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ORIGINAL ARTICLE

Observational Study

# Evaluation of thyroid profile among children aged 1-15 years with nephrotic syndrome: An observation study

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## Abstract

### *BACKGROUND*

The interaction between the kidney and the thyroid is important for normal function of both organs. In nephrotic syndrome, proteinuria leads to loss of several proteins, which in turn causes hypothyroidism.

### *AIM*

To assess the thyroid function in children with nephrotic syndrome.

### *METHODS*

This cross-sectional study was conducted in a tertiary center, Bhopal, from February 2020 to January 2021. Consecutive children aged 1-15 years admitted with nephrotic syndrome (first-time diagnosed and all relapse cases) were included in the study. A thyroid profile was sent along with routine investigations, and thyroid hormone status was assessed in nephrotic syndrome children.

### *RESULTS*

Of the 70 patients, 39 (55.7%) showed abnormal thyroid profiles; 19 (27.1%) had overt hypothyroidism, and 20 (28.6%) had subclinical hypothyroidism. Overt hypothyroidism was seen in 16.1% of newly diagnosed cases, 40% of second relapses, and 2.7% of frequently relapsed cases ($P < 0.001$). The mean serum free T3 and free T4 levels in frequent relapses were 2.50 ± 0.39 ng/dL and 0.78 ± 0.12 ng/dL, respectively, which were significantly lower than in newly diagnosed cases (2.77 ± 0.37 ng/dL and 0.91 ± 0.19 ng/dL, respectively). The mean thyroid-stimulating hormone (TSH) level was significantly higher in frequent relapses 5.86 ± 1.56 μIU/mL) and second relapse (5.81 ± 1.78 μIU/mL) than in newly diagnosed cases (4.83 ± 0.76 μIU/mL) and first relapse cases (4.74 ± 1.17 μIU/mL), ($P < 0.01$).

*CONCLUSION*
An abnormal thyroid profile was commonly observed in children with nephrotic syndrome, and overt hypothyroidism was more common in frequent relapse cases. Therefore, thyroid screening should be a part of the management of nephrotic syndrome so that hypothyroidism can be detected and managed at an early stage.

**Key Words:** Nephrotic syndrome; Hypothyroidism; Proteinuria; Children; Steroid-sensitive nephrotic syndrome; Steroid-resistant nephrotic syndrome



**Core Tip:** In nephrotic syndrome, proteinuria leads to loss of several proteins, which may lead to hypothyroidism. This cross-sectional study was conducted to assess the thyroid function in children with nephrotic syndrome aged 1-15 years. Of the 70 patients, 39 (55.7%) showed abnormal thyroid profiles, 19 (27.1%) had overt hypothyroidism, and 20 (28.6%) had subclinical hypothyroidism. Overt hypothyroidism was seen in 16.1% of newly diagnosed, 40% of second relapses, and 2.7% of frequently relapsed cases ($P < 0.001$). An abnormal thyroid profile was commonly observed in children with nephrotic syndrome, with overt hypothyroidism being more common in frequent relapse cases.

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## INTRODUCTION

Nephrotic syndrome is a glomerular disorder characterized by proteinuria greater than 40 mg/m$^2$/h, a low level of serum albumin (less than 2.5 g/dL), edema, and hypercholesterolemia (serum total cholesterol level greater than 250 mg/dL) [1]. The main proteins to which thyroid hormones bind in the bloodstream are thyroxine-binding globulin (TBG), prealbumin, and albumin. Urinary loss of hormone-binding proteins like transthyretin and TBG, as well as intermediate-sized plasma proteins (size 40–200 kDa) increases the excretion of thyroid-stimulating hormone (TSH) by lowering total T4, which, in turn, causes hypothyroidism[2-4]. In children and adolescents, hypothyroidism may lead to lethargy, weight gain, loss of concentration, and constipation; additionally, it may cause physical and mental retardation in children less than 2 years of age, if left untreated[5].

The thyroid function of children with nephrotic syndrome has been examined in earlier studies[6-8], which revealed a variable incidence of hypothyroidism. The prevalence of nephrotic syndrome in India is estimated to range from 12-16 per 100000, and the annual impact in children ranges from 2-7 per 100000[9]. Compared to Western countries, where the incidence is reported to be 2–3/100000 children, the incidence and prevalence in India are slightly higher (9–10/100000 and 12–16/100000 children, respectively)[7].

Since there were no studies of this kind in central India, we conducted the present study to explore more about this association. Hence, this study aimed to assess thyroid function among patients with nephrotic syndrome aged 1-15 years admitted to a tertiary center in Bhopal from February 2020 to January 2021.

## MATERIALS AND METHODS

A cross-sectional observational study was conducted at an academic tertiary care hospital from 1 February 2020 to 31 January 2021 after obtaining approval from the institutional ethical committee.

All new and relapse cases of nephrotic syndrome, aged 1 month to 15 years, who were consecutively admitted to our hospital, were included in the study. Nephrotic syndrome among children was diagnosed as per the International Study of Kidney Disease in Children guidelines: nephrotic range proteinuria with spot urine polymerase chain reaction of > -2, hypoalbuminemia < 2.5 g/dL, hyperlipidemia (serum cholesterol > 200 mg/dL), and edema[10]. Children whose records were not complete and were diagnosed with other renal or systemic diseases causing proteinuria, any known thyroid disorder, or any anti-thyroid/ thyroxine drugs, were excluded from the study.

A detailed clinical history was taken after obtaining informed consent from the parent/legal guardian and a thorough clinical examination was done. Venipuncture was performed after taking proper aseptic precautions, and a morning fasting sample of thyroid profile was taken, along with routine blood tests like complete blood count, liver function test, renal function test, and lipid profile. If there was a delay in the processing of the sample, the sample was stored at 4 °C. The serum levels of free T3, free T4, and TSH were measured with the immunoassay method. A fresh mid-catch morning urine sample was collected in a sterile container for routine microscopic examination.

The diagnosis of nephrotic syndrome requires the presence of edema, massive proteinuria (> 40 mg/m$^2$/h), hypoalbuminemia (< 2.5 mg/dL), and hyperlipidemia. Corticosteroids are the mainstay of therapy in nephrotic syndrome. Children with a first episode of nephrotic syndrome are likely to have steroid-responsive minimal-change nephrotic syndrome. The Kidney Disease Improving Global Outcome has provided definitions regarding responses to steroid therapy. Response is defined as an attainment of remission within the initial 4 week of corticosteroid therapy. Remission is a urine protein:creatinine ratio of < 0.2 or < 1 + protein on dipstick testing for 3 consecutive days. Relapse is an increase in the first-morning urine protein:creatinine ratio > 0.2 or 2 + or higher on dipstick testing for 3 consecutive days. Frequently relapsing is two or more relapses within 6 months after initial therapy or four relapses in 12 months. Steroid dependence is a relapse during steroid tapering or a relapse within 2 week of discontinuation of therapy. Steroid resistance is the inability to induce remission within 4 week of steroid therapy. All parameters were reviewed for evaluation of the study.

### *Statistical analysis*

All parameters were recorded in a pretested proforma and were reviewed for evaluation of data. Demographic variables were reported as counts and percentages. The statistical tests used were the $\chi^2$ test for analysis of thyroid status in nephrotic syndrome children according to relapse and association of thyroid status with sex, and steroid dependency. An analysis of variance (ANOVA) was used to compare biochemical parameters in nephrotic syndrome cases and compared among newly diagnosed cases and frequent relapse cases. A $P$ value of < 0.05 was considered statistically significant in the analysis. SPSS software version 25 (IBM Corp., Armonk, NY, United States) was used for analysis of the data.

## RESULTS

The study was conducted among 70 subjects, of which 58.6% were males. Out of 70 children, 55.7% children had hypothyroidism. Among 39 hypothyroid children, 20 (28.6%) had subclinical hypothyroidism, and 19 (27.1%) had overt hypothyroidism. Most children in our study (47.1%) belonged to the age group of 1-5 years. The demographic profile of the study is presented in Table 1.

Nephrotic syndrome cases were classified based on the occurrence and relapses, and most of the participants (31, 44.3%) belonged to newly diagnosed cases. Children were also classified based on steroid responsiveness, of which 56 (80%) children were steroid responsive. Overt hypothyroidism was seen in 16.1% of cases of newly diagnosed children, and 40% in second relapse cases; this was significantly higher (72.7%) in frequent relapse cases ($P$ < 0.001).

The mean TSH level of study subjects was 5.19 ± 1.32 μIU/mL. Similarly, free T4 levels were significantly decreased in patients with frequent relapse (0.78 ± 0.12 ng/dL) compared to newly diagnosed cases (0.91 ± 0.19 ng/dL) and first relapse cases (0.95 ± 0.11 ng/dL) (Table 2). Other biochemical parameters like glomerular filtration rate (GFR) were lower (59.90 ± 12.10) in frequent relapse cases compared to newly diagnosed cases (69.61 ± 17.79; $P$ < 0.01). We found a positive correlation of serum albumin with free T4 ($r$ = 0.322, $P$ = 0.007). Similarly, serum protein was positively correlated with free T4 ($r$ = 0.369, $P$ = 0.002) (Table 3). There was no significant correlation between serum albumin and serum-free T3 levels. The thyroid status of the study subjects was also assessed based on steroid dependency. Eight (57.1%) children among steroid-responsive subjects, and three (50.0%) among steroid-resistant subjects, had overt hypothyroidism (Table 4).

## DISCUSSION

In this observational study, thyroid profiles were estimated in 70 children, out of which 55.7% of children had hypothyroidism. Among these 39 children, subclinical and overt hypothyroidism was noted in 28.6% and 27.1% of the children, respectively. The incidence of abnormal thyroid function among nephrotic syndrome children was like that reported by Singh *et al*[9], who observed elevated TSH levels in 44.51% of nephrotic children. A previous study found a lesser percentage of hypothyroidism (36.3%) among 40 cases of nephrotic syndrome children aged between 1 year to 12 years[11]. Evaluation of thyroid hormone and proper follow-up are essential in nephrotic syndrome children as subclinical hypothyroidism may progress to overt hypothyroidism in 11% of children if appropriate measures are not taken[3].

Most of the children in our study (47.1%) were between the ages of 1 year and 5 years. A similar percentage of hypothyroidism (47.5%) was seen among children of less than 3 years of age in a study by Singh *et al*[9]. We found that nephrotic syndrome and subclinical hypothyroidism were seen more in male children (58.6% and 34.1%, respectively), whereas overt hypothyroidism has equal sex preponderance. Similarly, male preponderance was seen by Hajizadeh *et al* [12] where, out of 104 children with nephrotic syndrome, 41 (67.2%) were males and 20 (32.8%) were females.

In our study, most of the children fell into the category of newly diagnosed cases (44.3%) with a considerably higher mean TSH level among frequent and second relapse cases as compared to newly diagnosed and first relapse cases. Similar findings were reported by Mohamed *et al*[13], who they found that serum levels of free T3 and free T4 were significantly lower, but TSH was higher in relapse patients as compared to remission and control groups. The earlier studies also found a significantly lower concentration of free T4 levels among frequent relapse cases as compared to newly diagnosed cases and first relapse cases[14-16].

**Table 1 Demographic details of the study subjects, *n* = 70**

| Parameters | Number | Percentage |
|---|---|---|
| Age group in years | | |
| 0-1 | 2 | 2.9 |
| > 1 to 5 | 33 | 47.1 |
| 6-10 y | 30 | 42.8 |
| > 10 | 5 | 7.1 |
| Mean age in years | 5.88 ± 3.13 | |
| Sex | | |
| Male | 41 | 58.6 |
| Female | 29 | 41.4 |
| Area of residence | | |
| Rural | 41 | 58.6 |
| Urban | 29 | 41.4 |
| Types of nephrotic syndrome | | |
| Newly diagnosed | 31 | 44.3 |
| 1st relapse | 13 | 18.6 |
| 2nd relapse | 15 | 21.4 |
| Frequent relapse | 11 | 15.7 |
| Thyroid status in study subjects | | |
| Euthyroidism | 31 | 44.3 |
| Subclinical hypothyroidism | 20 | 28.6 |
| Overt hypothyroidism | 19 | 27.1 |
| Response to steroid therapy | | |
| Steroid responsive | 56 | 80 |
| Steroid dependant | 8 | 11.4 |
| Steroid resistant | 6 | 8.6 |

**Table 2 Biochemical parameters in study subjects, *n* = 70**

| Parameter | Newly diagnosed | 1st relapse | 2nd relapse | Frequent relapse | *P* value[1] |
|---|---|---|---|---|---|
| Free T3 | 2.77 ± 0.37 | 2.93 ± 0.16 | 2.57 ± 0.47 | 2.50 ± 0.39 | 0.01 |
| Free T4 | 0.91 ± 0.19 | 0.95 ± 0.11 | 0.84 ± 0.27 | 0.78 ± 0.12 | 0.03 |
| TSH | 4.83 ± 0.76 | 4.74 ± 1.17 | 5.81 ± 1.78 | 5.86 ± 1.56 | < 0.01 |
| GFR | 69.61 ± 17.79 | 69.46 ± 15.20 | 64.52 ± 13.85 | 59.90 ± 12.10 | < 0.01 |
| T. Cholesterol | 398.90 ± 67.25 | 432.0 ± 48.63 | 482.13 ± 48.63 | 476.91 ± 70.74 | 0.10 |
| TG | 411.0 ± 92.72 | 424.62 ± 82.79 | 433.07 ± 138.90 | 500.45 ± 151.38 | 0.27 |
| LDL | 396.64 ± 50.76 | 415.15 ± 53.30 | 416.40 ± 67.30 | 435.82 ± 67.54 | 0.16 |

[1]ANOVA test or Kruskal–Wallis H test was used.
GFR: Thyroid-stimulating hormone; LDL: Low-density lipoprotein; TG: Thyroglobulin; TSH: Glomerular filtration rate.

**Table 3 Correlation of thyroid function tests with serum albumin and protein**

| Variable | | Free T3 | Free T4 | TSH |
|---|---|---|---|---|
| S. albumin | *r* value | 0.036 | 0.322 | -0.165 |
| | *P* value[1] | 0.768 | 0.007 | 0.172 |
| | *n* | 70 | 70 | 70 |
| S. protein | *r* value | 0.187 | 0.369 | -0.227 |
| | *P* value[1] | 0.121 | 0.002 | 0.059 |
| | *n* | 70 | 70 | 70 |

[1]Spearman correlation coefficient was used.
S: Serum; TSH: Glomerular filtration rate.

**Table 4 Association of thyroid status with steroid responsiveness in study subjects, *n* = 70**

| Thyroid status | Steroid responsive | | Steroid resistant | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Euthyroidism | 29 (51.8) | 2 (14.3) | 1 (16.7) | 30(46.9) |
| Subclinical hypothyroidism | 16 (28.6) | 4 (28.6) | 2 (33.3) | 18 (28.1) |
| Overt hypothyroidism | 11 (19.6) | 8 (57.1) | 3 (50.0) | 16 (25.0) |
| *P* value[1] | < 0.01 | | 0.29 | |

Data are *n* (%).
[1]$\chi^2$ test was used.

Nephrotic syndrome is a glomerular disease, where renal damage affects absorption and excretory functions. It results in urinary loss of intermediate-sized plasma proteins and hormone-binding proteins such as TBG, transthyretin, and albumin, leading to a reduction in thyroid hormones causing hypothyroidism. Few studies have found a positive correlation of serum albumin and serum protein with free T4[17,18] which is in line with our study, as we also found a positive correlation of serum albumin ($P = 0.007$) and serum protein ($P = 0.002$) with free T4.

In our study, 11.4% of children were steroid dependent, of which 57.1% were overt hypothyroid and 28.6% were subclinically hypothyroid. A similar study conducted by Marimuthu *et al*[6] concluded that the prevalence of subclinical and overt hypothyroidism was high in idiopathic SRNS, with almost one-third of children having overt hypothyroidism. Since nephrotic syndrome affects the excretory function of the kidneys, GFR is normally lower in frequent relapse cases than in newly diagnosed cases; however, Lo *et al*[18] found no changes in GFR and serum creatinine levels before and after remission among patients with abnormal thyroid function.

The present study has a few strengths and limitations. The way the study participants were categorized based on their thyroid profile, steroid relapse history, and dependence is its strongest point. The main limitations of our study were the small sample size and lack of follow-up of patients. Also, the urine protein creatinine ratio could not be correlated with the thyroid profile.

## CONCLUSION

An abnormal thyroid hormone profile was observed in 55.7% of children with nephrotic syndrome, and a higher incidence of overt hypothyroidism was found in frequently relapsing cases. Therefore, screening of thyroid hormone should be a part of the management of patients with nephrotic syndrome.

## FOOTNOTES

**Author contributions:** Kumari P contributed to acquisition and drafting the article; Shrivastava J contributed to drafting the article; Agrawal A contributed to conceptualization and revising the article critically for important intellectual content; Kumari P and Agrawal A contributed to interpretation of data, data analysis; Kumari P and Shrivastava J contributed to the literature review; All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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**Informed consent statement:** The patients were recruited in the study after obtaining informed consent from the parent/legal guardian.

**Conflict-of-interest statement:** All authors declare that they have no conflicts of interest to disclose.

**Data sharing statement:** The dataset is available upon reasonable request.

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