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Research Paper

Thyroid Hormone Profile in Pediatrics With Nephrotic Syndrome Compared to Healthy Children

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ABSTRACT

Background and Aim: Nephrotic syndrome (NS) is one of the most common kidney diseases in pediatrics. It impacts thyroid hormones due to the urinary loss of hormone-binding proteins such as transthyretin, thyroxine-binding globulin (TBG), and albumin.

Objectives: This study aimed to compare the profile of thyroid hormones between children with a definite diagnosis of NS and healthy children.

Materials and Methods: This retrospective case-control study was performed in a pediatric university hospital between January 2011 and December 2021. The case group consisted of all children with a definite diagnosis of NS who were referred to our hospital, while healthy children who visited the hospital for routine checkups were randomly enrolled in the control group. All variables were compared between the case and control groups.

Results: The median age of children was 5.91±4.14 and 6.07±3.70 years in the control and case groups, respectively. Thyroid stimulator hormone (TSH) and thyroxin-4 (T4) levels were significantly higher and lower in the case group than in the control group, respectively (P<0.05). There was no significant difference between the case and control groups in free T4 levels (1.30±1.95 and 1.12±0.24 ng/dL, respectively; P=0.558).

Conclusion: Subclinical hypothyroidism is more common in children with NS. This may be due to albuminuria and the loss of TBG during active proteinuria stages.

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Introduction

One of the most common glomerular diseases is nephrotic syndrome (NS). It is characterized by substantial proteinuria (>3.5 g/24 hours), edema, hyperlipidemia, and hypoalbuminemia (<30 g/L) [1]. Its prevalence in pediatrics aged 1-10 years is 16 per 100000 [2]. Pediatrics with this syndrome are at risk of serious infections, while adults are at risk of thromboembolic events. As a primary endocrine organ, the growth and function of the kidneys are primarily related to thyroid gland function. Conversely, the kidneys play an important role in the elimination and metabolism of thyroid hormones [3, 4].

Thyroid hormone levels decrease as a result of the urinary loss of hormone-binding proteins, such as transthyretin, thyroxine-binding globulin (TBG), and albumin. Consequently, thyroid hormone levels in the blood reduce during nephrosis. Following this reduction, the production of Thyroid Stimulating Hormone (TSH) in the thyroid gland increases [5, 6]. Several studies have been performed on changes in thyroid hormones in children with NS [7, 8]. For example, Solarin et al. in Nigeria [9] reported that the prevalence of subclinical hypothyroidism was significantly higher than in their healthy control group. Additionally, Nithya et al. [10] reported a significant difference in children with NS and controls. This possible relationship has not been evaluated in Iranian pediatrics with NS. However, several studies have been conducted on other populations. Additionally, Iranian children are considered to be among the high-risk ethnicities for developing NS. Additionally, thyroid hormones play essential roles in maintaining the body's homeostasis. All of these reasons encouraged us to conduct this study.

Objectives

This study aimed to compare the profile of thyroid hormones between children with a definite diagnosis of NS and healthy children.

Materials and Methods

Study design

This retrospective case-control study was performed in a pediatric university hospital between January 2011 and December 2021. Inclusion criteria were a definite diagnosis of NS and an age of less than 15 years. We excluded patients with a history of other types of renal diseases, renal anomalies, any interventions on the renal system, a definite diagnosis of thyroid diseases, and thyroid anomalies. The case group consisted of all children with a definite diagnosis of NS who were referred to our hospital, while healthy children without underlying diseases who visited healthcare centers for routine checkups, such as vaccinations and height and weight monitoring, were randomly enrolled in the control group. It is noteworthy to mention that the two groups were matched in terms of age and gender. Written informed consent was obtained from all parents. All of the following variables were recorded for each participant: Age, gender, thyroid function tests, blood urea nitrogen (BUN), creatinine (Cr), albumin (Alb), urine protein in 24 hours, and urine protein-to-Cr ratio. Finally, these variables were compared between the case and control groups.

Statistical analysis

Data were analyzed using SPSS software, version 26 (IBM Corp., Armonk, N.Y., USA). We reported the Mean±SD, and frequency (number and percentile) for descriptive variables. Additionally, a t-test was used to analyze quantitative variables between the two groups. The $P<0.05$ was considered significant.

Results

Patient characteristics

In total, 80 participants enrolled in this case-control study. A total of 40 children with a definitive diagnosis of NS participated in the case group, including 21 males and 19 females. Moreover, 40 children participated in the control group, which was matched for sex and age. The median age of children was 5.91±4.14 and 6.07±3.70 years in the control and case groups, respectively.

There was no significant difference in terms of age between the two groups (P=0.852). Among the 40 patients in the case group, 39 had registered information about their race, while one patient did not. Of the 39 patients, 33 belonged to the Iranian race, and six cases were non-Iranian.

Laboratory tests

Table 1 presents demographic characteristics and the results of laboratory tests in the case group. Out of 40 patients, incomplete information in the patient's medical records existed for all laboratory tests except for TSH, Thyroxine-4 (T4), and free T4, which are the three main

Table 1. The results of laboratory tests in the case group

Parameter	No.	Mean±SD	Min	Max
TSH (mIU/L)	40	5.73±5.05121	0.9	20.50
T4 (kg/dL)	40	6.59±3.00024	0.10	12.09
Free T4 (ng/dL)	40	1.30±1.09507	0.4	18.20
Free T3 (pg/mL)	3	2.12±1.08333	0.1	4.20
T3 (pg/mL)	16	1.09±0.40574	0.2	1.7
BUN (mmol/L)	33	23.50±19.67277	4	85
Creatinine (mg/dL)	36	0.79±0.69470	0.3	3.98
Albumin (g/dL)	34	2.48±0.86752	1.4	4.6
24h urine protein concentration (mg/24 h)	15	6918.39±4883.0	32	26232
Urine Pro/Cr (mg/mmol)	16	18.71±18.020	0.15	73.6

Abbreviations: TSH: Thyroid stimulating hormone; T4: Thyroxine; T3: Triiodothyronine; BUN: Blood urea nitrogen; Pro: Protein; Cr: Creatinine.

parameters in determining hypothyroidism and its related types.

Hypothyroidism type in the case group

Among the 40 patients, 29 had normal thyroid tests (72.5%). Clinical hypothyroidism was diagnosed in five patients (12.5%). Moreover, based on the thyroid lab tests, subclinical hypothyroidism was identified in six patients (15%).

Thyroid parameters in nephrotic syndrome

Table 2 compares thyroid parameters, including TSH, T4, and free T4. TSH levels were significantly higher in the case group than in the control group (5.73±5.05 and 3.31±1.58 mIU/L, respectively; P=0.006). Moreover, T4 levels were significantly lower in the case group compared to the control group (6.59±3.00 and 9.11±2.29, respectively; P<0.001). There was no significant difference between the case and control groups in free T4 levels (1.30±1.09507 and 1.12±0.24 µg/dL, respectively; P=0.558).

Discussion

The thyroid gland and kidney are associated with each other bilaterally. The growth of the kidney is affected by the function of the thyroid gland, and the kidney plays a key role in the metabolism of thyroid hormones [3]. Therefore, NS as one of the most common glomerular diseases may affect these hormones [1]. Abnormalities in thyroid gland function are common in NS. NS disrupts thyroid gland function through insufficient binding to carrier proteins, low concentrations of circulating thyroid hormones, and altered storage of iodine in the thyroid gland [11]. However, previous studies have reported a wide variety of thyroid hormone levels in children with NS.

Table 2. Comparing thyroid parameters between the two groups

Parameter	Mean±SD		P
	Case	Control	
TSH (mIU/L)	5.73±5.05	3.31±1.58	0.006
T4 (µg/dL)	6.59±3.00	9.11±2.29	<0.001
Free T4 (ng/dL)	1.30±1.09507	1.12±0.24	0.558

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Our findings revealed that 72.5%(29/40) of patients with NS in the case group had normal thyroid gland hormones. Additionally, 12.5%(5/40) of cases had clinical hypothyroidism, and 15%(6/40) had subclinical hypothyroidism. In contrast, the number of abnormal thyroid hormone profiles in the study by Jung et al. [12] was higher than our results (16/31 versus 11/40). However, their sample size was smaller, even though their proportion of abnormal profiles was higher.

Nithya et al. [10] reported that subclinical hypothyroidism is more common in NS patients, which aligns with our results. This is evidenced by significantly higher TSH levels and significantly lower T4 levels compared to the control group. However, there was no significant difference in terms of free T4 between the two groups. These findings meet the criteria for the diagnosis of subclinical hypothyroidism. Our hypothesis for the increase in TSH levels was that the T4 level, which is bound to TBG, decreases in the blood due to the loss of TBG. This is because NS patients experience proteinuria that contains TBG [13]. Additionally, several have shown that thyroid function abnormalities occur in NS patients at the proteinuria stage, with TSH levels being higher in these patients with active disease than in healthy groups when there is hypoalbuminemia and proteinuria. This is attributed to a negative relationship between TSH and serum albumin [14, 15]. However, interpreting the interactions between renal function in pediatric NS and thyroid gland function presents an important challenge for clinicians involved in the management of children with NS.

Conclusion

Subclinical hypothyroidism is more common in NS children. This condition is primarily due to the loss of proteins, such as TBG, which is bound to T4, through proteinuria in pediatric patients with NS.

There were some limitations to the current study: 1) some potential confounding factors were not evaluated, and 2) the study was a case-control design, which may introduce biases in evaluating the relationship; therefore, a clinical trial would be a better option for studying this correlation.

An important limitation of our study was the lack of clinical registration for some children diagnosed with NS. In addition, if this study is conducted prospectively, its results could be more reliable.

Ethical Considerations

Compliance with ethical guidelines

This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Qom University of Medical Sciences (Code: IR.MUQ.REC.1400.087). Informed consent was obtained from all parents of the children involved.

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Authors' contributions

Conceptualization: Mohammad Reza Razavi; Methodology: Mohsen Akhavan Sepahi; Supervision and validation: Mohammad Reza Razavi; Formal analysis: Mohammad Aghaali; Investigation: Mahdi Zarei and Mohammad Hossein Afshari; Resources: Mohammad Reza Razavi; Data curation: Mahdi Zarei, Mobina Riahi, and Mohammad Hossein Afshari; The original draft preparation: Alireza Sharifi; Review, and editing: Alireza Sharifi and Sahar Ghaedsharaf; Visualization: Mobina Riahi; Project administration: Mahdi Zarei and Sahar Ghaedsharaf; Funding acquisition: Mohammad Reza Razavi.

Conflict of interest

The authors declared no conflict of interest.

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