

Subclinical hypothyroidism in pediatric nephrotic syndrome: the correlations with albumin, globulin, and proteinuria

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Abstract

Background Nephrotic syndrome causes loss of medium-sized plasma proteins and binding proteins, resulting in thyroid hormone deficiency.

Objective To assess for potential correlations between subclinical hypothyroidism in pediatric nephrotic syndrome with albumin, globulin, and proteinuria.

Methods This cross-sectional study was conducted in the Department of Pediatrics, Hasan Sadikin General Hospital, Bandung, West Java. All types of nephrotic syndrome patients aged 1 month to < 18 years were included. Blood and urine specimens were collected from the patients for albumin, globulin, thyroid function (T3, fT4 and TSH), and proteinuria tests and analyzed with standard techniques.

Results There were 26 subjects, 20 males and 6 females. Ten subjects developed subclinical hypothyroidism, with mean albumin and thyroid-stimulating hormone (TSH) levels of 0.92 g/dL and 6.9 mIU/L, respectively. There was a negative correlation between albumin level and subclinical hypothyroidism ($r_{pb} = -0.702$; $P < 0.001$) and a positive correlation between proteinuria and subclinical hypothyroidism ($r = 0.573$; $P = 0.003$). Univariate logistic regression analysis revealed that globulin had no impact on the presence of subclinical hypothyroidism, but albumin and proteinuria did have such an impact. The odds ratios of albumin and proteinuria with subclinical hypothyroidism were 27.00 (95%CI 1.69 to 17.7) and 19.80 (95%CI 1.94 to 201.63), respectively.

Conclusion Subclinical hypothyroidism correlates with serum albumin level and proteinuria in nephrotic syndrome patients. The low serum albumin level has a high likelihood of subclinical hypothyroidism. [Paediatr Indones. 2020;60:91-6; doi: <http://dx.doi.org/10.14238/pi60.2.2020.91-6>].

Keywords: *nephrotic syndrome; subclinical hypothyroidism; serum albumin; proteinuria*

Nephrotic syndrome can affect children of any age, from infancy to adolescence, but is most commonly seen among school-aged children and adolescents. Nephrotic syndrome (NS) is a glomerular disease characterized by excessive urinary protein excretion, hypoproteinemia, and edema with or without hyperlipidemia. Proteinuria occurs due to increased permeability of the glomerular capillary walls, which disrupts reabsorption in the proximal tubular epithelial cells.¹⁻³ Based on the response to corticosteroids, NS patients are categorized as having either steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome (SRNS). Further definitions in SSNS include remission, relapse, frequently relapsing NS and steroid-dependent NS.⁴ Children with SRNS also have a protracted clinical course and may have long-standing proteinuria.^{5,6}

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Patients with NS tend to experience a state of hypoproteinemia and proteinuria. Thyroid hormone in the circulation is bound to proteins, mainly thyroid-binding globulin (TBG), prealbumin, and albumin. The proteins serve to maintain thyroid hormone levels in physiological conditions.^{3,7,8} Loss of thyroid hormones may lead to low free thyroid hormone levels unless production is increased under the influence of thyroid-stimulating hormone (TSH). Furthermore, loss of albumin and TBG may reduce the binding capacity for thyroid hormones, resulting in a decrease in total triiodothyronine (T3) and thyroxine (T4) concentrations.^{2,9} Nephrotic syndrome patients have a variable thyroid hormone profile. During nephrosis, thyroid hormone concentrations decrease while serum TSH concentrations increase in untreated children. Thyroid hormone levels return to normal during remission. These hormonal changes are strongly related to the degree of proteinuria and albumin levels in NS patients.^{6,9} Most thyroid hormone deficiencies that occur in NS cases are subclinical.^{9,10} Subclinical hypothyroidism is characterized by increased TSH levels based on references, accompanied by normal levels of fT4. Subclinical hypothyroidism can be categorized as mild or severe for TSH level increase to between 4.5-10 mIU/L or > 10 mIU.^{6,11,12}

To our knowledge, no comprehensive study has evaluated thyroid function in pediatric NS cases of in our hospital. Therefore, we aimed to analyze for possible correlations between the occurrence of subclinical hypothyroidism with serum albumin, globulin, and proteinuria in NS patients in Hasan Sadikin General Hospital.

Methods

This cross-sectional study was conducted in Hasan Sadikin General Hospital, Bandung, West Java, from March to May 2019, after approval from the Hasan Sadikin General Hospital Ethics Committee. The inclusion criteria were patients aged 1 month to < 18 years, diagnosed with NS, hospitalized at Hasan Sadikin General Hospital, Bandung, and whose parents provided informed consent for participation. Patients who had thyroid abnormalities before being diagnosed with NS, liver disorders, or severe malnutrition were excluded. Patient's age, gender,

type of nephrotic syndrome, and treatment was evaluated. Patients were examined about levels of thyroid function (T3, T4 and TSH levels), urea, serum creatinine, albumin, globulin, total protein, and levels of proteinuria during hospitalization by the medical personnel. Estimated glomerular filtration ratio (eGFR) was calculated using the Schwartz formula that used serum creatinine, height and an empirical constant. The main outcomes assessed in this study were levels of T3, fT4, and TSH, in order to analyse for possible correlations between the occurrence of subclinical hypothyroidism to albumin and globulin levels, and proteinuria in NS patients.

Hypoalbuminemia was defined as serum albumin < 2.5 g/dL. Massive proteinuria was defined as urinary protein $\geq 2+$ by dipstick test.¹³

Steroid-resistant NS was defined as no remission after full dose treatment of 2 mg/kg/day of prednisone for 4 weeks. Another study defined SRNS as no occurrence of remission after administration of 8 weeks of prednisone at 60 mg/body surface area/day or 2 mg/kg body weight/day for 4 weeks, followed by 40 mg/body surface area/day or 1.5 mg/kg body weight in 4 weeks.^{4,13} In this study, SRNS was defined as no remission after full dose treatment of 2 mg/kg/day of prednisone for 4 weeks.

Steroid-sensitive NS included remission, relapse, frequently relapsing NS and steroid-dependent NS. Recurrent NS was defined as relapse ≥ 2 times in the first 6 months after the initial response or ≥ 4 times in a 1 year period. Remission was defined as negative or trace proteinuria (proteinuria < 4 mg/body surface area/hour) for 3 consecutive days in 1 week. Relapse was defined as proteinuria $\geq 2+$ (proteinuria > 40 mg/body surface area/hour) for 3 consecutive days in 1 week. Relapse was divided into frequent and infrequent relapse. Infrequent relapse was relapse less than 2 times in the first 6 months after the initial response or less than 4 times per year, whereas frequent relapse occurred more than 2 times in the first 6 months after the initial response or ≥ 4 times in 1 year period.^{4,13}

Subclinical hypothyroidism (SH) was defined as an increase TSH serum levels > 4.5 mIU/L with a normal serum of fT4.^{6,11,12}

Patient data collected were age, sex, anthropometric assessment of height/age and weight/age, type of corticosteroid, type of NS, type of chemo-

therapy, and kidney function assessment of glomerular filtration rate. Univariate analysis was done to describe the characteristics of the study subjects listed above. Categorical data were presented in numbers and percentages and numerical data were presented in median, minimum, and maximum values.

Bivariate analysis was done to determine potential correlations between the occurrence of subclinical hypothyroidism with serum albumin, globulin, and proteinuria using biserial point correlation, because the data types were numerical and categorical. Logistic regression analysis was done to assess the risk of serum albumin, globulin, and proteinuria on the presence of subclinical hypothyroidism. Data were tested descriptively and data analysis was carried out using *Statistical Product and Service Solution (SPSS) for Windows version 18.0*, with 95% confidence level and P value ≤ 0.05 .

Results

The study was conducted on 26 children with NS. Subjects' characteristics are shown in **Table 1**.

Types of chemotherapy and corticosteroids administered are shown in **Table 2**. No significant difference was found between the occurrence of subclinical hypothyroidism and type of chemotherapy, corticosteroids, or the number of chemotherapy cycles.

The serum and urinary protein and kidney function profiles are shown in **Table 3**. The lowest total protein, albumin, and globulin levels were 2.9 g/dL, 0.2 g/dL, and 2.6 d/dL, respectively. Statistically significant differences were found between the

occurrence of subclinical hypothyroidism and total protein, albumin, and proteinuria. Lower total protein, lower albumin, and higher proteinuria were associated with the occurrence of subclinical hypothyroidism ($P < 0.05$ for all).

Thyroid function measurements are shown in **Table 4**. The median T3, fT4, and TSH levels were 0.69 ng/mL, 1.2 ng/mL, and 6.9 mIU/L, respectively, in subjects with subclinical hypothyroidism.

The correlations between serum albumin, globulin, proteinuria and subclinical hypothyroidism are shown in **Table 5**. Subclinical hypothyroidism was negatively correlated to albumin level ($r = -0.702$; $P < 0.001$), indicating that subjects with low albumin levels had a high likelihood of subclinical hypothyroidism. However, globulin level had no significant correlation to subclinical hypothyroidism. In addition, a positive correlation was found between proteinuria and subclinical hypothyroidism ($r = 0.573$; $P = 0.003$).

Univariate logistic regression analysis was performed to determine the impact of serum albumin, globulin, and proteinuria on the presence

Table 1. Baseline characteristics of subjects

Characteristics	Subclinical hypothyroidism	
	Yes (n=10)	No (n=16)
Mean age (SD), years	4.1 (3.5)	8.0 (4.0)
Gender, n		
Male	7	13
Female	3	3
Type of NS, n		
SSNS	3	2
SRNS	7	14

SSNS=steroid-sensitive NS, SRNS=steroid-resistant NS

Table 2. Types of chemotherapy and corticosteroids

Variables	Subclinical hypothyroidism		P value
	Yes (n=10)	No (n=16)	
Mean chemotherapy cycles (SD)	3 (2)	4 (2)	0.271 ^a
Type of chemotherapy, n (%)			0.091 ^b
None	4	2	
Cyclophosphamide	5	14	
Mycophenolate mofetil	1	0	
Type of corticosteroid, n (%)			0.625 ^c
Methylprednisolone	8	14	
Prednisone	2	2	

Note: analysis using: (a) unpaired T-test, (b) Chi-square, (c) Fisher's exact

Table 3. Serum and urinary protein and kidney function profiles

Variables	Subclinical hypothyroidism		P value
	Yes (n=10)	No (n=16)	
Median total protein (range), g/dL	4.2 (2.9-5.5)	6.0 (3.8-7.9)	<0.001 ^{a*}
Median albumin (range),g/dL	0.92 (0.20-2.60)	2.71 (0.70-3.80)	<0.001 ^{a*}
Median globulin (range), g/dL	3.23 (2.6-3.6)	3.27 (2.6-4.5)	0.814 ^a
Median urea (range), mg/dL	25.2 (8.0-120.7)	19.2 (5.0-95.0)	0.268 ^b
Median creatinin (range), mg/dL	0.27 (0.03-1.06)	0.35 (0.12-2.21)	0.510 ^b
Median eGFR (range), mL/min/1.73 m ²	157 (42-771)	142 (29-327)	0.752 ^b
Proteinuria, n (%)			0.012 ^{c*}
Negative	1	11	
≥2+	9	5	

Note: analysis using: (a) unpaired T-test, (b) Mann-Whitney, (c) Chi-square

Table 4. Thyroid function

Variables	Subclinical hypothyroidism		P value
	Yes (n=10)	No (n=16)	
Median T3, ng/mL	0.69 (0.4-1.1)	1.14 (0.4-1.7)	0.002 ^{a*}
Median fT4 (range), ng/mL	1.2 (0.2-2.2)	1.4 (0.9-2.0)	0.281 ^a
Median TSH (range), mIU/L	6.9 (5.3-19.5)	1.8 (0.6-4.0)	< 0.001 ^{b*}

Note: analysis using: (a) unpaired T-test, (b) Mann-Whitney, (c) Chi-square

of subclinical hypothyroidism in NS patients, (Table 6). Albumin and proteinuria had a significant impact on the presence of subclinical hypothyroidism (OR 27.00, 95%CI 1.69 to 17.7 and OR 19.80, 95%CI 1.94 to 201.63, respectively).

Serum globulin did not show statistically significant effect on subclinical hypothyroidism (P=0.805). In contrast, the odds ratio (OR) of albumin for subclinical hypothyroidism was 27.00, indicating that albumin < 2.5 g/dL increases the risk of subclinical hypothyroidism by 27.00 times. The odds ratio of proteinuria for subclinical hypothyroidism was 19.80.

Table 5. Analysis of albumin, globulin and proteinuria with subclinical hypothyroidism

Variables	Subclinical hypothyroidism	
	r coefficient	P value
Albumin, g/dL	-0.702a	<0.001*
Globulin, g/dL	-0.048a	0.407
Proteinuria	0.573b	0.003*

Note: analysis using correlation: (a) biserial point, (b) phi

Table 6. Univariate logistic regression analysis of subclinical hypothyroidism with albumin, globulin, and proteinuria

Variables	Logistic regression coefficient		P value
	Odds ratio (OR)	95% CI for OR	
Albumin, g/dL	27.00	1.69 to 17.7	0.006*
Globulin, g/dL	1.30	0.17 to 10.17	0.805
Proteinuria	19.80	1.94 to 201.63	0.012*

Discussion

Nephrotic syndrome changes the concentrations of thyroid hormones, primarily due to loss of protein in serum and urine. In our study, thyroid function was evaluated in children with nephrotic syndrome. Of the 26 NS cases, there were 20 males and 6 females. Ten out of 26 subjects had subclinical hypothyroidism, mean age at presentation of 4.1 years, and were clinically euthyroid, with increased TSH (median 6.9 mIU/L).

Previous studies have reported that in NS, thyroid hormone levels decrease while serum (TSH) levels increase. Also, several studies have found a

correlation between proteinuria, serum TSH, and T4 levels.² We found a direct relationship between protein excretion in urine and increased in serum TSH levels. We suggest that NS patients have an increased risk of subclinical hypothyroidism. Abnormalities in thyroid function are seen in patients with proteinuria. Specifically, TSH levels were higher in patients with proteinuric renal diseases compared to controls.⁹ In addition, thyroid profiles of children with untreated NS indicated massive urinary losses of T4, T3 TBG, fT4, and fT3.¹⁴ Our study demonstrates correlation between albumin level, proteinuria and subclinical hypothyroidism, based on the logistic regression univariate analysis (OR 27.00, 95%CI 1.69 to 17.7 and OR 19.80, 95%CI 1.94 to 201.63, respectively). Proteinuria results in loss of thyroid hormones, most probably caused by loss of thyroxin-binding globulin and albumin, thus stimulating TSH production.

A previous study found that the mean serum T3 and T4 in children during nephrosis were within normal limits, however, mean TSH was higher than normal during nephrosis. They concluded that NS patients commonly have a state of mild or subclinical hypothyroidism during proteinuria, although they are clinically euthyroid.¹⁰ Another study reported that NS patients had an increased risk of subclinical hypothyroidism, but thyroid function returned to the normal when the non-thyroid illness was resolved.¹⁵ We also found that serum T3 and T4 levels were in the normal range and TSH was increased.

In our study, seven children with SRNS had subclinical hypothyroidism. Prolonged proteinuria in children with SRNS may exhaust the thyroid reserve and potentiate tubular injury, resulting in impaired reabsorption of low molecular weight proteins and leading to overt hypothyroidism, if left untreated. It is possible that hypothyroidism is a consequence, not only of urinary loss of thyroid hormones, but also of a failure of the thyroid gland to compensate for this loss.⁶ Actually, the low level of serum thyroid hormone can inhibit the expression of glucocorticoid receptor (GR), with manifestations of steroid resistance.¹⁵

A meta-analysis showed that thyroid hormone replacement therapy significantly improved the remission of the NS patients.¹⁵ The decision to treat a child with subclinical hypothyroidism in long-term may involve a lifetime of thyroid hormone replacement and frequent monitoring of total or free T4 and TSH levels.

The limitations of this study included not measuring free T3 and total T4 in the serum thyroid hormone profiles. Nor did we measure the total amount of urinary loss of thyroid hormones. In addition, the small number of subjects was due to using the consecutive sampling method during a limited period of time.

In conclusion, subclinical hypothyroidism in NS patients has correlations to lower albumin level and higher proteinuria. The hormonal changes are related to the degree of proteinuria and to serum albumin levels. Subclinical hypothyroidism needs to be considered in NS patients as it is a potentially health-threatening and treatable complication. Early thyroid hormone administration might improve the prognosis. Prospective, observational studies are needed to determine the etiology and pathogenesis of this health-threatening, potentially treatable complication.

Conflict of interest

None declared.

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