

## Thyroid Function in Childhood Nephrotic Syndrome

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DOI: 10.36347/sjams.2019.v07i09.045

| Received: 13.09.2019 | Accepted: 21.09.2019 | Published: 30.09.2019

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### Abstract

### Original Research Article

Children with Nephrotic syndrome while in nephrosis commonly have a state of mild or subclinical hypothyroidism although they are clinically euthyroid. Loss of thyroxine (T4) and thyroxine binding Globulin (TBG) leads to decrease in total T4 and increase in TSH. A prospective observational study was conducted in children with Nephrotic syndrome over a period of 18 months from January 2013 to June 2014. Objective: To compare the thyroid function of Nephrotic children during nephrosis with that in remission and with healthy controls. Methods: 40 Nephrotic Children between 3-12 years of age in initial episode or in relapse were enrolled in this study. Their thyroid function (Serum FT4, TSH and Thyroglobulin) during nephrosis and while in remission was compared with age-matched healthy controls. Results: Mean age of study population was 83.8 +/- 34.21 months compared to 83.18 +/- 36.6 months in controls. Male: Female ratio was 1.8:1. Mean value of serum FT4 in children during nephrosis was 1.17±0.24 µg/ml and was comparable to the control population (1.16±0.14 µg/ml). Serum TSH in nephrosis was higher than controls {Median (range): 3.08 (90.61-20.00) Vs 1.75 (0.12-6.36) MIU/L, P-0.008}. Serum Thyroglobulin was significantly higher in Nephrotic children in comparison to controls (Median (range): 86.56 (5.34-206.50) Vs 17.18 ng/ml (1.36-134.2), P - 0.001}. Comparison of thyroid status (Serum FT4, TSH and Thyroglobulin) during nephrosis and while in remission showed no significant difference in FT4 but TSH was significantly high in nephrosis as compared to in remission {Median (range): 3.08 (0.61-20) Vs 1.65 (0.45-6.08) MIU/L, P - 0.001}. Thyroglobulin is significantly elevated during nephrosis and it became normal in remission (Median (range): 86.56 ng/ml (5.34-206.50) Vs 39.87 ng/ml (1.32-212.0) P 0.002}. Thyroglobulin showed significant negative correlation with serum albumin (P-0.03) and positive correlation with protein excretion. High thyroglobulin suggests normal response of thyroid gland to TSH. Clinical hypothyroidism was observed in none of the subjects. Our findings confirm the impact of urinary loss of protein on thyroid gland in Nephrosis and this is the first study assessing thyroglobulin in childhood Nephrosis.

**Keywords:** Thyroid function, Nephrotic Syndrome, Free Thyroxine (FT4), Thyroglobulin, TSH, Hypothyroidism.

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## INTRODUCTION

Nephrotic syndrome results in urinary loss of intermediate sized plasma proteins (40– 200 kDa). Massive proteinuria with losses of various thyroid hormone binding proteins, such as thyroxine-binding globulin (TBG), transthyretin and albumin, may result in a reduction of hormone levels and feedback elevation of thyroid-stimulating hormone (TSH) [1]. Several studies have found a correlation between proteinuria

and serum TSH and urinary T4 levels [2-4]. However, the clinical significance of these thyroid hormone variations is not clear. Thyroid possibly compensates for the loss by increasing the free fraction of the hormones, thus maintaining euthyroid state. However, if the free fraction is increased secondary to loss of bound thyroid hormones in urine we expect feedback suppression and lower levels of TSH in Nephrosis. However TSH levels were found to be high in

Nephrotic syndrome and the increase in TSH correlates well with the degree of proteinuria.

Although total T4 and T3 may be low secondary to urine loss of thyroxine-binding globulin, serum levels of free thyroxine (FT4) and freeT3 (FT3) are usually normal, so Nephrotic individuals are considered to be metabolically euthyroid [5]. However, patients with low thyroid reserve may develop hypothyroidism consequent to this urinary loss [6, 7]. Primary hypothyroidism has been described in congenital nephrotic syndrome, with urinary loss of thyroid hormones resulting in increased TSH level *in utero* [8-10]. This suggests the possibility that significant amounts of thyroid hormones are also lost in proteinuric states resulting in a total body negative balance. Considering the role of thyroid hormone on growth and metabolism in children and the impact of hypothyroidism on cardiovascular, CNS and musculoskeletal system in health and disease, it is prudent to assess the thyroid status in Nephrosis [5].

Thyroglobulin (TG) is a 660 kDa dimeric protein produced by the follicular cells of the thyroid. It is a storage form of T3 and T4 in the colloid. Its level increases upon stimulation of thyroid gland by TSH. Upon TSH stimulation, the colloid re-enters the cell within minutes and T3 and T4 are discharged from the basal portion of the cell. Thyroglobulin is primarily used as a tumour marker to evaluate the effectiveness of treatment and relapse in differentiated thyroid cancer. However Serum thyroglobulin levels also reflect the response of thyroid gland to TSH in Nephrosis. In this study, we examined whether thyroid function was impaired in children with nephrotic syndrome compared with the same patients in remission and age matched controls, by measuring serum concentrations of FT4, TSH and thyroglobulin.

## MATERIAL AND METHODS

A hospital based prospective observational study was conducted after obtaining hospital ethics committee clearance in children with Nephrotic syndrome between 3 to 12 years. Children with primary Nephrotic Syndrome who satisfy the following inclusion criteria, i.e. either first episode or relapse as evidenced by oedema, urine protein to creatinine ratio more than 2.0 glomerular filtration rate (GFR) more than 60 ml/minute by modified Schwartz formula and with no history or clinical evidence of other chronic illness, diabetes mellitus, hypothalamic, pituitary or thyroid disease and not receiving thyroid hormone supplements or any medication known to cause thyroid impairment were enrolled after obtaining written informed consent from parents and assent for children over 7 years.

After detailed history and physical examination including growth assessment by WHO standards, fasting venous blood samples were obtained

under aseptic precautions for thyroid function studies. Relevant investigations including urinalysis, spot urinary protein creatinine ratio, renal function test, serum total protein and albumin were done. Creatinine clearance was obtained by modified Schwartz formula. FT4 and TSH were estimated by chemiluminescence micro particle immunoassay method and serum thyroglobulin by electro chemiluminescence. Data was entered on a pre prepared performa. Children were treated as per the standard guidelines. 12 weeks after attaining remission, blood investigations were repeated. Age and sex matched control group of healthy children were selected from the immunization clinic after thorough history, physical examination, growth and anthropometric assessment. All biochemical parameters were done in the control group also. Serum FT4, TSH, Thyroglobulin values were compared between the cases and controls and between cases before and after achieving remission. Correlation of Serum Albumin and urine protein creatinine ratio with TSH, FT4 and thyroglobulin profile were ascertained.

The data were processed using PASW statistics 18. Continuous variables were indicated by mean  $\pm$  standard deviation and median (range) as applicable and categorical variables were mentioned as percentages. Mean values for Continuous variables in nephrotic children and controls were analysed using independent t-test and Mann-Whitney U test. Paired t-test and Wilcoxon signed rank test were used to compare continuous variables in nephrotic children at recruitment and at 12 weeks after remission. Correlation between two independent variables was estimated using Pearson's correlation coefficient (r). P value less than <0.05 were considered statistically significant.

## RESULTS

40 children with Nephrotic syndrome from January 2013 to June 2014 were recruited based on the inclusion and exclusion criteria. 40 age and sex matched healthy controls were also taken. The demographic profile and general characteristics of the study population is shown in Table-1. There were 26 boys and 14 girls in the study group. Male: Female ratio was 1.8:1. Mean age was 83.8 $\pm$ 34.3 months as compared to the control population which was 83.18  $\pm$  36.6 months.

87.5% (35) children were steroid sensitive while 12.5% (5) were steroid resistant. Out of the 5 steroid resistant children 3 had FSGS and 2 minimal lesion on renal histology. 52.5% (21) were frequent relapsing or steroid dependent. 27.5% (11) infrequent relapsers and 7.5% (3) had first episode. 32% (14) of Nephrotic children had stunting compared to 10% (4) in the control group and this difference was statistically significant (P=0.0001). All children were clinically euthyroid.

Thyroid profile of 40 children in Nephrosis was compared with controls as shown in Table-2. Serum FT4 in children during nephrosis was comparable to the control group (1.17±0.24 µg/ml vs 1.16±0.14 µg/ml). There was no significant difference between the two groups. Serum TSH in nephrosis was higher than controls {Median (range):3.08 (90.61-20.00) Vs 1.75 (0.12-6.36) MIU/L, P-0.008} and Serum Thyroglobulin was significantly higher in Nephrotic children in comparison to controls (Median (range):86.56 ng/ml (5.34-206.50) Vs 17.18 ng/ml (1.36-134.2), P 0.001}.

Comparison of Thyroid profile during nephrosis and 12 weeks after achieving remission are shown in Table-3. Serum FT4 level during nephrosis and during remission were within normal limits and there was no statistically significant difference (1.17± 0.24 µg/ml Vs 1.08±0.42 µg/ml). Serum TSH was significantly higher in Nephrosis as compared to that in remission {Median (range):3.08 (0.61-20) Vs 1.65 (0.45-6.08) MIU/L, P 0.001}. Thyroglobulin is significantly elevated during nephrosis and it became normal after achieving remission {Median (range):86.56 ng/ml (5.34-206.50) Vs 39.87 ng/ml (1.32-212.0), P 0.002}. Serum thyroglobulin showed

significant negative correlation with serum albumin (p 0.03) and positive correlation with protein excretion.

There were 5 children with SRNS. We found no significant difference in mean values of FT4 (1.14+/- 0.382 vs 1.39+/-0.679. P-0.22) or TSH (3.78 +/- 3.64 VS 2.48 +/- 1.09 P - 0.44) between steroid sensitive and steroid resistant children during proteinuric phase. Serum Thyroglobulin was high in all these children irrespective of steroid responsiveness.

In our study, serum thyroglobulin showed significant negative correlation with serum albumin in Nephrosis (P- 0.03) (See Figure-1).

Table-4 shows correlation between serum albumin and serum TSH, FT4, TG in the study population and controls. There was significant negative correlation between serum albumin and thyroglobulin. The negative correlation between serum albumin and serum TSH in Nephrosis was insignificant. Positive correlation between serum albumin and serum FT4 was also insignificant. There was no statistically significant correlation between degree of proteinuria and serum free T4, TSH and thyroglobulin.

**Table-1: Characteristics of study population in comparison with controls**

Parameter	Nephrotic children (Mean ± SD)	Controls (Mean ± SD)
Age (months)	83.8+/-34.3	83.18+/-36.6
Urine PC Ratio	6.27+/-4.95	0.02+/-0.04
Serum Albumin(gm/dl)	2.38+/-0.88	4.0+/-0.49
Serum Creatinine (mg/dl)	0.55+/-0.15	0.48+/-0.16
GFR(ml/mt)	91.36+/-25.43	93+/-18.53
S. Cholesterol (mg/dl)	495+/-189	126.23+/-16.83

**Table-2: Comparison of Thyroid profile in children with Nephrotic syndrome and controls**

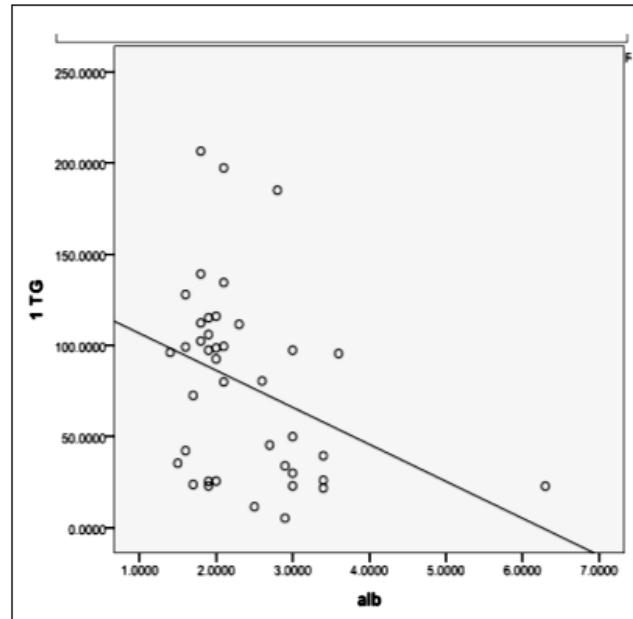
Parameter	Nephrotic Children	Control	P Value
FT4(µg/ml) Mean±SD	1.17±0.42	1.16±0.14	0.886
TSH(MIU/L) Median (Range)	3.08 (0.61-20)	1.65 (0.45-6.08)	0.008
Thyroglobulin(ng/ml) Median ( Range)	86.56 (5.34-206.50)	17.18 (1.36-134.2)	0.001

**Table-3: Comparison of Thyroid Profile in Nephrosis and in Remission (n=40)**

Parameter	Nephrosis	Remission	P Value
FT4(µg/ml) Mean ± SD	1.17±0.42	1.08±0.24	0.252
TSH(MIU/L) Median (Range)	3.08 (0.61-20)	2.03 (0.54-9.04)	0.001
Thyroglobulin(ng/ml) Median (Range)	86.56 (5.34-206.50)	39.87 (1.32-212.00)	0.002

**Table-4: Correlation between serum Albumin and serum free T4, TSH and thyroglobulin**

Parameter	Nephrotic Children		Controls	
	Pearson Correlation coefficient	P value	Pearson Correlation coefficient	P value
TSH	-.243	.131	.196	.226
FT4	.216	.181	.070	.668
Thyroglobulin	-.344	.030	-.001	.998



**Fig-1: Correlation of Thyroglobulin and serum albumin: Significant Negative correlation between serum Albumin and Thyroglobulin (P=0.030) in Nephrotic Syndrome (N=40)**

## DISCUSSION

Thyroid hormones, thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>) play important roles in the maturation and development of the skeleton. They affect endochondral calcification and the entire process of cartilage growth [11]. They also play a very important role in renal development, kidney structure, renal hemodynamic status and glomerular filtration rate (GFR) [5]. They are necessary for the maintenance of water and electrolyte homeostasis and function of many transport systems along the nephron [12].

Thyroid kidney interaction in Nephrotic syndrome is complex. Nephrotic syndrome results in urinary loss of intermediate sized plasma proteins (40–200 kDa) including thyroid hormone binding proteins such as thyroxine binding globulin (TBG), transthyretin and albumin leading to reduction in thyroid hormones [5]. The free fraction (FT<sub>3</sub> and FT<sub>4</sub>) constitutes only 0.3% of Triiodothyronine (T<sub>3</sub>) and 0.02% of tetraiodothyronine (T<sub>4</sub>) [6]. Urinary losses of thyroxine binding globulin (TBG), other thyroid hormone binding proteins and T<sub>4</sub> bound to them result in a low total T<sub>4</sub> concentrations in approximately 50 percent of nephrotic patients with a relatively normal glomerular filtration rate (GFR) [1]. Urinary losses of thyroid hormones in patients with proteinuria increase TSH concentrations by triggering stimulation of the hypothalamus–pituitary–thyroid axis. If thyroid gland is able to compensate for urinary hormone losses, euthyroid state is maintained.

We studied thyroid status in Nephrotic children in comparison with healthy controls and the same subjects 12 weeks after achieving remission. All children were clinically euthyroid. We found no

significant difference in Serum FT<sub>4</sub> between children in nephrosis and the control group. Serum TSH in Nephrotic children was significantly higher than controls. The increase in serum TSH in Nephrotic syndrome may be attributed to negative feedback from marked urinary loss of TBG [2]. Gilles R *et al.*, reported normal total T<sub>3</sub> and T<sub>4</sub> but significantly higher TSH in patients with proteinuria, but the clinical importance of this finding is very limited because just one percent had overt hypothyroidism.

Our data showed significantly elevated serum thyroglobulin in Nephrotic children in comparison to the controls. Thyroglobulin increases when more thyroxine is released from thyroid gland in response to TSH. Hence, elevated thyroglobulin level in nephrosis indicates a good response of thyroid gland to TSH stimulation. To our knowledge, this is the first study assessing thyroglobulin levels in nephrotic children. Comparison of Thyroid profile during nephrosis and 12 weeks after achieving remission revealed no statistically significant difference between FT<sub>4</sub> but TSH was significantly higher in Nephrosis as compared to in remission. Vidhi Sahni *et al.*, also reported that most children with NS were clinically euthyroid with increased TSH level during nephrosis while serum T<sub>3</sub> and T<sub>4</sub> were within normal range. Serum TSH level became normal after achieving remission [3]. Afroz *et al.*, also reported significant increase in TSH level during nephrosis which normalized during remission. No significant difference between T<sub>3</sub> and T<sub>4</sub> level was observed. They suggested that children with nephrotic syndrome commonly have a state of mild or subclinical hypothyroidism during proteinuria [13]. Ito S *et al.*, have found that the mean serum free T<sub>4</sub> and free T<sub>3</sub> concentrations were significantly lower in the untreated Nephrotic than in the same patients in remission, and

the mean serum TSH levels were significantly higher in the untreated patients [4].

Amit Dagan *et al.*, reported thyroid profile of four children with steroid-sensitive nephrotic syndrome (SSNS). TSH level at disease onset ranged from 10 to 20 mIU/L and FT4, from 9 to 7 pmol/L (mildly low). Values normalized 1–2 weeks after disease remission. They also showed that the serum level of TSH in steroid-resistant nephrotic syndrome (SRNS) ranged from 5 to 10 mIU/L, which is lower than expected in patients with hypothyroidism and also lower than in the patients with new-onset SSNS. This finding may be due to the urine loss of TSH, a low-molecular-weight protein (LMWP). SRNS is associated with a greater loss of LMWP than SSNS [14]. In our series there were 5 children with SRNS. We found no significant difference in mean values of FT4 between steroid sensitive and steroid resistant children. Kapoor *et al.* studied thyroid profile in 20 children aged 1-16 years with SRNS and similar number of controls. They found an overt hypothyroidism with low FT4 (normal values: 0.7–2.0 ng/mL) and elevated serum TSH above reference values (0.45–4.5 mIU/L) [15].

R. Gilles *et al.*, Ito S *et al.*, and Afroz *et al.*, reported negative correlation of TSH with serum albumin 2, 4, and 13. Guo *et al.*, reported that serum albumin levels correlated with free and total T3 and T4 concentrations, but negatively correlated with TSH. Proteinuria correlated with TT3, TT4 and FT4 levels, but not FT3 or TSH in their study. The correlation between serum albumin and thyroid function was stronger than for proteinuria [16]. However in our study correlation of serum albumin with serum TSH was statistically not significant possibly due to small sample size. Our data showed significant negative correlation of serum thyroglobulin with serum albumin in Nephrosis (p value 0.03).

Several studies have found a correlation between proteinuria and serum TSH and urinary T4 levels. Ito S *et al.* found significant positive correlation of daily urinary protein excretion with urinary excretion of T3, T4 and TBG. These findings provide evidence of mild hypothyroidism in children with untreated Nephrotic syndrome because of losses of T4, T3, free T4, free T3 and TBG into the urine<sup>3</sup>. In our study the urinary levels of thyroid hormones were not assessed. We found positive correlation Serum TSH with urinary protein creatinine ratio, but statistically not significant possibly due to small sample size.

#### Strength and Limitation of the Study

Being a prospective study on thyroid function in Nephrotic children, with follow up of the thyroid status in remission, the observations from this study underscores the fact that there is no need for thyroid supplementation in childhood nephrotic syndrome as these children have a normal FT4 during nephrosis. The

small sample size is the limitation and more studies are required before making definitive conclusions on thyroid hormone replacement therapy, in addition to glucocorticoids in children with nephrotic syndrome.

## CONCLUSION

Nephrotic syndrome results in urinary loss of various thyroid hormone binding proteins, such as thyroxine-binding globulin (TBG), transthyretin and albumin. This causes a reduction of hormone levels. Thyroid possibly compensates for the loss by increasing the free fraction of the hormones and by feedback elevation of thyroid-stimulating hormone (TSH), thus maintaining euthyroid state

In summary, this study provides evidence of euthyroid status in all Nephrotic children in comparison with the same patients in remission and age-matched healthy controls. Thyroid gland response in Nephrosis was normal as evidenced by the increase in serum TSH, thyroglobulin and normal levels of FT4. Rise in TSH and thyroglobulin were spontaneously corrected once remission was achieved. Being clinically euthyroid, none of the children in our study needed thyroxine supplements.

**Source of Support:** SAT Hospital Health Education Society in the form of grant (SAT Endowment Project)

**Funding:** The study was conducted with funds received as part of SAT Hospital endowment project

**Acknowledgement:** SAT Hospital Health Education Society for the grant as part of SAT Endowment Project.

**Conflict of interest:** None.

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

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