Original Article

Thyroid Dysfunction in Children Aged 1–8 Years with Nephrotic Syndrome: A Cross-Sectional Hospital-Based Study

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Abstract

Background: Nephrotic syndrome (NS) causes significant urinary loss of thyroid-binding proteins, potentially leading to thyroid dysfunction that may impact growth and neurodevelopment in affected children. Limited data exist regarding routine thyroid function screening in pediatric NS. The objective is to assess thyroid function status in children aged 1–8 years with nephrotic syndrome and to evaluate the correlation between disease activity and thyroid hormone abnormalities. **Material and Methods:** A cross-sectional study enrolled 70 children aged 1–8 years diagnosed with nephrotic syndrome over a period of 18 months. Thyroid function tests (T3, T4, TSH), biochemical parameters, and renal function were assessed. Data were analyzed using descriptive statistics and correlation analysis. **Results:** Among 70 children, 75% exhibited elevated TSH levels, 73% had reduced T4, and 60% had decreased T3 levels. Significant negative correlation was observed between serum albumin and TSH ($r = -0.22$, $p = 0.02$), while positive correlations existed between serum albumin and T3 ($r = 0.3$, $p = 0.01$) and T4 ($r = 0.16$, $p = 0.05$). Mean TSH levels were significantly higher during active disease phases (first episode 6.75±1.4 µIU/mL, relapse 6.36±1.7 µIU/mL) compared to remission (2.83±0.4 µIU/mL; $p = 0.001$). T3 levels showed significant variation across disease phases ($p = 0.002$). Children with steroid-resistant nephrotic syndrome (SRNS) had the highest mean TSH (7.34±1.5 µIU/mL). **Conclusion:** Thyroid dysfunction, particularly subclinical hypothyroidism, is highly prevalent in pediatric nephrotic syndrome, especially during active disease phases. Routine thyroid function screening should be considered as part of comprehensive NS management to detect and treat endocrine complications early.

Keywords: Thyroid dysfunction, nephrotic syndrome, children, subclinical hypothyroidism, TSH.

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Introduction

Nephrotic syndrome (NS) is a common glomerular disorder in pediatric populations, characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and generalized edema.[1,2] The pathophysiology of NS involves increased glomerular permeability due to podocyte injury, leading to excessive loss of plasma proteins in the urine. This loss affects not only albumin but also critical proteins including immunoglobulins, coagulation factors, and thyroid hormone transport proteins such as thyroxine-binding globulin (TBG), transthyretin, and albumin-bound thyroid hormones.[3,4]

While NS predominantly affects the renal system, it has significant systemic consequences through protein loss. The loss of thyroid-binding proteins—TBG, transthyretin, and albumin—which transport thyroid hormones in circulation, can lead to altered thyroid hormone levels despite a normally functioning thyroid gland.[5] This phenomenon necessitates systematic investigation into thyroid hormone alterations in pediatric NS patients, particularly in early childhood when thyroid function is crucial for growth and neurodevelopment.[6]

Thyroid hormones—thyroxine (T4) and triiodothyronine (T3)—play pivotal roles in metabolism, brain development, and overall growth in children.[7] Disruptions in thyroid function, particularly even mild hypothyroidism, can significantly impact cognitive and physical development in young children.[8] Since NS leads to urinary loss of carrier proteins, total T4 and T3 levels are often decreased in affected children, creating diagnostic challenges between total and free hormone level discrepancies.[9]

Epidemiological Context: Nephrotic syndrome is an important public health concern affecting approximately 1–3 per 100,000 children annually worldwide, with prevalence around 16 per 100,000.[10] Most cases are diagnosed between ages 1–8 years, with peak incidence at 2–6 years. This period is crucial for physical and cognitive development, making early diagnosis and management essential for preventing long-term complications.[11] The chronic nature of NS with frequent relapses and prolonged immunosuppressive therapy imposes significant burden on healthcare systems and families,

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particularly in low- and middle-income countries.[12]

Knowledge Gaps: While it is known that NS affects thyroid hormone levels through proteinuria-induced loss of carrier proteins, several critical gaps remain. First, there is no standardized protocol for routine thyroid function screening in pediatric NS patients, leading to variability in clinical practice.[13] Second, limited studies have tracked thyroid function longitudinally, making it unclear whether thyroid dysfunction persists, resolves, or worsens with disease progression. Third, there is no consensus on whether nephrotic children with subclinical hypothyroidism benefit from levothyroxine therapy or if thyroid function normalizes upon disease remission.[14] Fourth, the long-term effects of thyroid hormone alterations on physical growth and neurodevelopment in pediatric NS patients remain underexplored.[15]

This cross-sectional study was conducted to systematically evaluate thyroid function status in children aged 1–8 years with nephrotic syndrome and to investigate the clinical significance of thyroid hormone alterations and their correlation with disease severity and proteinuria status.

Materials and Methods

This is a Cross-sectional observational study conducted at Department of Pediatrics, Gandhi Medical College and Hospital, Secunderabad, Telangana, India during May 2023 to September 2024 (18 months) with the study population being children aged 1–8 years diagnosed with nephrotic syndrome admitted to the pediatric ward.

Inclusion Criteria:

- Children aged 1–8 years
- Clinical diagnosis of nephrotic syndrome
- Written informed consent from parents/guardians

Exclusion Criteria:

- Dysfunction of hypothalamic-pituitary axis
- Pre-existing thyroid disorders or autoimmune diseases
- Chronic infections (Tuberculosis, Hepatitis, Malaria)
- Diabetes mellitus
- Cystic fibrosis
- Malabsorption syndrome or moderate-to-severe protein-energy malnutrition
- Chronic renal or hepatic diseases

Study Procedure: Institutional ethics approval was obtained before study initiation (Rc No. IEC/GMC/2023/08/208 dated 29-04-2023). Written informed consent was secured from parents/guardians of all enrolled children. Detailed demographic data (age, gender, address), clinical history (facial puffiness, decreased urine output, abdominal distension, dysuria), drug history (steroids, antihypertensives, diuretics), and vital signs (BP, heart rate, respiratory rate) were recorded. Abdominal girth was measured.

Systemic examination including cardiovascular, respiratory, central nervous system, and per-abdominal examination was performed. Laboratory investigations included:

- Urinalysis and 24-hour urine protein estimation
- Urine protein-to-creatinine ratio
- Complete blood count
- Renal function tests (blood urea, serum creatinine)
- Serum electrolytes (sodium, potassium)
- Serum protein and serum albumin
- Liver function tests
- Lipid profile
- Thyroid function tests: Total T3, Total T4, TSH (measured using immunoassay)

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using IBM SPSS version 21. Categorical variables were summarized as frequencies and percentages. Continuous data were presented as mean ± standard deviation (SD) or median with interquartile ranges depending on data normality (assessed by Kolmogorov-Smirnov test). Proportions were compared using chi-square test or Fisher's exact test. Correlation analysis (Pearson correlation) was performed between serum albumin and thyroid function parameters. Comparison of thyroid hormones across different NS types was performed using appropriate statistical tests. Significance was set at $p < 0.05$.

Results

Patient Characteristics: Among 70 children enrolled, 42 (60%) were male and 28 (40%) were female. Age distribution showed 34.28% aged 1–3 years, 57.14% aged 4–6 years, and 8.57% aged 7–8 years, with peak involvement in the 4–6 years age group.

Generalized edema involving face, arms, and legs was present in all children (100%). Weight gain was documented in 90% (n = 63), decreased urine output in 71.4% (n = 50), and breathlessness in 57.1% (n = 40) of patients.

Regarding nephrotic syndrome type: 42.8% (n = 30) were in relapse, 25.7% (n = 18) in remission, 21.4% (n = 15) had first episode, 7.1% (n = 5) had steroid-dependent NS, and 2.8% (n = 2) had steroid-resistant NS.

Laboratory Findings: Urinalysis revealed straw-colored urine with acidic pH and normal specific gravity in all participants. Proteinuria was prominent: 65.7% (n = 46) showed 4+ and 34.2% (n = 24) showed 3+ proteinuria. Pus cells 0–5/hpf were present in 82.8% (n = 58).

Complete blood count showed mean hemoglobin of 8.32±0.4 g/dL (mild-to-moderate anemia), mean RBC 4.22±1.6 $\times 10^6/\mu L$, hematocrit 26.5±1.4%, MCV 76.93±5.1 fL (suggesting microcytic anemia), normal TLC 9.14±0.8 $\times 10^3/\mu L$, and normal platelets 237.44±42.8 $\times 10^3/\mu L$.

Biochemical parameters revealed significantly reduced mean total protein of 4.76±0.32 g/dL and mean serum albumin of 2.18±0.44 g/dL, confirming active nephrotic state. Kidney function tests showed mild elevation in blood urea (26.33±7.92 mg/dL) consistent with prerenal azotemia, while serum creatinine (0.56±0.11 mg/dL) remained normal, indicating preserved glomerular filtration. Serum electrolytes were normal: sodium 138.4±0.6 mEq/L and potassium 3.78±0.3 mEq/L.

Thyroid Function Status

Table 1: Thyroid Function Status Among Study Participants (Normal Reference Values: TSH 0.5–5.5 mIU/L, T4 5.5–13.5 µg/dL, T3 2.8–3.0 ng/dL)

Thyroid Parameter	Normal Values	Abnormal Values	Mean ± SD	p-value
T3 (ng/dL)	28 (40%)	42 (60%)	2.6±0.9	0.001*
T4 (µg/dL)	26 (37%)	44 (73%)	4.97±1.65	0.001*
TSH (mIU/L)	17 (24%)	53 (75%)	9.42±3.8	

Analysis revealed statistically significant reductions in T3 (p = 0.001) and T4 levels, with 60% showing decreased T3 and 73% showing decreased T4. Elevated TSH was found in 75% of participants, reflecting compensatory pituitary response to diminished thyroid hormone levels.

Correlation Between Serum Albumin and Thyroid Function

Table 2: Association of lipid profile with type of stroke

Lipid profile	HS (n=20)	IS (n=180)	Total	P value
Total cholesterol(mg/dL)	180(172-192)	204(192-220)	203(189.5-219.75)	0.128*
Triglyceride(mg/dL)	146(136-208)	173(148-214)	172.5(146.5-212.5)	0.348*
VLDL(mg/dL)	29.2(27.2-41.6)	34.6(29.6-42.8)	34.5(29.3-42.5)	0.348*
LDL(mg/dL)	113.2(96.8-121.8)	135.4(128-155.8)	134.3(122.85-155.05)	0.133*
HDL(mg/dL)	36(36-42)	36(30-37)	36(30.5-37)	0.361*

Serum albumin showed significant negative correlation with TSH (r = -0.22, p = 0.02), indicating that lower serum albumin associates with higher TSH. Positive correlations existed between serum albumin and T4 (r = 0.16, p = 0.05) and between serum albumin and T3 (r = 0.3, p = 0.01), demonstrating that higher albumin levels associate with better thyroid hormone levels.

Thyroid Hormones Across Disease Phases

Table 3: Comparison of T3 and T4 Levels Across Disease Types (p = 0.002 for T3, p = 0.23 for T4)

T3 Levels (ng/dL)	First Episode	Relapse	Remission	SDNS	SRNS
Mean ± SD	1.23±0.21	1.26±0.34	1.45±0.61	1.34±0.78	1.22±0.65
T4 Levels (µg/dL)	First Episode	Relapse	Remission	SDNS	SRNS
Mean ± SD	6.74±1.2	6.85±1.5	9.43±1.1	6.27±0.59	7.21±0.96

Mean T3 levels were lowest during first episode (1.23±0.21 ng/dL) and relapse (1.26±0.34 ng/dL), significantly increasing during remission (1.45±0.61 ng/dL; p = 0.002). T4 levels showed a similar pattern (p = 0.23), with lowest values in first episode (6.74±1.2 µg/dL) and highest during remission (9.43±1.1 µg/dL), though the difference was not statistically significant.

TSH Levels Across Disease Phases

Table 4: Comparison of TSH Levels in Different Nephrotic Syndrome Types (* p < 0.05)

Disease Phase/Type	Mean TSH ± SD (mIU/L)	Range	p-value
First episode	6.75±1.4	4.2–10.15	0.001*
Relapse	6.36±1.7	2.21–10.6	
Remission	2.83±0.4	2.27–3.79	
SDNS	6.58±1.1	3.56–8.73	
SRNS	7.34±1.5	5.75–8.22	

Mean TSH was significantly elevated during active disease phases. First episode showed TSH 6.75±1.4 mIU/L, relapse 6.36±1.7 mIU/L, markedly dropping to 2.83±0.4 mIU/L in remission (p = 0.001). SRNS showed the highest TSH (7.34±1.5 mIU/L), followed by first episode (6.75±1.4 mIU/L), suggesting more profound thyroid dysfunction in steroid-resistant disease.

Discussion

This cross-sectional study of 70 children aged 1–8 years with nephrotic syndrome demonstrates a high prevalence of thyroid dysfunction, particularly during active disease phases. The findings highlight an important yet often overlooked endocrine complication of pediatric NS.

Prevalence of Thyroid Dysfunction: The current study found thyroid abnormalities in 75% of children (elevated TSH), 73% (reduced T4), and 60% (reduced T3), aligning with earlier reports highlighting frequent thyroid dysfunction in pediatric NS. Mohamed et al,[16] reported thyroid abnormalities in 65% of pediatric NS cases during relapse with elevated TSH and reduced T3/T4. Aldhafiri et al,[17] observed subclinical or overt hypothyroidism in 40–60% of children with idiopathic NS, particularly during active proteinuria. Omar et al,[18] in a 2024 comparative study, reported subclinical hypothyroidism in 54% of steroid-resistant and 12% of steroid-sensitive NS patients. These findings consistently demonstrate thyroid dysfunction as a frequent complication requiring clinical attention.

Mechanisms of Thyroid Dysfunction in NS: The statistically significant negative correlation between serum albumin and TSH (r = -0.22, p = 0.02) and positive correlations with T3 and T4 provide mechanistic insights. The loss of thyroid-binding proteins (TBG, transthyretin, and albumin-bound thyroid hormones) through proteinuria directly reduces circulating thyroid hormone levels. Although free hormone levels may initially remain normal through compensatory mechanisms,

prolonged proteinuria leads to progressive dysfunction. Kumari et al,[19] demonstrated that TSH levels were significantly elevated in children with moderate-to-severe proteinuria, even when T3 and T4 remained low-normal. This pattern is consistent with the "sick euthyroid syndrome" seen in systemic illness, where TSH elevation represents pituitary compensation for inadequate peripheral thyroid hormone availability.

Disease Activity and Thyroid Dysfunction: A critical finding is the strong association between disease activity and thyroid dysfunction. Mean TSH was significantly higher during active disease phases (first episode 6.75±1.4 mIU/L, relapse 6.36±1.7 mIU/L) compared to remission (2.83±0.4 mIU/L; $p = 0.001$). T3 levels similarly showed significant variation ($p = 0.002$), suggesting that thyroid dysfunction is a dynamic process tied to proteinuria severity. Afroz et al,[20] observed lower T3 levels during acute phases with normalization during remission, supporting the reversible nature of dysfunction. This pattern is further supported by Jung et al,[21] who noted significant correlation between urinary protein-creatinine ratio and serum T3, T4, and free T4 during nephrotic phase, with correlations disappearing after remission.

Steroid-Resistant Nephrotic Syndrome and Thyroid Status: Children with SRNS exhibited the highest mean TSH (7.34±1.5 mIU/L), indicating more profound thyroid dysfunction compared to other NS types. This finding aligns with observations by Sharma et al,[22] who reported higher frequency of subclinical hypothyroidism in SRNS patients compared to steroid-sensitive forms, attributing this to prolonged disease activity and persistent proteinuria. The persistence of proteinuria in SRNS creates sustained loss of thyroid-binding proteins and thyroid hormones, potentially explaining the greater degree of TSH elevation.

Clinical Implications: The study's findings underscore several clinical implications. First, routine thyroid function screening should be considered standard of care in pediatric NS management, particularly during active disease phases. Second, subclinical hypothyroidism, while often asymptomatic biochemically, may have significant effects on growth trajectory and neurodevelopment in young children if left untreated. Third, the reversibility of thyroid dysfunction upon disease remission suggests that thyroid status monitoring should be ongoing throughout the disease course. The high prevalence of thyroid dysfunction in this hospitalized cohort may reflect the study's focus on children with moderate-to-severe disease requiring hospital admission. The predominance of relapsing NS (42.8%) and significant proportion with SDNS/SRNS (9.9%) indicates a cohort with more active or complicated disease. Therefore, findings may not fully represent all children with NS in the community.

Study Strengths and Limitations: The study's strengths include systematic thyroid function assessment using standardized laboratory methods, comprehensive biochemical characterization of NS, and correlation analysis with relevant clinical parameters. However, limitations include single-institution design restricting generalizability, cross-sectional methodology preventing assessment of temporal thyroid function changes, modest sample size potentially limiting statistical power, absence of longitudinal follow-up data, and incomplete adjustment for confounding factors (nutritional status, infection, diuretic/steroid effects). Additionally, the study did not track free thyroid hormone levels or thyroid antibodies, which would provide more complete endocrine assessment.

Conclusion

This study demonstrates that thyroid dysfunction, particularly subclinical hypothyroidism characterized by elevated TSH and reduced T3/T4, is highly prevalent in children aged 1–8 years with nephrotic syndrome, especially during active disease phases including first episode, relapse, and steroid-resistant forms. Significant correlations between serum albumin and thyroid hormone status underscore the mechanism of protein loss-induced thyroid dysfunction.

The reversibility of thyroid abnormalities with disease remission suggests that thyroid dysfunction in nephrotic syndrome is a dynamic process linked to proteinuria severity. These findings support the implementation of routine thyroid function screening as an integral component of comprehensive pediatric NS management to facilitate early detection and timely intervention in preventing growth and neurodevelopmental complications.

Recommendations for Clinical Practice:

1. Routine thyroid function assessment (TSH, free T4, free T3) should be performed at NS diagnosis and during disease monitoring
2. Children with persistent proteinuria or SRNS warrant closer thyroid surveillance
3. Levothyroxine supplementation should be considered for confirmed hypothyroidism, particularly during active disease phases
4. Thyroid function should be reassessed after disease remission to determine if supplementation can be discontinued
5. Growth parameters should be monitored carefully in children with concurrent NS and thyroid dysfunction

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Conflicts of interest

There are no conflicts of interest.

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