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Original Research

Interrelation of Free Thyroid Hormone levels and Serum proteins in Malnourished Children at Rural Tertiary Care Hospital in Andhra Pradesh

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ABSTRACT:

Background: Primary acute malnutrition in children is the result of inadequate food supply caused by socioeconomic, political, and environmental factors, and it is most commonly seen in low- and middle-income countries. There are marked change in secretion and metabolism of thyroid hormones and in structure of thyroid gland in PEM. There is limited data and studies available regarding concentration of FT3 and FT4 levels in PEM children. **Method:** A Prospective observational Study done at rural tertiary care hospital. 100 Out of 112 children in the 6 months to 60 months of age diagnosed as PEM were analysed for the study during 2 years and 4 months. Study participants were divided on the basis of WHO staging for acute malnutrition. Detail clinical assessment of nutritional status was carried out along with history and anthropometric measurement in case Performa. Thyroid function test and Serum proteins was done. Statistical Analysis was performed. **Results:** In our study a very highly significant correlation noted between low FT3 and type of malnutrition. The mean FT4 value in children with SAM was less than children with MAM. The difference between the two groups of cases was found to be statistically highly significant ($p<0.001$).We observed that there was no correlation between TSH values and the type of malnutrition. The mean serum proteins, albumin and globulin were significantly lower and a positive correlation with type of malnutrition. A/G ratio was decreased in both SAM and MAM children and highly significant correlation with low FT3. FT4 had a significant correlation with decreased A/G ratio. There was no significant relation between the A/G ratio and TSH. **Conclusion** It is also important to bear in mind whether total (TT4, TT3) or free (FT4, FT3) Thyroid Hormone are measured, as changes in circulating binding proteins can seriously confound interpretation of TT4 and TT3 concentrations.

Keywords: Protein energy malnutrition (PEM), free T3, freeT4, Thyroid stimulating hormone (TSH) , Serum proteins, Severe acute malnutrition (SAM), Moderate acute malnutrition (MAM)

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INTRODUCTION

Primary acute malnutrition in children is the result of inadequate food supply caused by socioeconomic, political, and environmental factors, and it is most commonly seen in low- and middle-income countries .[1,2]. Acute malnutrition is responsible for almost one third of all deaths in children <5 years of age and causes intellectual or cognitive impairment among those who survive [2]. More than 500 000 deaths each year among children under 5 years of age are attributable to marasmus, using the WHZ <−3 definition, accounting for >7% of all mortality in this age group [3]. At any given time, some 18 million children in low income and middle-income countries are estimated to suffer from marasmus [3], most of them in Asia [4]. However, this is likely a vast underestimate as it does not take into account children aged 6–59 months with mid upper arm circumference (MUAC) <115 mm, nor has the incidence or prevalence of kwashiorkor been accurately quantified [5]. As per NFHS-3 report the prevalence of underweight, stunting and wasting in children under five year of age in India was 43%, 48% and 20% respectively [6].

Thyroid hormones (TH) play an important role in regulation of lipid and carbohydrate metabolism and are necessary for normal growth and maturation. Absence of thyroid hormone causes mental and physical slowing, mental retardation and dwarfism [7]. There are marked change in secretion and metabolism of thyroid hormones and in structure of thyroid gland in protein energy malnutrition (PEM). These result in reduction of activity of thyroid gland and hence decrease in triiodothyronine (T3) and thyroxine (T4). 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 [8]. Assessment of TH status in PEM has been difficult, since reductions in circulating binding protein levels will lead to reductions in total circulating TH, as noted above. As detailed below, the duration of malnutrition appears important in determining alterations in the hypothalamic-pituitary-thyroid axis. In acute malnutrition, there is a reduction in total T4 and T3 levels secondary to reduced plasma proteins, with maintained euthyroidism, whereas prolonged malnutrition often results in overriding of the adaptive mechanisms, resulting in hypothyroidism as defined by low levels of T3, the active form of the hormone [9].

Several studies have been done to estimate the serum total protein, serum albumin, T3 and T4 levels in PEM. There is limited data and studies available regarding concentration of the free T3 (FT3) and free T4 (FT4) levels in children with PEM. In this study, an attempt has been made to study the concentration of serum total protein, serum albumin, FT3 and FT4 and their interrelation.

MATERIALS AND METHODS

Objective: To study interrelation of free thyroid hormone levels and serum proteins in malnourished children at rural tertiary care hospital of Andhra Pradesh.

Study design: Prospective Observational Study done at a tertiary care hospital in a rural area.

Inclusion criteria: 6 months to 60 months of age Children diagnosed as PEM.

Exclusion criteria: Children with

1. Primary disorder of hypothalamic–pituitary–thyroid function.
2. Heparin therapy.
3. Chronic kidney and liver diseases.
4. Urinary tract infection.
5. Chronic infection such as Tuberculosis.
6. Major congenital anomalies and metabolic disorders.

Place and duration of study: The study was performed in Paediatric ward at Nimra Institute of Medical Sciences Hospital, Jupudi (V), Vijayawada Krishna (District) Andhra Pradesh. The study was carried out from January 2018 to April 2020, for a period of 2 years and 4 months.

Consent: The ethical approval for the study was obtained from the institutional ethics committee. An informed written consent was sought from parents of eligible children before the commencement of the study. After explaining about purpose of study, outcome and explaining that respondent can refuse and withdraw from study at anytime. All related information was conveyed in local language. Confidentiality about identification details of patients was maintained.

METHODOLOGY:

Study participants were divided on the basis of WHO staging for acute malnutrition, or wasting, is defined using anthropometric cut-offs and clinical signs. The currently accepted definitions, set out by the WHO, are as follows:

Moderate acute malnutrition (MAM), defined as weight-for-height- z-score (WHZ) between −2 and −3 or mid-upper arm circumference (MUAC) between 115 millimeters and <125 millimeters (WHO 2012) **[10]**

Severe acute malnutrition (SAM), defined as WHZ < −3 or MUAC < 115 millimeters, or the presence of bilateral pitting edema, or both (WHO 2013) **[11]**

Detail clinical assessment of nutritional status was carried out.

Weight (>1 yr) was taken on a digital weighing scale and for infants it was taken on Infant digital weighing scale. Height (>2 yr) was measured by Stadiometer and for infants length was taken by Infantometer. Children more than 2 years were made to stand upright with heel, buttocks, shoulder blade and occiput touching the wall and Frankfurt plane parallel to floor. Mid arm circumference was taken over the left triceps, with the arm hanging by the Side, a non stretchable tape passed around the circumference of the arm at the Midpoint of left arm, midway between acromion process and olecranon process.

Weight for height –Weight of the child divided by ideal weight of a normal child of same height *100.

4ml blood sample was collected in a plain test tube with all aseptic precautions along with other blood investigations to avoid repeat venous puncture. Samples were transported to the laboratory within half an hour. Whenever testing was delayed for more than 24 hours, serum specimens were stored at 2-8°C to analyze it on the next day. Assessment of total Serum Proteins was done with Albumin and Globulin, Albumin /Globulin ratio was calculated, Thyroid Function test – Thyroid stimulating hormone (TSH), FT3, FT4 was done. TSH was done by Ultra Sensitive Sandwich Chemi Luminescent Immuno Assay (fully automated analyser Roche Cobas e411), FT3 and FT4 done by competitive luminescent immune assay (fully automated analyser Roche Cobas e411). Serum proteins – Biuret test - An aqueous sample is treated with an equal volume of 1% strong base (sodium or potassium hydroxide most often) followed by a few drops of aqueous copper sulphate. If the solution turns purple, protein is present. 5–160 mg/mL can be determined. A peptide of a chain length of at least 3 amino acids is necessary for a significant, measurable colour shift with these reagents. Serum Albumin Bromocresol Green dye binding method. Serum globulin was calculated as Total Proteins minus Serum Albumin**.** A study flow diagram has been depicted in Figure 1.

Statistical Analysis:—Data entry was done in MICROSOFT EXCEL. Data analysis was done with the use of SPSS and MS-EXCEL. Graphs and tables were prepared by MS-EXCEL. Software package SPSS was used to analyze the data were summation, multiplication, division, percentage along with mean, median, mode, range, frequency, standard deviation, Unpaired t test and degree of freedom.

p value of < 0.001 was highly significant, < 0.05 was significant and ≥ 0.05 as not significant.

RESULT AND DISCUSSION

Mean values of FT3, FT4 and TSH levels are depicted in Table 1. In our study a very highly significant correlation noted between low FT3 and type of malnutrition. Similar findings were also echoed in the studies done by Dhanjal GS et al.**[12]** Shaheen B et al. the mean FT3 value in cases was 1.5 pg/ml±0.3 and in controls was 2.3 pg/ml±0.5 (one -way ANOVA; $p < 0.0001$) while in study conducted by Shahjadi S et al. mean FT3 value in cases divided into two groups marasmus group and kwashiorkor group were 3.16±0.30 pmol/L and 3.10±0.26 pmol/L respectively and control group was 6.46±0.76 pmol/L (unpaired Student 't' test; $p<0.001$).**[13,14]** There was a significant decrease in the mean FT3 values in PEM patients in the study done by Shahjadi S et al. when compared to control group but there was no statistically significant difference within subgroups of cases.**[14]** Decreased FT3 levels in PEM children is probably due to low binding proteins, impaired thyroxin monodeiodination in liver which leads to decreased peripheral conversion of T4 to T3 and elevated corticosteroids which is often seen in children with malnutrition (acts by inhibiting 5' deiodinase system) and low T4 levels in children with PEM can be due to fall in thyroid secretion rate, depletion of reserves and failure of the adaptive mechanism.

In spite of the normal FT4 levels, mean FT4 value in children with SAM was less than children with MAM (Table 1). The difference between the two groups of cases was found to be statistically highly significant ($p<0.001$). In the study conducted by Dhanjal GS et al **[12]** as well as Shaheen B et al, the mean FT4 value in cases was 1.42ng/ml ± 0.31 and in controls was 1.66ng/dl ± 0.39 (one –way ANOVA; $p<0.0001$).**[13]** We observed that there was no correlation between TSH values and the type of malnutrition. This finding is similar to some studies. Sandeep M et al, Abrol et al. and Turkay S et al. in their study found no significant difference in TSH when PEM children**.[15,16,17]** In contrast to our study, Orbak Z et al, **[18]** found that mean TSH levels of children with PEM were higher as compared to controls. Sanjeev kumar et al **[19]** studied effect of malnutrition on thyroid Hormone; with increasing severity of malnutrition, the serum concentration of T3 and T4 progressively decreased and that of serum TSH increased. TSH levels in children with PEM is possibly due to T4 undergoing intracellular monodeiodination to form T3 at pituitary level causing negative feedback inhibition of secretion of TSH, central unresponsiveness to low T3 levels due to low intracellular receptor capacity.

Mean values of Serum proteins and Albumin-Globulin ratio are depicted in Table 1. The mean serum proteins, albumin and globulin were significantly lower. There was a positive correlation (Unpaired t test, $p<0.05$) between decreased proteins, albumin and globulin with type of malnutrition. There was no significant correlation between Albumin& Globulin (A/G) ratio and the type of malnutrition but it was decreased in both SAM and MAM patients. Similar studies by Sandeep M et al, Adegbusi et al, Sah SP et al, Shaheen B et al and Rahman MA et al. showed reduction in serum total protein, albumin,

globulin and A/G ratio were correlating well with severity of malnutrition. **[15, 20, 21, 13, 22]** The alterations in serum total protein and serum albumin in PEM could be explained on the basis of decreased protein intake and reduced biosynthesis. The alterations in serum total protein and serum albumin in PEM could be explained on the basis of decreased protein intake and reduced biosynthesis.

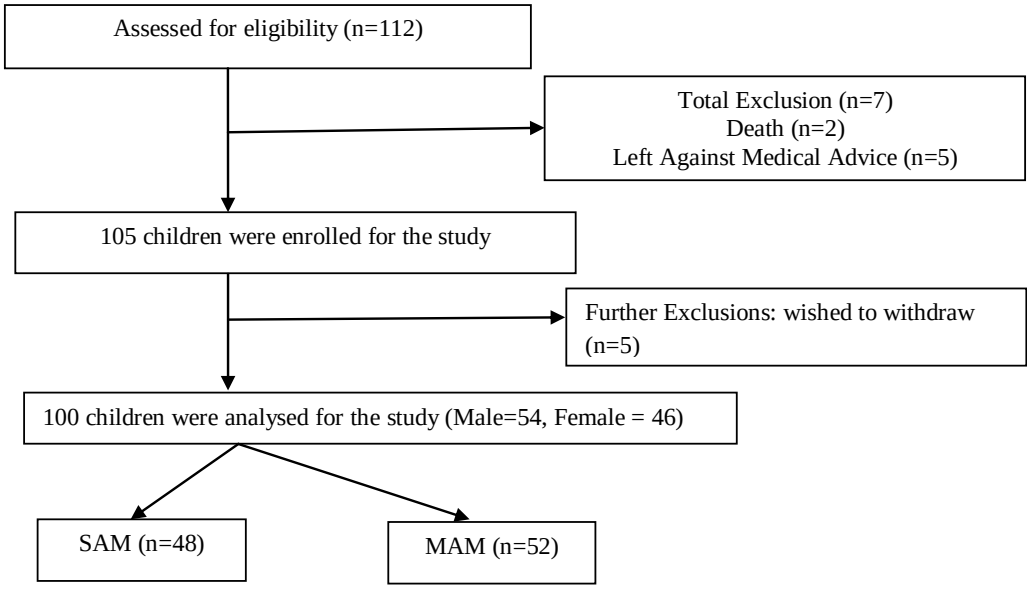
Table no 1: Association of Thyroid Hormones, Serum proteins and Albumin-Globulin ratio with type of Malnutrition

Parameters	MAM (Mean ± SD)	SAM (Mean ± SD)	p value	Unpaired t test
Free T3 (pmol/l)	3.71±1.76	2.38±0.84	<0.001	4.881
Free T4 (ng/l)	1.63±0.66	1.15±0.62	<0.001	3.687
TSH (mIU/l)	3.30±1.5	3.21±2.1	0.810	0.241
Total Protein (gm/dl)	5.31±0.92	4.36±0.63	<0.001	5.931
Albumin (gm/dl)	2.71±0.57	2.16±0.42	0.003	3.051
Globulin (gm/dl)	2.56±0.68	2.20±0.47	0.003	3.051
Albumin-Globulin ratio	1.15±0.44	1.02±0.31	0.104	1.643

Table no 2: Association of Thyroid Hormones with Albumin-Globulin Ratio

Thyroid Hormones	Albumin-Globulin Ratio (Mean ± SD)		p value	Unpaired t test
	≤ 1	> 1		
Free T3 (pmol/l)	2.68±1.03	3.59±1.93	0.007	-2.775
Free T4 (ng/l)	1.25±0.62	1.60±0.72	0.014	-2.520
TSH (mIU/l)	3.16±1.95	3.40±1.71	0.518	-0.649

Figure1: Study Population Flow Diagram



Our study showed (Table 2) highly significant ($p<0.007$) correlation between decreased A/G ratio with low FT3. FT4 was normal but there was a significant ($p<0.01$) correlation between FT4 value and decreased A/G ratio. There was no significant relation between the A/G ratio and TSH. it was probably due to low circulating plasma proteins.

LIMITATIONS:

1. Measurement of thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA) was not done. As extreme changes in TBG and TBPA concentrations can potentially affect some FT4 assays **[23]**
2. The lack of subgroup analysis of the study was also a drawback.

CONCLUSION

1. Concentration of FT3, FT4, decreased as the severity of malnutrition increases (SAM< MAM). The altered thyroid hormone status in PEM is to tide over excessive metabolic stimulation and energy consumption and protects the malnourished child with low calorie reserve from an early death.
2. Concentration of TSH may not decrease probably because of negative feedback inhibition of secretion of TSH at pituitary.
3. The reduction in protein is due to decreased intake of proteins and reduced biosynthesis.
4. Future studies with a larger sample size and in multiple centres are warranted to validate the study findings. With consideration of TBG and TBPA concentration are also encouraged. It is also important to bear in mind whether total (TT4, TT3) or free (FT4, FT3) Thyroid Hormone are measured, as changes in circulating binding proteins can seriously confound interpretation of TT4 and TT3 concentrations.

REFERENCES

1. Grover, Z.; Ee, L.C. Protein energy malnutrition. Pediatr. Clin. N. Am. 2009, 56, 1055–1068. [CrossRef]
2. Koletzko, B. Pediatric Nutrition in Practice;World Review Nutrition Dietetics: Basel, Karger, 2015; Volume 113,pp. 139–146. [CrossRef]
3. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–51.
4. Ahmed T, Hossain M, Mahfuz M, et al. Severe acute malnutrition in Asia. Food Nutr Bull 2014;35:S14–26.
5. Briend A, Collins S, Golden M, et al. The burden of severe acute malnutrition estimated in the Lancet series is a minimum rather than an actual estimate. Lancet 2013;382:1549.
6. International Institute for Population Sciences. National family health survey 3 (NFHS-3), 2005-06: India. Mumbai, India: International Institute for Population Sciences; 2006.
7. Barrett KE, Barman SM, Boitano S, Brooks HL. The thyroid gland. In: Ganong's review of Medical Physiology. 23rd ed. New York: McGraw-Hill; 2010: 301-14.
8. Brown PI, Brasel JA. Endocrine changes in the malnourished child. In: Suskind RM, Suskind LL, editors. Nestle nutritional workshop series. Vol. 19. New York:Raven Press; 1990:213-28.
9. Pamela I. Brown and Jo Anne Brasel. Endocrine Changes in the Malnourished Child, Nestle Nutrition Workshop Series. Nestec Ltd. Vevey/Raven Press, Ltd. New York. 1990; Vol.19: 213-222.
10. Alcoba G, Kerac M, Breysse S, Galetto-Lacour C, Salpeteur A., and others. 2013. "Do Children with Uncomplicated Severe Acute Malnutrition Need Antibiotics? A Systematic Review and Meta-Analysis." PLoS One 8 (1): E53184. [PMC free article] [PubMed]
11. Annan R A, Webb P, Brown R. 2014. "Management of Moderate Acute Malnutrition: Current Knowledge and Practice." CMAM Forum Technical Brief. http://www.cmamforum.org/Pool/Resources/MAM-management-CMAM-Forum-Technical-Brief-Sept-2014.pdf.
12. Gurdeep S. Dhanjal, Mrigind Singh. Thyroid hormone status in children with protein energy malnutrition a hospital based case control study. Int J Contemp Pediatr. 2017 Mar;4(2):351-355.
13. Shaheen B, Haji IM, Suma MN. Serum FT3, FT4, TSH and proteins in children with protein energy malnutrition. Int J Pharm Bio Sci. 2013;4(3):834-9.
14. Shahjadi S. Serum T3 and TSH level in severe PEM. J Dhaka Med Coll. 2011;20(2):174-7.
15. Sandeep M., Krishnamurthy B. Thyroid hormone status in children with protein energy malnutrition. Int J Contemp Pediatr. 2016 Feb;3(1):193-199.
16. Abrol P, Verma A, Hooda HS. Thyroid hormone status in protein energy malnutrition in Indian children. Indian J Clinical Biochemistry. 2001;16(2):221-3.
17. Turkay S, Kus S, Gokalp A, Baskin E, Onal A. Effects of protein energy malnutrition on circulating thyroid hormones. Indian Pediatr. 1995;32(2):193-7.
18. Orbak Z, Akin Y, Varoglu E, Tan H. Serum thyroid hormone and thyroid gland weight measurements in protein-energy malnutrition. J Pediatr Endocrinol Metab. 1998;11(6):719-24.
19. Kumar S, Nadkarni J, Dwivedi R. Thyroid hormone status in malnourished children. Indian Pediatr. 2009;46(3):263-4.
20. Adegbusi H, Sule MS. Anthropometric and biochemical assessment among under five children in Kusada local government area, Katsina state, Nigeria. Bajopas. 2011;4(2):137-40.
21. Sah SP et al. Effect of PEM on thyroid status, serum total protein and A/G ratio in pre-school going children. Int J Res Med Sci. 2017 Oct;5(10):4486-4489.
22. Rahman MA, Mannan MA, Rahman MH. Serum iron and total iron binding capacity in severely malnourished children. Bangladesh J Pharmacol. 2007; 2:61-5.
23. O. Koulouri et al. / Best Practice & Research Clinical Endocrinology & Metabolism 27 (2013) 745–762.

ABBREVIATIONS

1. MUAC - mid upper arm circumference
2. TH - Thyroid hormone
3. PEM - protein energy malnutrition
4. T3 – triiodothyronine
5. T4 – thyroxine
6. FT3– free T3
7. FT4– free T4
8. SAM – severe acute malnutrition
9. MAM – moderate acute malnutrition
10. TSH – Thyroid stimulating hormone
11. A/G ratio – Albumin & Globulin