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RESEARCH ARTICLE

Analysis of FT4 and TSH Hormone Levels in Relating Albumin, Globulin, and Cholesterol in Children with Nephrotic Syndrome

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ABSTRACT

Nephrotic syndrome is a prevalent kidney disorder in children, marked by symptoms such as excessive protein in the urine (proteinuria), elevated cholesterol levels (hypercholesterolemia), low blood protein levels (hypoproteinemia), and swelling (edema). The loss of proteins in the urine, including albumin and thyroid-binding globulin, can potentially disrupt thyroid hormone levels in these children. To examine the relationship between FT4 and TSH hormone levels with albumin, globulin, and cholesterol in children diagnosed with nephrotic syndrome. This cross-sectional observational study was carried out between January and July 2024 at Dr. Wahidin Sudirohusodo Hospital in Makassar. A total of 80 pediatric patients, aged 2 to 18 years, with nephrotic syndrome, were included. The study involved measuring hormone levels and assessing their correlation with albumin, globulin, and cholesterol levels. FT4 levels were low in 37.5% of patients and typical in 62.5%. There was a strong positive correlation between FT4 and albumin levels ($r = 0.537$, $p < 0.001$), as well as between FT4 and globulin levels ($r = 0.381$, $p = 0.015$). Conversely, TSH levels showed a negative correlation with albumin ($r = -0.517$, $p = 0.001$) and with globulin ($r = -0.432$, $p = 0.005$). Significant associations were identified between FT4, TSH, and the levels of albumin, globulin, and cholesterol in patients with nephrotic syndrome.

INTRODUCTION

Nephrotic syndrome is a frequent kidney condition in children, defined by severe protein loss in the urine (greater than 40 mg/m^2/day, over 50 mg/kg/day, or a urine protein/creatinine ratio exceeding 2 mg/mg), low blood albumin levels (≤3 mg/dL), swelling (edema), and high cholesterol levels (≥200 mg/dL). (Coates et al., 2024)(1) (Alatas et al) (11). Massive proteinuria, caused by decreased glomerular filtration, hyponatremia, and altered urine osmolality, leads to significant protein loss. Hormones produced by the thyroid depend on proteins for their transportation, such as thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), transthyretin, and albumin. The thyroid hormones—thyroxine (T4) and triiodothyronine (T3)—are crucial for the growth and development of the kidneys, as well as for regulating fluids and maintaining electrolyte balance. Abnormal thyroid levels significantly affect metabolic rate: thyroid hormone deficiency lowers metabolism by 40% below average, while excessive thyroxine secretion would increase basal metabolism rate by 60-100%. The roles of FT4 and TSH hormones, which are mainly protein-bound (99,5% of T3 and 99,9% of T4), are critical for understanding the systemic effects of protein loss in nephrotic syndrome. The reduction of albumin and TBG results in less binding of thyroid hormones, which can lead to lower levels of T3 and T4, potentially causing subclinical hypothyroidism.

Over the last decade, the occurrence of nephrotic syndrome has risen in children aged 1 to 18 years, increasing from 1.99 cases per 100,000 to 4.71 cases per 100,000. In Indonesia, the incidence stands at 6 cases per 100,000 among children under 14 years old. The incidence of nephrotic syndrome decreases with age. Patients with nephrotic syndrome tend to have high TSH levels and low serum

T3 and T4. Other studies have found a relationship between hypothyroidism and albumin levels, as well as proteinuria in nephrotic syndrome patients, indicating that low albumin levels are associated with subclinical hypothyroidism.

This study aims to examine the levels of FT4 and TSH hormones in connection with albumin, globulin, and cholesterol levels in pediatric patients diagnosed with nephrotic syndrome. Previous research has yielded inconsistent results regarding thyroid function in these patients; some studies indicate a higher occurrence of thyroid dysfunction, while others report no significant link. These varying outcomes may stem from differences in the populations studied, research methodologies, and the specific thyroid hormone parameters assessed. The hypothesis posits that there would be a significant correlation between these parameters in patients with nephrotic syndrome.

The benefit of this research is to provide comprehensive education and therapy for nephrotic syndrome patients by considering the long-term effects of treatment. No prior study has analyzed FT4 and TSH hormone levels in nephrotic syndrome patients in Sulawesi, particularly in Makassar. The findings of this research could serve as a basis for assessing the progression of the disease and preventing recurrence and complications. It can also serve as a reference for another researcher.

PARTICIPANTS & METHODS

A cross-sectional observational study from January to July 2024 at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. The study included 80 pediatric patients, aged from 1 month to 18 years, who had been diagnosed with nephrotic syndrome. Inclusion criteria ensured that all patients had confirmed nephrotic syndrome with adequate clinical and laboratory data available. Blood samples were collected for FT4, TSH, albumin, globulin, and cholesterol analysis. Hormone levels were measured using standard biochemical methods. Statistical analyses were conducted to assess correlations—statistical analyses using SPSS Statistics for Windows, Version 26.0. Standard data were analyzed using Student's t-test or ANOVA, while non-normal data were evaluated with rank-sum tests. Categorical data were examined using chi-square tests or Fisher's exact test. Associations between clinical parameters were assessed using Spearman correlations. Logistic regression models were employed for the multivariate analysis of risk factors for thyroid dysfunction. Confidence intervals (CI) for odds ratios (OR) were calculated based on the standard error of the coefficient, and a p-value of less than 0.05 was deemed statistically significant.

FINDINGS

1. Patient characteristics

A total of 80 patients between 1 month and 18 years were diagnosed with nephrotic syndrome participated in the study. Inclusion criteria ensured that all patients had confirmed nephrotic syndrome with adequate clinical and laboratory data available. Throughout the study period, 30 patients diagnosed with nephrotic syndrome aged between 2 and 7 years were identified, along with 50 patients aged between 8 and 18 years. Of the total cohort, 44 patients were male and 36 were female. The initial demographics and clinical characteristics of the patients included in the study are outlined in Table 1.

Table 1: Characteristics of study subjects

Characteristics	FT4 Hormone			TSHs Hormone		
	Low (n = 30)	Normal (n = 50)	High (n = 0)	Low (n = 10)	Normal (n = 42)	High (n = 28)
Sex						
Male	16 (36,3%)	28 (63,6%)	0 (0%)	8 (18,1%)	20 (45,4%)	16 (36,3)
Female	14 (3%)	22 (61,1%)	0 (0%)	2 (5,5%)	22 (61,1%)	12 (75%)
Age (years)						
2-7	18 (60%)	12 (40%)	0 (0%)	2 (6,6%)	10 (33,3%)	18 (60%)
8-20	12 (24%)	38 (76%)	0 (0%)	8 (16%)	32 (64%)	10 (20%)
Nutritional status						

Undernutrition	2 (20%)	8 (80%)	0 (0%)	0 (%)	8 (80%)	2 (20%)
Adequate nutrition	28 (40%)	42 (60%)	0 (0%)	10 (14,2%)	34 (48,5%)	26 (37,1%)
Albumin						
Hypoalbuminemia	30 (55,5%)	24 (44,4%)	0 (0%)	0 (0%)	26 (48,1%)	28 (51,9%)
Normal	0 (0%)	26 (100%)	0 (0%)	10 (38,4%)	16 (61,6%)	0 (0%)
Globulin						
Hypoglobulinemia	18 (64,2%)	10 (35,8%)	0 (0%)	4 (14,2%)	8 (28,5%)	16 (57,1%)
Normal	12 (23%)	40 (77%)	0 (0%)	6 (11,5%)	34 (65,3%)	12 (23%)
Total cholesterol						
Hypercholesterolemia	30 (40,5%)	44 (59,5%)	0 (0%)	6 (8,1%)	40 (54%)	28 (37,8%)
Normal	0 (0%)	6 (100%)	0 (0%)	4 (66,7%)	2 (33,3%)	0 (0%)
Nephrotic syndrome						
First Attack Idiopathic NS	16 (57,2%)	12 (42,8%)	0 (0%)	6 (17,6%)	10 (29,4%)	18 (52,9%)
Steroid dependant NS	0 (0%)	14 (100%)	0 (0%)	0 (0%)	12 (100%)	0 (0%)
Rarely relapsing NS	6 (37,5%)	10 (62,5%)	0 (0%)	0 (0%)	10 (83,4%)	2 (16,6%)
Frequently relapsing NS	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)
Steroid resistant NS	6 (30%)	14 (70%)	0 (0%)	4 (20%)	10 (50%)	6 (30%)

Table 1. Describes the characteristics of FT4 and TSH hormones in the research sample based on gender, age, nutritional status, levels of albumin, globulin, and cholesterol, as well as the classification of nephrotic syndrome.

The results of this study align with those of Sun HEe Jung (2), who found that out of 31 children with nephrotic syndrome, 16 (51.6%) showed abnormal thyroid hormone profiles: 6 had overt hypothyroidism, 8 patients with subclinical hypothyroidism, and 2 patient had low T3 syndrome. Madhumita (3) reported an increase in TSH and a decrease in T3 and T4 levels, specifically in 50 pediatric patients with remission of nephrotic syndrome. The aetiology of thyroid disorders in these patients is mainly due to thyroid hormones being primarily bound to proteins (globulin, prealbumin, and albumin). Damage to podocytes and proximal tubular function leads to protein filtration, including albumin. Additionally, FT4 and FT3 hormones may be filtered by the glomeruli and lost in urine. This decrease in FT4 and FT3 levels stimulates increased TSH secretion through a negative feedback mechanism to the anterior pituitary (Basu et al., 2022). Although thyroid dysfunction has been documented in patients with nephrotic syndrome, some studies report a low prevalence. This may be due to limited sample sizes and the unclear impact of proteinuria duration and hypoalbuminemia on FT4 and TSH levels.

Among patients with first-attack nephrotic syndrome, FT4 levels decreased in 16 patients (57.2%), while TSH levels increased in 18 patients (52.9%). These numbers were higher compared to other types of nephrotic syndrome, likely due to massive proteinuria in idiopathic nephrotic syndrome, which reduces albumin and globulin levels, subsequently lowering FT4 levels as well. This decrease in FT4 triggers a negative feedback response to the hypothalamus, resulting in increased TSH levels. This aligns with existing literature, which indicates that low albumin and globulin due to massive proteinuria leads to decreased FT4, as these hormones are bound to proteins like albumin and globulin. In cases of steroid-sensitive and steroid-dependent nephrotic syndrome, FT4 and TSH levels generally remain within the normal range, likely because patients have already received corticosteroid therapy, restoring albumin and globulin levels. In relapsing nephrotic syndrome, 6 patients (37.5%) experienced decreased FT4 levels, and in frequent relapses, both patients had increased TSH levels, potentially due to renewed massive proteinuria affecting albumin and globulin

levels. In steroid-resistant nephrotic syndrome, 6 patients (30%) exhibited decreased FT4 and increased TSH levels, possibly resulting from podocyte and glomerular basement membrane damage, along with impaired proximal tubular function, leading to reduced albumin and globulin levels, which directly impacts FT4 and TSH hormones.

2. Comparison of clinical characteristics among FT4 and TSH hormone levels with albumin, globulin and total cholesterol levels

Table 2: Comparison between FT4 and TSH hormone levels, albumin, globulin, and total cholesterol levels

	Albumin	Globulin	Total cholesterol
FT4 hormone level (ng/dl)	*0,000	*0,000	*0,000
TSH hormone level (µIU/ml)	*0,001	0,138	*0,000

Statistical analysis conducted with the Paired T-test revealed a significant difference between FT4 hormone levels and the levels of albumin, globulin, and cholesterol (p=0.000). Additionally, the analysis indicated an essential difference between TSH hormone levels and albumin levels (p = 0.001); additionally, a significant association was observed between TSH levels and cholesterol levels (p=0.000). However, no significant difference was found between TSH hormone levels and globulin levels (p=0.138).

These findings align with the research by Deepak Jain et al. in India(4), which indicates that low albumin levels in nephrotic syndrome affect TSH and FT4 hormones in the blood. Similarly, a retrospective study by Ling-Zhi Li et al. (5) in China involving 317 nephrotic syndrome patients found that low albumin levels also impact FT4 and TSH levels. In patients with nephrotic syndrome, massive proteinuria leads to hypoalbuminemia. TSH and FT4 hormones bind to proteins, prealbumin, albumin, and globulin to reach their target organs. Consequently, in nephrotic syndrome patients with massive proteinuria and hypoalbuminemia, low FT4 levels send negative feedback signals to the pituitary gland, stimulating increased TSH levels.

In contrast to the study by Erni Nuraini et al.(6) at Hasan Sadikin Hospital in Bandung in 2020, which found no significant results between globulin levels and FT4 and TSH hormone levels in nephrotic syndrome patients, several factors may explain this lack of meaningful correlation. The most likely explanation is that hormone-binding proteins for TSH and FT4 in the blood are predominantly associated with albumin rather than globulin.

Consistent with the findings of Mohamed Abd et al. (7) in Egypt in 2020, a significant correlation was found between cholesterol levels and FT4 hormone levels, with a statistical result of $p < 0.001$. The primary cause of increased cholesterol in nephrotic syndrome is the elevation of nearly all serum lipid levels (cholesterol and triglycerides). Additionally, hypoproteinemia stimulates overall protein synthesis in the liver, including lipoproteins. Furthermore, fat catabolism decreases due to reduced plasma lipoprotein lipase levels, the primary enzyme that removes fats from plasma (Liu & Peng, 2022). (8) Alterations in FT4 and TSH levels also impact lipolysis within adipose tissue, prompting the release of free fatty acids. This process leads to increased triglyceride levels and a reduction in High-Density Lipoprotein (HDL). Lower HDL levels subsequently contribute to an increase in Low-Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL), which, in turn, elevate total cholesterol levels. (Liu & Peng, 2022). Consequently, the rise in total cholesterol levels in patients may be attributed to nephrotic syndrome itself, potentially exacerbated by disruptions in FT4 and TSH hormones.

3. Correlations between thyroid hormone with albumin, globulin and cholesterol levels

Table 3: Correlation between FT4 hormones levels with albumin, globulin and total cholesterol levels

FT4 level	Albumin	Globulin	Total Cholesterol
Pearson correlation	0,537	0,381	-0,525
p value	0,000	0,015	0,001

The analysis demonstrated a notable positive correlation between FT4 and albumin, with a correlation coefficient of r = 0.537 and a p-value below 0.001. Likewise, a significant positive correlation was found between FT4 and globulin, evidenced by a correlation coefficient of r = 0.381 and a p-value of 0.015. Conversely, FT4 exhibited a negative correlation with cholesterol, shown by a correlation coefficient of r = -0.525 and a p-value of 0.001.

Table 4: Correlation between TSH hormones levels with albumin, globulin and total cholesterol levels

TSH level	Albumin	Globulin	Total Cholesterol
Pearson correlation	-0.517	-0,432	0,191
p value	0,001	0,005	0,238

The analysis demonstrated significant negative correlations between TSH and both albumin and globulin levels. Specifically, TSH exhibited a negative correlation with albumin, with a correlation coefficient of r=−0.517 and p-value 0.001. Similarly, A significant negative correlation was observed between TSH and globulin, with a correlation coefficient of r = -0.432 and p-value of 0.005.

The findings are consistent with those of Gu et al. (9), who found a significant correlation between FT4 and TSH serum hormones and serum albumin in 164 pediatric nephrotic syndrome patients, with r = -0.513 and p = 0.001 ($p < 0.05$). Similarly, Atish Kumar et al. (10) observed a significant correlation between serum albumin and the levels of FT4 and TSH. This study also found significant correlations between FT4 and TSH hormones with globulin, with r = 0.381 (p = 0.015) and r = -0.432 (p = 0.005), indicating that FT4 and TSH bind to globulin, albeit weakly compared to albumin. In contrast, a study by 2020 Erni Nuraini et al. at Hasan Sadikin Hospital discovered no significant correlation, reporting r = -0.048 and p = 0.407 ($p > 0.05$). Elevated cholesterol levels in nephrotic syndrome patients were also associated with reduced FT4 levels, indicating that thyroid dysfunction may exacerbate lipid abnormalities in these patients. The absence of a significant correlation between TSH and cholesterol could be due to the complex interaction between thyroid hormones and lipid metabolism, which warrants further investigation.

The research conducted in this study identified a significant connection between thyroid dysfunction, hypoalbuminemia, hypoglobulinemia, and abnormal lipid metabolism in children diagnosed with nephrotic syndrome, particularly concerning FT4 and TSH. The relationship between TSH and albumin, as well as FT4 and cholesterol, supports the hypothesis of thyroid hormone binding disruption due to protein loss. The notable positive correlation between FT4 and both albumin and globulin emphasizes how proteinuria in nephrotic syndrome affects thyroid function. Hypoalbuminemia and hypoglobulinemia in NS lead to decreased binding of thyroid hormones, resulting in lower circulating FT4 levels. These findings align with previous studies that reported similar thyroid dysfunctions in nephrotic syndrome patients, emphasizing the need for routine thyroid function monitoring within this group.

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