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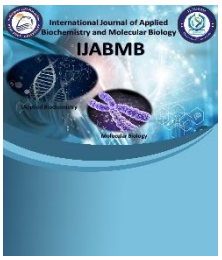

The association of steroid-resistant nephrotic syndrome with non-autoimmune thyroid in children

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Running Title: The nephrotic syndrome with non-autoimmune thyroid in children

Abstract

Background: Nephrotic syndrome is a significant chronic illness that frequently causes relapses in children. Treatment with corticosteroids is the primary approach. But a lot of cases either have serious negative effects from treatment or are resistant to it. MMF stands for mycophenolate, a novel and safer immunosuppressive drug.

Objective: Studying the thyroid function in children with steroid-resistant nephrotic syndrome (SRNS) is the goal.

Patients and methods: Thirty patients diagnosed by both clinical and laboratory studies with idiopathic nephrotic syndrome were recruited from the outpatient clinic for nephrology.

Results: The free T3 level was significantly higher in SR, SD and DC groups as compared to control group. Free T4 was significantly lower in both SR and SD groups as compared to control group. There was no difference between the four groups regarding serum TSH level. There was no significant difference between the three groups regarding free T3 and TSH levels. Free T4 level was significantly lower in SR group as compared to Dc group. There were significant negative correlations between free T3 and protein/creatinine ratio while Free T4 showed significant positive correlations with albumin.

Conclusion: Although none of our patients exhibited subclinical non-autoimmune hypothyroidism, their free T4 levels were lower than those of the control group. In patients with proteinuria and steroid-resistant nephritic syndrome, this could be a sign of T4 loss in the urine.

Keywords: steroid-resistant Nephrotic syndrome, hypothyroidism, children.

Introduction

The most prevalent glomerular condition in children is idiopathic nephrotic syndrome (INS), which is characterized by hypoalbuminemia, edema, and high proteinuria (1). Focal segmental glomerulosclerosis (FSGS) and minimal change nephrotic syndrome (MCNS) are common histologic variations (2). The response to corticosteroid treatment is the primary predictor of disease evolution rather than the histologic diagnosis. It is true that children with steroid-sensitive (SS) nephritic syndrome are less likely than those with steroid-resistant (SR) nephrotic syndrome to experience end-stage renal disease (3).

Variations in plasma TH levels are linked to NS. Serum total thyroxine (T4) and occasionally total T3 levels are decreased because of urinary losses of binding proteins, such as transthyretin or prealbumin, albumin, and TH bound to them. The severity of proteinuria and the levels of serum albumin are both correlated with these hormonal changes. However, since unbound T4 and T3 values are often normal, patients frequently maintain their euthyroid status (4).

This shows that the thyroid may maintain the patient's euthyroid state by compensating for hormonal urine losses. On the other hand, overt hypothyroidism can occur in patients with limited thyroid reserve. In a similar vein, individuals with hypothyroidism may require more exogenous levothyroxine because of NS (5). There have been reports of primary hypothyroidism connected to congenital NS (CNS). The hypothalamus-pituitary-thyroid axis is stimulated by TH urine loss linked to intrauterine large proteinuria, which raises plasma thyrotropin (TSH) levels (6).

Iodine deficiency and hunger are further contributing causes. TH urine losses, however, are the primary reason because additional renal purification therapy combined with bilateral nephrectomy totally restores CNS-associated hypothyroidism and allows for the cessation of levothyroxine hormone medication (4).

For children with CNS, some writers advise levothyroxine supplementation as a therapy because it promotes normal growth (7).

There is variation in the thyroid hormone profile of children having idiopathic nephrotic syndrome. In children not receiving treatment, thyroid hormone concentrations fall during nephrosis while blood thyroid stimulating hormone (TSH) levels rise (8).

During remission, thyroid hormone levels return to normal. Numerous investigations have discovered a relationship between urine T4 levels and serum TSH as well as proteinuria (9). There is variation in the thyroid hormone profile of children having idiopathic nephrotic syndrome. In children who are not receiving treatment, thyroid hormone concentrations fall during nephrosis while blood thyroid stimulating hormone (TSH) levels rise (8).

During remission, thyroid hormone levels return to normal. Numerous investigations have discovered a relationship between urine T4 levels and serum TSH as well as proteinuria (9). In addition to having a lengthy clinical course, children with steroid-resistant nephrotic syndrome (SRNS) may also have persistent proteinuria. There is a shortage of knowledge on thyroid disorders in children having SRNS, although it has a persistent and progressive course (9).

The aim of this study was to determine the thyroid status of children with steroid resistant nephritic syndrome (SRNS).

Patients and methods

Patients with NS who were being followed up at Beni Suef University Hospital's Pediatric Nephrology outpatient clinic participated in this study.

There were forty pediatric patients total, split into four groups: Ten patients with steroid-resistant NS make up group one; ten patients with steroid-dependent NS make up group two; ten patients with steroid-sensitive nephrotic syndrome who have stopped treatment for at least three months make up group three; and ten normal children make up group four.

Inclusion criteria included children with well-established INS aged 1- 18 years with normal kidney function tests. Exclusion criteria included patients with congenital nephrosis, Patients with secondary nephrotic syndrome, Patients with impaired kidney function tests, and Patients known to have thyroid dysfunction.

Written parental consent, a complete history (including name, age, sex, complaint, onset, course, and duration of edema, urine color, dysuria, headache, prior history of similar conditions or family history, hospital admission, treatment, relapses, and renal biopsy) was suspected in all patients. thorough clinical examination, including head and neck, cardiovascular, gastrointestinal, neurological, and upper and lower limb examinations in addition to the general appearance and vital signs.

Measurement of serum BUN, creatinine, Na, K, albumin, cholesterol, protein/creatinine ratio in urine by colorimetric assays, and measurement of serum freeT3, T4 and TSH using ELISA technique were performed.

80% of patients in SR group were on immunosuppressant at the time of the study; 30% were on cyclophosphamide, 20% were on MMF and 30% were on cyclosporine while only 50% of SD group were on immunosuppressant; 10% were on MMF and 40% were on cyclosporine. All patients in SR group underwent renal biopsy (5 patients had FSGS, 4 patients had MCNS, and 1 patient had MesPGN) while in SD group only 5 patients underwent renal biopsy; 4 of them had MCNS and 1 patient had FSGS.

Results

Table 1 showed that there was no significant difference between all groups regarding age, height, weight and BMI. Age of onset was significantly higher in both SR and SD groups as compared to DC group with p value of 0.029 and 0.003 respectively.

Table 1. Comparison between all groups regarding age, height, weight BMI and age of onset

	SR group Mean±SD	**SD group** Mean±SD	**D.C group** Mean±SD	**Control** Mean±SD	P value
Age (Year)	7.7±3.6	10.1±3.2	9.1±2.6	8.9±4.2	0.477
Height (cm)	116.6±21.2	128.7±20.7	129.1±18.0	120.7±20.9	0.439
Weight (kg)	24.2±13.1	31.1±13.5	31.3±11.7	26.1±11.3	0.485
BMI	16.7±3.2	17.9±2.2	18.2±2.8	17.1±2.8	0.604
Age of onset (Year)	4.8±1.8	4.4±0.8	3.4±0.5	-	Pa=0.528, b=**0.029,** c=**0.**

SR=steroid resistant, SD = steroid dependent, DC = discontinued steroid therapy group. P value is significant if < 0.05 Pa = comparison between SR and SD groups. b= comparison between SR and DC groups. c= = comparison between SD and DC groups.

Figure 1 showed that in SR there was 4 males and 6 females, in SD group 9 males and 1 female, in DC group 8 males and 2 females and in control group there was 6 males and 4 females.

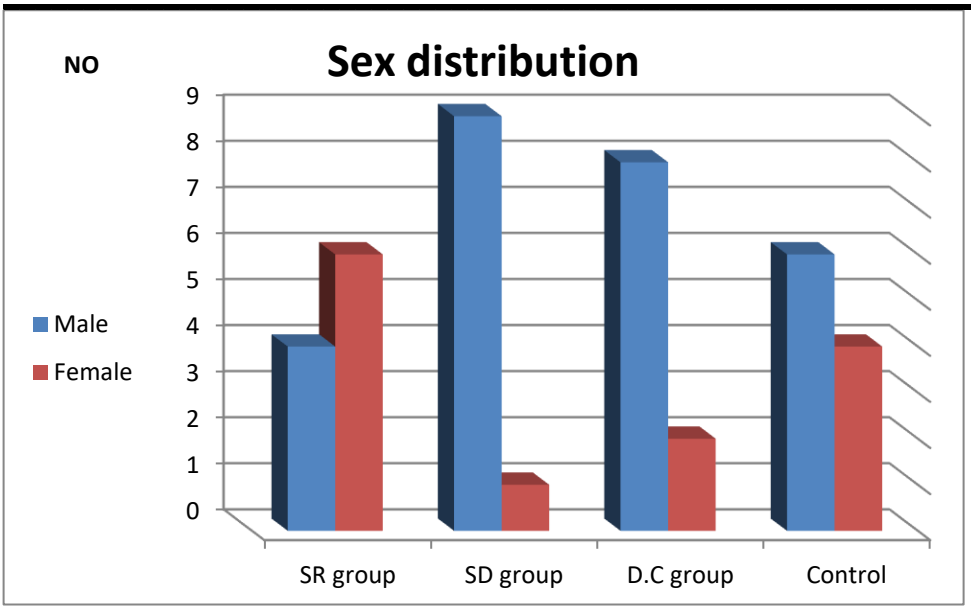

Figure 1: Sex distribution in all groups.

Table 2 showed that SBP was significantly higher in SR, SD and DC groups as compared to control group with p values of 0.002, 0.001 and 0.002 respectively. There was no significant difference between the four groups as regards DBP.

Table 2 Comparison between the three diseased groups and control groups as regards SBP and DBP

	SR group *Mean±SD*	***SD group*** *Mean±SD*	***D.C group*** *Mean±SD*	***Control*** *Mean±SD*	*P value*
SBP	*112.0±6.3*	*116.0±5.2*	*112.0±4.2*	*103.0±8.2*	*Pa=**0.002**, b=**0.001**, c=**0.002***
DBP	*69.0±7.4*	*73.0±9.5*	*68.0±7.9*	*70.0±6.7*	*Pa=0.779, b=0.403, c=0.576*

SBD= systolic blood pressure, DBP= diastolic blood pressure. Pa= comparison between SR and control groups. b= comparison between SD and control groups. c= comparison between DC and control groups.

Table 3 showed that there was no significant difference between SR, SD and DC groups regarding both systolic and diastolic blood pressures.

Table 3 Comparison between SR, SD and DC groups regarding systolic and diastolic blood pressures.

	SR group Mean±SD	**SD group** Mean±SD	**D.C group** Mean±SD	P value
SBP	112.0±6.3	116.0±5.2	112.0±4.2	Pa=0.156, b= 1, c=0.156
DBP	69.0±7.4	73.0±9.5	68.0±7.9	Pa=0.266, b=0.779, c=0.167

SBD= systolic blood pressure, DBP= diastolic blood pressure. Pa= comparison between SR and control groups. b= comparison between SD and control groups. c= comparison between DC and control groups.

Table 4 showed that there was no significant difference between SR, SD, and DC groups as compared to control group as regarding serum creatinine, Na and K levels. Urea and cholesterol levels were significantly higher in the SR group as compared to control group with p value of 0.014 and 0.001 respectively. Serum albumin was significantly lower in SR in comparison to control group (p= 0.001) and Ptn/creat was significantly higher in both SR and SD groups as compared to control (p= 0.001).

Table 5 showed that there was no significant difference between SR, SD, and DC groups regarding serum creat, Na and K levels. Serum urea was significantly higher in SR group as compared to DC group (p= 0.033). As regarding serum albumin, it was significantly lower in the SR group as compared to both SD and DC groups (p= 0.001). Serum cholesterol was significantly higher in the SR group as compared to both SD and DC groups (p= 0.009 and 0.003 respectively) and Ptn/Cr was significantly higher in both SR and SD groups in comparison to Dc group (p=0.001 and 0.002) respectively.

Table 4 Comparison between the three diseased groups and control group as regarding laboratory data

	SR group Mean±SD	**SD group** Mean±SD	**D.C group** Mean±SD	**Control** Mean±SD	**P value**
Urea(mg/dl)	32.1±18.7	25.9±7.5	21.6±4.3	19.8±5.3	Pa=**0.014,** b=0.207, c=0.707
Creat(mg/dl)	0.5±0.2	0.5±0.1	0.4±0.1	0.5±0.1	Pa=0.563, b=0.772, c=0.053
Na(mEq/L)	141.6±4.5	142.3±2.4	143.3±2.4	141.7±1.9	Pa=0.929, b=0.684, c=0.243
K(mEq/L)	4.7±0.6	4.3±0.3	4.5±0.3	4.4±0.4	Pa=0.144, b=0.646, c=0.798
Alb(gm/dl)	3.3±0.9	4.1±0.4	4.4±0.3	4.2±0.2	Pa=**0.001,** b=0.732, c=0.549
Cholesterol(mg/dl)	252.5±140.9	160.1±22.9	146.9±38.9	120.4±18.5	Pa=**0.001,** b=0.242, c=0.432
Ptn/Cr ratio	1.3±0.7	0.9±0.6	0.2±0.1	0.1±0.04	Pa=**0.001,** b=**0.001,** c=0.088

Creat= creatinine, Na= sodium, K= potassium, Alb= albumin, Ptn/Cr= protein / creatinine ratio in urine
Pa= comparison between SR and control groups. b= comparison between SD and control groups. c= comparison between DC and control groups.

Table 5 Comparison between SR, SD and DC groups regarding laboratory data.

	SR group Mean±SD	**SD group Mean±SD**	**D.C group Mean±SD**	**P value**
Urea	32.1±18.7	25.9±7.5	21.6±4.3	Pa=0.200, b=0.033, c=0.371
Creat	0.5±0.2	0.5±0.1	0.4±0.1	Pa=0.772, b=0.117, c=0.066
Na	141.6±4.5	142.3±2.4	143.3±2.4	Pa=0.620, b=0.210, c=0.443

K	4.7±0.6	4.3±0.3	4.5±0.3	Pa=0.058, b=0.224, c=0.476
Alb	3.3±0.9	4.1±0.4	4.4±0.3	Pa=0.001, b=0.001, c=0.348
Cholesterol	252.5±140.9	160.1±22.9	146.9±38.9	Pa=0.009, b=0.003, c=0.694
Ptn/Cr ratio	1.3±0.7	0.9±0.6	0.2±0.1	Pa=0.186, b=0.001, c=0.002

Pa = comparison between SR and SD groups. b= comparison between SR and DC groups c= = comparison between SD and DC groups.

Table 6 showed that the free T3 level was significantly high in SR, SD and DC groups as compared to control group (p=0.01, 0.031, 0.03) respectively. Free T4 was significantly lower in both SR and SD groups as compared to control groups (p= 0.001 and 0.02) respectively. There was no difference between the four groups regarding serum TSH level.

Table 6 Comparison between the three diseased groups and control group as regarding free T3, free T4 and TSH

	SR group Mean±SD	**SD group** Mean±SD	**D.C group** Mean±SD	**Control** Mean±SD	**P value**
Free T3	0.9±0.4	1.1±0.6	0.9±0.5	0.5±0.2	Pa=**0.011,** b=**0.031,** c=**0.030**
Free T4	1.0±0.3	1.5±0.5	1.9±0.9	2.2±0.8	Pa=**0.001,** b=**0.022,** c=0.295
TSH	1.6±1.0	1.4±1.0	1.3±0.7	1.4±0.9	Pa=0.638, b=0.843, c=0.710

Pa= comparison between SR and control groups**.** b= comparison between SD and control groups. c= comparison between DC and control groups**.**

Table 7 showed that there was no significant difference between the three groups regarding free T3 and TSH levels. Free T4 level was significantly lower in SR group as compared to Dc group (p=0.003).

Table 7 Comparison between SR, SD and DC groups as regarding T3, T4 and TSH

	SR group Mean±SD	**SD group** Mean±SD	**D.C group** Mean±SD	**P value**
Free T3	0.9±0.4	1.1±0.6	0.9±0.5	Pa=0.260, b=1, c=0.260
Free T4	1.0±0.3	1.5±0.5	1.9±0.9	Pa=0.077, b=**0.003,** c=0.189
TSH	1.6±1.0	1.4±1.0	1.3±0.7	Pa=0.505, b=0.402, c=0.862

Pa = comparison between SR and SD groups. b= comparison between SR and DC groups c= = comparison between SD and DC groups.

There were significant negative correlations between free T3 and protein/creatinine ratio (figure 3) while Free T4 showed significant positive correlations with albumin (figure 4).

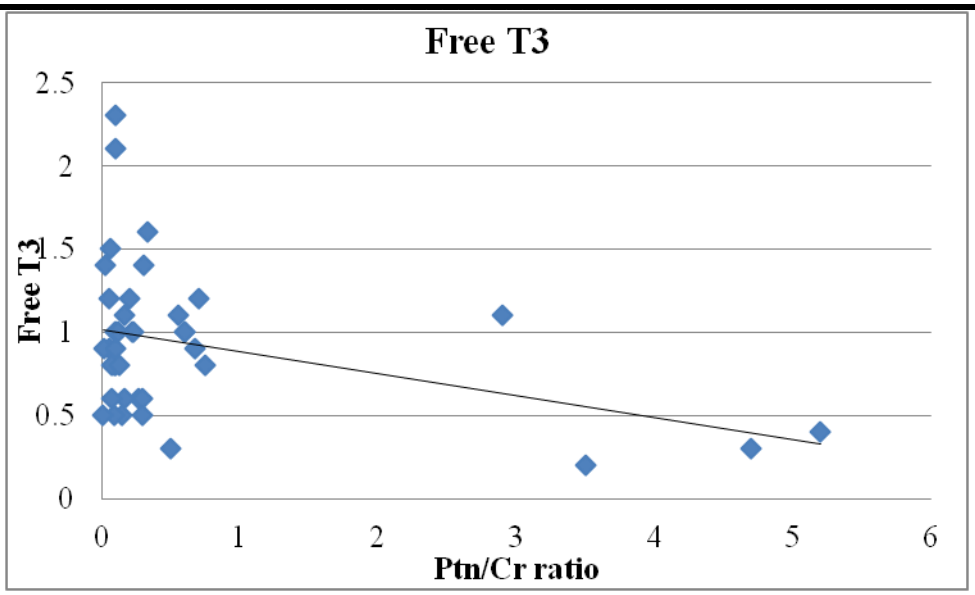

Figure 3 correlation between free T3 and ptn/cr ratio

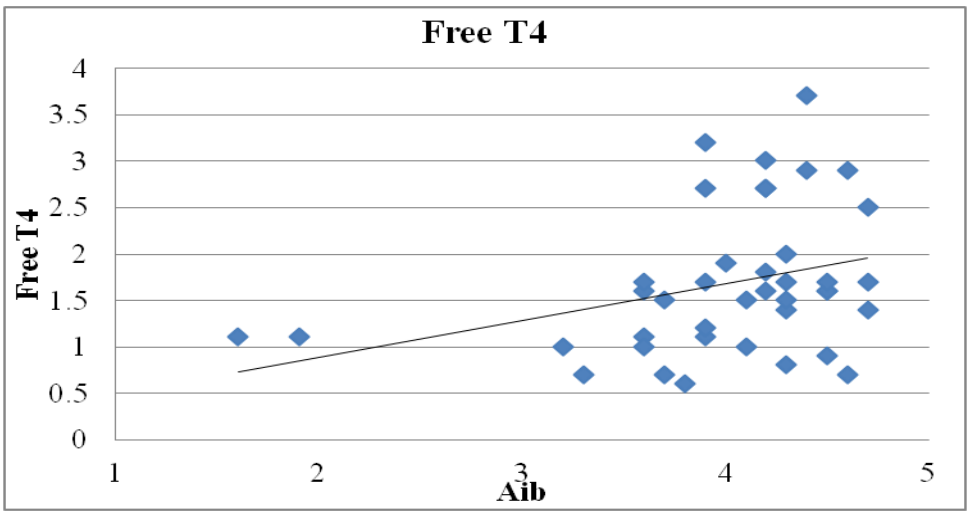

Figure 4 correlation between free T4 and serum albumin

Discussion

Regarding baseline data, the four groups were similar as regard age, weight, BMI. Although it was statistically insignificant, the height was lower in SRNS group than SSNS group with, SDNS group and control group. This can be explained by the effect of long-standing steroid treatment on the growth and chronic course of the disease.

This was consistent with research by Kapoor et al. (2014), which found that while there was not a significant difference in height between the groups under investigation, it was lower in the SRNS group than in the control group. According to a study by Mohamed et al. (2012), children with nephrotic syndrome had lower heights than children in the control group.

Despite there being no significant difference between the 3 groups of SRNS, SDNS and remission group as regards SBP and DBP, the SBP was significantly higher in in SRNS group, in SD group, and in remission group as compared to the control group. This can be explained by side effects of steroids in blood pressure or due to Dyslipidemia and endothelial dysfunction. Ahmed et al, 2012 (11) reported 15 patients from 175 patients of the study were hypertensive (percent 7.9%). in a study conducted in Benin-city in 1998, by Ibadin, et al ,1998 (12) showed a higher incidence of hypertension (41.4%) in patient with nephritic syndrome compared to control group. In contrast to our findings Mary, et al,2007 (13) reported that there was no significant difference between all groups as regards SBP.

Regarding the biochemical profile, there was no significant difference between the 4 groups as regards serum Creatinine, Na and K. This comes in agreement with results of study done by Kapoor K, 2014 (9). Blood Urea level was slightly elevated in SRNS group in comparison to SDNS group.

This can be explained by the catabolic effect of prolonged steroid use, increased protein intake in this patient and hypovolemia due to generalized edema.

In the study of Kapoor K, 2014 (9) blood urea showed no significant difference in SRNS group in comparison to control group.

In the current study serum albumin was significantly lower in SRNS in comparison to SDNS, remission group and control group. In the study done by Kapoor K, 2014 (9), serum albumin in SRNS in comparison to control. The same results were achieved by Mohamed et al, 2012 (10) in patients with nephrotic syndrome in relapse compared to that in remission group.

Serum cholesterol was significantly higher in SRNS in comparison to SDNS with remission group and control group. The same results were reported by Kapoor et al 2014 (9). In Mohamed et al 2012 (10) the mean cholesterol level was significantly higher in the relapsing group compared to remission group.

Regarding proteinuria, A/C ratio was significantly higher in SRNS as compared to remission and control groups. The same results were achieved by D'Amico G et al 2003 (14). In the study done by Kapoor K, 2014 (9) proteinuria was more in SRNS group and in control group.

As regards renal pathology, In our study focal segmental in SR group glomerulosclerosis (FSGS) was the most common pathology occurring in 50% of biopsies, Minimal change nephrotic syndrome (MCNS) was 40% of biopsies and mesangial proliferative glomerulonephritis (MPGN) each occurred in 10% of biopsies but in SD group

Minimal change nephrotic syndrome (MCNS) was 40%, glomerulosclerosis (FSGS) was 10%. in study done by Kapoor K, 2014 (9) it was 70 % Minimal change nephrotic syndrome (MCNS), 20% focal segmental glomerulosclerosis (FSGS), 5% membranoproliferative glomerulonephritis (MPGN)and 5 % membranous glomerulonephritis (MGN).

Ozkaya et al, 2004 (15) showed an increased occurrence of MPGN in the biopsy samples (thirty-four percent), FSGS in twenty-three percent, MCNS and MesPGN in only nineteen percent and seventeen percent respectively, and seven percent other pathological disorders. Indian study conducted by Gulati et al, 2006 (16), demonstrated that FSGS was the commonest lesion accounting for 59%. of all patients followed by mesangial proliferative Glomerulonephritis. In the study of Lamia'a Samir et al 2011 (17) focal segmental sclerosis (FSGS) including its subtypes, (23.4%), followed by mesangial proliferative glomerulonephritis (MesPGN) representing (22.4%) of the cases, and minimal change 18.4 % of cases. In Doe et al 2006 (18) who mentioned that "minimal change disease and focal segmental glomerulosclerosis (FSGS) were the most predominant pathologies on histological analysis. These variations may be due to the difference in the indications of biopsy in different centers.

Regarding thyroid profile: Free T4 was significantly lower in SR group than other groups: SD group, DC group and control group. Despite none of our patients had a free T4 below normal value but 3 patients of them had level of low normal values.

There was a positive correlation between free T4 and serum albumin level, this may be an indicator of loss of T4 in urine. in contrast to this, In the study done by Kapoor K, 2014 (9) Thirty percent of children suffering from SRNS showed subclinical thyroid hypofunction, a prevalence far higher than the two percent or so found in children who were otherwise healthy in the study by Rapa A et al. (2009). Similarly, a recent series of five SRNS children who developed non-autoimmune hypothyroidism was reported by Dagan et al. (2012) (20).

Proteinuria and autoimmune processes have been implicated in the pathophysiology of these thyroid abnormalities. Thyroid-binding globulin, prealbumin, and albumin are the primary proteins to which thyroid hormone is bound in the bloodstream (21). According to Afroz S et al. (2011) (8), there is an increase in the urine secretion of total T3, total T4, and TBG throughout nephrosis, which returns to normal during remission.

This could result from persistent proteinuria. Tubular epithelial cells may gradually decline the body's ability to absorb several LMW proteins. After anatomic damage has occurred, there might not be any more anatomic damage. Even though there seems to be a decrease in the fractional removal of HMW and LMW proteins, which would indicate an improvement in the impairment of the selectivity along with the permeability of a glomerular filter, some LMW proteins could be still lost (14).

Hypothyroidism may result from the thyroid gland's inability to produce enough thyroid hormones to make up for the hormones lost through urine (4). In patients with proteinuria, subclinical hypothyroidism is more prevalent than overt hypothyroidism (22). Since TSH has a molecular weight of 28,500 Da, it is an LMW protein and children with SRNS may have a greater amount of LMW proteins in their urine (23).

In comparison to the control group, the SR group had decreased free T4 (Kapoor K, 2014, 9). Hypothyroidism may result from the thyroid gland's inability to produce enough thyroid hormones to make up for the hormones lost through urine (4). In patients with proteinuria, subclinical hypothyroidism is more prevalent than overt hypothyroidism (22).

First off, since corticosteroids are frequently employed in treating patients with proteinuria, they directly reduce the release of TSH from the pituitary, which is an LMW protein that may be lost in the urine of children having SRNS, which is linked to an increased loss of LMW proteins (23). (24). Lower amounts of TRH mRNA in the brain's hypothalamus are caused by glucocorticoids, and this is probably the main reason why the pituitary secretes less TSH (25) These occurrences might be the cause of our children's normal serum TSH levels and lack of overt thyroid dysfunction.

In our research, the SR group's free T3 value was noticeably higher than that of the SD group and the DC group relative to the control group. A negative connection was seen between proteinuria and free T3. On the other hand, the research conducted by

Kapoor K in 2014 (9) revealed that the SRNS group had lower free T3 levels than the control group.

There was no difference in TSH levels between the SR group, SD group, DC group, and control group. In contrast, the SR group had a higher TSH level than the control group according to Kapoor K, 2014 (9).

Conclusion:

Although none of our patients exhibited subclinical non-autoimmune hypothyroidism, their free T4 levels were lower than those of the control group. In patients with proteinuria and steroid-resistant nephritic syndrome, this could be a sign of T4 loss in the urine.

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