loss of subcutaneous tissue and muscle mass. It affects every organ system, as PEM progresses organ dysfunction develops and leads to variety of clinical features; several metabolic derangements are expected.

Hepatic synthesis of serum proteins decreases and depressed levels of circulating proteins are observed. With increasing severity there is increasing failure in the homeostatic mechanism of the body and it damages the immune defense, which may result in infection and death.<sup>6,7</sup>

Thyroid hormone plays an important role in regulation of lipid and carbohydrate metabolism and is necessary for normal growth and maturation. Absence of thyroid hormone causes mental and physical slowing, mental retardation and dwarfism.<sup>8</sup> PEM is associated with iodine, vitamin A and iron deficiencies leading to anemia, increasing the risk of death and disability from diarrhea, acute respiratory infection and vaccine preventable diseases particularly measles. There is marked change in secretion and metabolism of thyroid hormones and in structure of thyroid gland. These result in reduction of activity of thyroid gland and hence decrease in triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>). The alteration of thyroid function is attributed to changes in iodine metabolism and decreased level of circulating proteins. These changes play an important role in the adaptive process of energy and protein metabolism in children with PEM; and help in conservation of energy when energy producing substrate is scarce and protects the child from early death due to low calorie reserve.<sup>9</sup>

Several studies have been done to estimate the individual biochemical parameters in PEM. However, few studies have been conducted to see if there is any correlation between serum thyroid hormone levels and serum total protein, albumin levels in children with PEM. In this study, an attempt has been made to study the concentration of serum thyroid hormone levels in PEM children and its correlation with serum total protein and albumin levels.

## METHODS

The present study was a cross sectional hospital based case control study; it consisted of children in age group 1-5 years. They were evaluated at Department of Pediatrics, Mysore Medical College and Research Institute, Mysore during the term January 2012 to December 2012. Approval from Institutional ethics committee was obtained prior to start of study.

One hundred twenty-five children with Protein Energy Malnutrition (PEM) as per Indian Academy of Pediatrics (IAP) classification of PEM based on weight for age were included in the study as cases (whose weight for age was less than 80% of expected for age constituted cases, they were further subdivided into: Grade I- weight for age of 80-71%, Grade II- weight for age of 70-61%, Grade III- weight for age 60-51% and Grade IV- weight for age  $\leq 50\%$ ) and equal number of age and sex matched healthy children formed the control group (whose weight for age was more than 80% of expected for age).<sup>10</sup> None of the children with PEM included in the study had chronic

infection like tuberculosis, HIV, malabsorption syndrome, protein losing nephropathy, endocrine disorders and congenital anomalies.

Subjects were included in the present study after obtaining informed written consent from parents/guardian. Details were entered in predesigned proforma. Thorough history in particularly history of previous hospitalization for illness like acute diarrheal disease, lower respiratory tract infection, measles and the nutritional history of child was taken, following which detailed anthropometric measurements and systemic examination was done. Weight was recorded to the nearest 100g, length/height of the child was measured to the nearest cm, mid arm circumference (MAC) was measured to the nearest mm; head circumference (HC) and chest circumference were measured to the nearest 0.5cm.

Taking aseptic precaution, 3ml of venous blood was collected and was kept in EDTA (Ethylene Diamine Tetra acetic Acid) vacutainer and test tube. EDTA blood was used for haemoglobin (Hb) and total white blood cells (WBC) count estimation. The blood sample collected in test tube was centrifuged at 5000 rpm (rotation per minute) for 5 minutes; serum thus obtained was used to estimate T<sub>3</sub>, T<sub>4</sub>, thyroid stimulating hormone (TSH), serum total protein and albumin. T<sub>3</sub>, T<sub>4</sub> and TSH were estimated by chemiluminescence method (using Immulite 1000 Immunoassay system- Siemens). Serum total protein was estimated by Biuret method, serum albumin was estimated by Bromocresol green dye method (BCG dye). Haemoglobin and total WBC count were estimated by using auto analyzer (Sysmex).

The data obtained was entered in MS Excel spread sheet; the results were expressed in mean  $\pm$  standard deviation (SD) for continuous variables and as percent (%) for categorical data. Observations were statistically analyzed using Epi Info software version 3.5.1. Descriptive statistics was applied for categorical data. Independent sample- t test, One-way ANOVA and Scheffe's post hoc test were used. Pearson's correlation coefficient was used to determine correlation between different variables. P value of  $<0.05$  was considered statistically significant.

## RESULTS

A total of 250 children in age group 1-5 years were included in the study. 139 children included in the study were male and 111 were female (sex ratio M: F: 1.25:1). The lowest aged child included was 12 months in both cases and controls, and oldest aged included being 59 months in cases and 60 months in controls. Majority of cases in present study belonged to Grade II PEM (n= 41) followed by Grade III PEM (n= 34), Grade I PEM (n= 32) and Grade IV PEM (n= 18).

Age and sex distribution among both the study groups was identical and is depicted in Table 1. Mean age of

cases (PEM group) was 29.49 months and controls was 29.26 months, mean weight of cases was 8.26 kg and of controls was 12.44 kg, mean length/height of cases was

80.51 cm and that of controls was 88.77 cm, mean MAC in cases was 12.35 cm and controls was 13.64 cm.

**Table 1: Comparison of age, gender distribution and anthropometric measurements among cases (PEM group) and controls.**

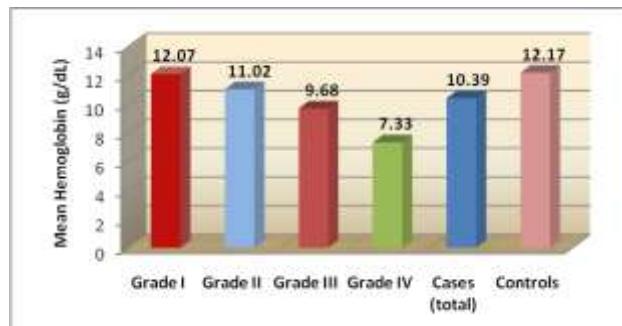
Parameter	Cases (n=125)	Controls (n=125)	t-value	p-value
Age (months)±SD	29.49±12.82	29.26±13.27	0.141	0.888
Gender (Male: Female)	68:57	71:54	0.024(c*)	0.703
Weight (kg)±SD	8.26±1.76	12.44±2.81	-14.082	<0.001
Length/ Height (cm)±SD	80.51±8.73	88.77±8.23	-7.691	<0.001
MAC (cm)±SD	12.35±1.06	13.64±0.44	-12.494	<0.001
Chest circumference (cm)±SD	46.22±2.85	49.18±3.06	-7.885	<0.001
Head circumference (cm)±SD	45.91±1.89	47.05±1.87	-4.804	<0.001

**Table 2: Mean serum total protein, albumin levels in various grades of PEM and controls.**

Variable	Total protein			Albumin		
	Mean (g/dL)±SD	t-value	p-value	Mean (g/dL)±SD	t-value	p-value
A (n=32)	6.81±0.62	-2.761	0.006	3.74±0.44	-5.747	<0.001
B (n=41)	6.49±0.60	-6.033	<0.001	3.49±0.39	-9.837	<0.001
C (n=34)	5.97±0.66	-9.743	<0.001	3.1±0.42	-13.829	<0.001
D (n=18)	5.54±0.65	-10.299	<0.001	2.77±0.57	-13.064	<0.001
Cases total (n=125)	6.29±0.76	-9.761	<0.001	3.34±0.55	-14.156	<0.001
Controls (n=125)	7.15±0.61			4.22±0.41		

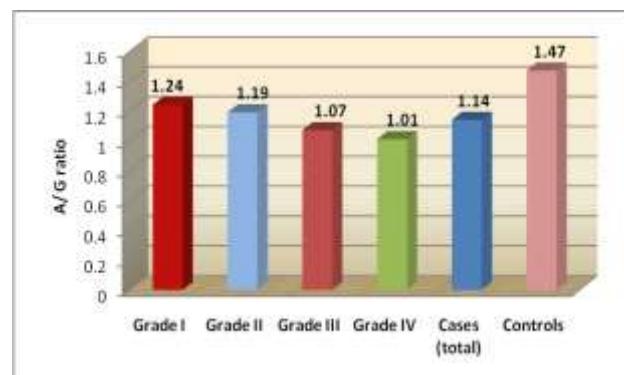
A- Grade I PEM; B- Grade II PEM; C- Grade III PEM; D- Grade IV PEM; SD- Standard deviation.

82 children in PEM group had pallor whereas only 38 children included in controls had pallor, the difference observed was statistically significant ( $p <0.001$ ). Mean hemoglobin levels of various grade of PEM and controls is depicted in Figure 1. The mean hemoglobin levels in cases was significantly lower as compared to controls ( $p <0.001$ ). When mean Hemoglobin levels of individual grades of PEM was compared with controls, it was observed that there was no significant difference observed between Grade I PEM and controls, whereas there was statistically significant difference that was observed in Grade II to Grade IV PEM in comparison to controls ( $p= 0.004$  in Grade II,  $<0.001$  in Grade III and IV PEM).



**Figure 1: Mean haemoglobin levels in various grades of PEM and controls.**

Mean serum total protein and albumin levels of cases and controls are shown in Table 2. Mean serum total protein and albumin levels was significantly lower in cases compared to controls ( $p <0.001$ ). When the mean value of serum total protein and albumin levels of different grades of PEM was compared with controls, it was observed that these parameters were significantly lower in each group as compared to controls.



**Figure 2: Albumin/ Globulin ratio in various grades of PEM and controls.**

Albumin/ Globulin ratio (A/G ratio) of cases and controls is depicted in Figure 2. A/G ratio was significantly lower in cases as compared to controls. When comparison was made between different grades of PEM and control, A/G

ratio was significantly lower in all grades of PEM as compared to controls.

Mean  $T_3$ ,  $T_4$  and TSH levels of cases and controls is depicted in Table 3 and Table 4. Mean  $T_3$ ,  $T_4$  and TSH levels in PEM group was 129.48 ng/dL, 8.18  $\mu$ g/dL and 2.52 mIU/L respectively and that of controls were 159.82 ng/dL, 9.37  $\mu$ g/dL and 2.50 mIU/L respectively. Mean  $T_3$  and  $T_4$  levels were significantly lower in cases

as compared to controls ( $p < 0.001$  for both parameters). When mean  $T_3$  and  $T_4$  levels of individual grades of PEM was compared to controls it was observed that in Grade I PEM the mean values were comparable with controls with no significant difference, whereas in other grades of PEM these parameters were significantly lower as compared to controls. Mean TSH levels of cases and controls was identical.

**Table 3: Mean  $T_3$ ,  $T_4$  levels in various grades of PEM and controls.**

Variable	$T_3$		$T_4$			
	Mean (ng/dL)±SD	t-value	p-value	Mean ( $\mu$ g/dL)±SD	t-value	p-value
A (n=32)	151.77±27.51	-1.303	0.195	8.97±1.9	-1.110	0.269
B (n=41)	134.93±22.56	-4.604	<0.001	8.37±1.66	-3.122	0.002
C (n=34)	119.94±39.69	-6.097	<0.001	7.92±1.68	-4.177	<0.001
D (n=18)	95.44±33.89	-7.906	<0.001	6.87±1.54	-5.518	<0.001
Cases total (n=125)	129.48±35.51	-7.089	<0.001	8.18±1.82	-5.150	<0.001
Controls (n=125)	159.82±32.07			9.37±1.82		

A-Grade I PEM; B- Grade II PEM; C- Grade III PEM; D- Grade IV PEM; SD- Standard deviation;  $T_3$ - Triiodothyronine;  $T_4$ - Thyroxine.

**Table 4: Mean TSH levels in various grades of PEM and controls.**

Variable	TSH		
	Mean (mIU/L)±SD	t-value	p-value
A (n=32)	2.37±1.11	-0.561	0.576
B (n=41)	2.47±1.02	-0.152	0.879
C (n=34)	2.71±1.41	0.905	0.367
D (n=18)	2.54±1.16	0.147	0.883
Cases total (n=125)	2.52±1.17	0.144	0.885
Controls (n=125)	2.50±1.14		

A- Grade I PEM; B- Grade II PEM ;C- Grade III PEM; D- Grade IV PEM; SD- Standard deviation; TSH- Thyroid stimulating hormone.

**Table 5: Correlation between thyroid hormones ( $T_3$ ,  $T_4$  and TSH) and Hb, serum total protein and albumin in cases (PEM group).**

Parameter	Hb		Total protein		Albumin		A/ G ratio	
	r	p	r	P	r	p	r	P
$T_3$	0.404	<0.001	0.361	<0.001	0.345	<0.001	0.144	0.109
$T_4$	0.212	0.018	0.294	0.001	0.263	0.003	0.077	0.395
TSH	-0.12	0.892	0.025	0.778	0.062	0.489	0.074	0.414

$T_3$ - Triiodothyronine;  $T_4$ - Thyroxine; TSH- Thyroid stimulating hormone; Hb- Haemoglobin; A/G ratio- Albumin/ globulin ratio.

Mean hemoglobin, total protein, albumin, A/G ratio,  $T_3$ ,  $T_4$  among cases (PEM group) showed significant decrease with increase in severity of malnutrition, with maximal reduction in the parameters been observed in Grade IV PEM (One-way ANOVA;  $p < 0.001$ ). However the mean TSH value was similar in all grades of PEM with no significant difference (One-way ANOVA;  $p = 0.691$ ).

On applying Pearson's correlation coefficient to identify correlation between the various blood parameters in cases (PEM group), it was observed that mean  $T_3$ ,  $T_4$  levels of cases had a significant positive correlation with hemoglobin levels, serum total protein and albumin levels. TSH levels had no correlation with these parameters. A/G ratio did not correlate with  $T_3$ ,  $T_4$  and TSH levels (Table 5).

## DISCUSSION

Protein energy malnutrition continues to be a major problem throughout the developing world.<sup>11</sup> In India almost half of children under the age of 5 years are suffering from various grades of PEM.<sup>5</sup> As already stated effects of PEM on the body are protean involving almost all the organ systems, PEM leads to failure in homeostatic mechanism of the body leading to increased susceptibility of an individual to infections.<sup>6,7</sup> Globally, nearly half of under-five deaths are attributed to PEM either as direct/ indirect cause.<sup>3</sup> PEM is associated with reduction in synthesis of plasma proteins.<sup>12</sup> It affects several aspects of secretion and metabolism of thyroid hormones.<sup>9</sup> Hormones play important role in energy and protein metabolism in PEM.<sup>13</sup> This study was conducted to know about thyroid hormones level in children with PEM and its correlation with serum total protein and albumin.

A total of 250 children of age group 1 year to 5 years were included, of which 125 were suffering from PEM, rest were healthy controls. Sex ratio in the study was 1.25:1 (M:F: 139:111), both cases and control group were age and sex matched. Majority of children enrolled were in the age group 12-18 months (30.4% in cases and 32.8% in controls), higher prevalence of PEM in this age group explains the importance of the need for continued breast feeding and appropriate introduction of complementary feeds. Number of children from urban and rural area was similar in both cases (53.6% and 46.4% respectively) and controls (55.2% and 44.8% respectively). Majority of children in both cases (49.6%) and controls (42.4%) belonged to class IV socio economic status (SES) as per modified Kuppuswamy classification.<sup>14</sup> There was no significant difference in SES among both groups ( $p=0.572$ ). As our hospital is a government institute which caters mainly to patients from lower socioeconomic strata, hence had a higher distribution in class IV SES.

Mean hemoglobin level in cases (PEM group) was lower than controls (10.39, 12.17 respectively). Study conducted by Adegbusi HS et al, found that mean hemoglobin level in under-nourished group was significantly lower in comparison to that of well-nourished children.<sup>15</sup> Lower hemoglobin in PEM children is due to iron, vitamin, trace elements and protein deficiencies, which is often found in children suffering from PEM.

In the present study it was observed that mean serum total protein, albumin levels and A/G ratio in cases was significantly lower as compared to controls (Table 2, Figure 2). On comparison of these parameters in different grades of PEM among each other it was observed that the reduction in serum total protein, albumin and A/G ratio were correlating well with severity of malnutrition (One-way ANOVA;  $p < 0.001$ ) with maximal decrease been noted in Grade IV PEM. Study conducted by Adegbusi

HS et al, also found that mean serum total protein and albumin levels were significantly lower in under-nourished children as compared to well-nourished children ( $p < 0.05$ ).<sup>15</sup> Similar findings were noted by Rahman MA et al.<sup>16</sup> The alterations in serum total protein, albumin and A/G ratio in PEM could be explained on the basis of decreased protein intake and reduced biosynthesis.

In the present study mean  $T_3$  and  $T_4$  levels (Table 3) were significantly lower in cases as compared to controls ( $p < 0.001$ ). Mean  $T_3$  and  $T_4$  levels of Grade I PEM was similar to that of controls, and that of Grade II –IV was significantly lower as compared to controls. It was observed that the  $T_3$  and  $T_4$  levels decreased with increase in severity of malnutrition, with maximal decrease been noted in Grade IV PEM. Studies conducted by Abrol P et al and Turkey et al have showed similar results (Table 6, Table 7).<sup>17,18</sup> Similar results are reported by study done by Kumar S et al, Orbak Z et al and study conducted by Das BK et al, found that mean  $T_3$  levels was significantly lower in malnourished children as compared to controls, however in their study they found no significant difference in mean  $T_4$  levels of cases and controls.<sup>19-21</sup> Low  $T_3$  levels in children with PEM is probably due to low binding proteins, impaired thyroxine monodeiodination in liver which leads to decreased peripheral conversion of  $T_4$  to  $T_3$  and elevated corticosteroids which is often seen in children with malnutrition (acts by inhibiting 5' deiodinase system) and low  $T_4$  levels in children with PEM can be due to fall in thyroid secretion rate, depletion of reserves and failure of the adaptive mechanism.

In the present study mean TSH levels in cases and controls were similar; TSH level of different grades of PEM was also similar. Studies conducted by Abrol P et al, Turkey et al and Das BK et al, also showed similar results.<sup>17,18,21</sup> In contrast to present study, study conducted by Orbak Z et al, found that mean TSH levels of children with PEM were higher as compared to controls, study conducted by Kumar S et al, found that mean TSH levels showed a positive increase with increase in severity of PEM with maximum increase been observed in grade III PEM (One-way ANOVA;  $p=0.015$ ).<sup>19,20</sup> Normal TSH levels in children with PEM is possibly due to  $T_4$  undergoing intracellular monodeiodination to form  $T_3$  at pituitary level causing negative feedback inhibition of secretion of TSH, central unresponsiveness to low  $T_3$  levels due to low intracellular receptor capacity.

In the present study it was observed that  $T_3$ ,  $T_4$  values of PEM children (cases) showed a significant positive correlation with hemoglobin, serum total protein and albumin.  $T_3$ ,  $T_4$  values did not correlate with A/G ratio. Serum TSH levels in cases did not show correlation to any of the above parameters. Study conducted by Onuora et al found that  $T_3$ ,  $T_4$  changes in children with under-nutrition, marasmus and kwashiorkor had a significant

correlation with serum plasma protein levels.<sup>22</sup> Study conducted by Das BK et al found that T<sub>3</sub> level had a

strong correlation with serum total protein and albumin.<sup>21</sup>

**Table 6: Comparison of T<sub>3</sub> levels of present study and other studies.**

Grade of PEM	T <sub>3</sub> (ng/dL) (Mean±SD)		
	Present study (n=250)	Abrol P et al <sup>17</sup> (n=100) mean± SE	Turkey et al <sup>18</sup> (n=161) mean± SE
Grade I	151.77±27.51(NS)	126.9±12.2 (NS)	145±4.38*
Grade II	134.93±22.56***	122.4±10.7*	140±4.9 (NS)
Grade III	119.94±39.69***	106.5±9.8***	126.2±10.98*
Grade IV	95.44±33.89***	90.3±9.9***	114.43±16.65*
Total cases	129.48±35.51***	111.5±5.6***	139.96±3.19*
Controls	159.82±32.07	157.8±8.54	156.87±3.5

SD- Standard deviation; T<sub>3</sub>- Triiodothyronine; \*p <0.05; \*\*\*p <0.001; NS- Not significant; SE- Standard error.

**Table 7: Comparison of T<sub>4</sub> levels of present study and other studies.**

Grade of PEM	T <sub>4</sub> (μg/dL) (Mean±SD)		
	Present study (n=250)	Abrol P et al <sup>17</sup> (n=100) mean±SE	Turkey et al <sup>18</sup> (n=161) mean±SE
Grade I	8.97±1.9 (NS)	9.4±0.5*	8.9±0.27 (NS)
Grade II	8.37±1.66**	9±0.8*	8.28±0.38 (NS)
Grade III	7.92±1.68***	8±0.8**	7.97±0.74*
Grade IV	6.87±1.54***	7.7±0.5***	6.93±0.6*
Total cases	8.18±1.82***	8.5±0.3***	8.47±0.21*
Controls	9.37±1.82	10.55±0.6	9.29±0.25

SD- Standard deviation; T<sub>4</sub>- Thyroxine; \*p <0.05; \*\*\*p <0.001; NS- Not significant; SE- Standard error.

## CONCLUSION

To conclude Protein energy malnutrition is associated with reduction in T<sub>3</sub> and T<sub>4</sub> levels without any alteration in TSH levels. The altered thyroid hormone status in children with PEM is perhaps a defense mechanism against excessive metabolic stimulation and energy consumption and protects the malnourished child with low calorie reserve from an early death.

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**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Ethics Committee

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