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Low T3 Syndrome in Adult Patients with Nephrotic Syndrome

Erişkin Nefrotik Sendromlu Hastalarda Düşük T3 Sendromu

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ABSTRACT

OBJECTIVE: The aim of this study is to evaluate the frequency of thyroid dysfunction in adult patients with nephrotic syndrome and to investigate the relation between nephrotic syndrome and low triiodothyronine (T3) syndrome.

MATERIAL and METHODS: Thirty three adult patients with nephrotic syndrome and 20 healthy controls were included in the study. Serum thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were measured by chemiluminescent immunoassay. Proteinuria was measured in a 24-hour urine collection. Estimated Glomerular Filtration Rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) equation.

RESULTS: The mean age of the patients was 49±17 years. The mean levels for the parameters measured were as follows: serum albumin, 22±5 (g/L); urinary protein excretion in 24 hour collections, 7.8±4.5 (g/day), serum creatinine 1.32±0.66 (mg/dL) ; serum TSH, 3.2±3.1 (mIU/mL).; fT3, 2.5±0.6 (pg/mL), and fT4, 1.0±0.30 (ng/dL). In nephrotic syndrome patients, the mean serum TSH level was significantly higher whereas mean fT3 level was significantly lower when compared to the levels in the control group. Serum fT3 level correlated positively with serum albumin (r:0.56, p:0.01) and fT4 (r:0.51, p:0.03) and negatively with total cholesterol (r:-0.39, p:0.03). Seven (21%) patients were hypothyroid, 3 (9%) were hyperthyroid, and 11 (33%) had low T3 syndrome.

CONCLUSION: Thyroid dysfunction, low T3 syndrome in particular, is frequent in adult patients with nephrotic syndrome. The free T3 level correlates with the severity of nephrotic syndrome. Further studies are necessary regarding the clinical importance of low T3 syndrome.

KEY WORDS: Thyroid hormone, Thyroid dysfunction, Low T3 syndrome, Low fT3, Nephrotic syndrome

ÖZ

AMAÇ: Bu çalışmanın amacı, erişkin nefrotik sendromlu olgularda tiroid disfonksiyonu sıklığını değerlendirmek, ve düşük triiodotironin (T3) sendromu ve nefrotik sendrom arasındaki ilişkiyi incelemektedir.

GEREÇ ve YÖNTEMLER: Tiroid fonksiyon parametreleri olan, 33 erişkin nefrotik sendromlu olgu ve 20 sağlıklı kontrol çalışmaya alındı. Serum tiroid sitimüle edici hormon (TSH), serbest tiroksin (fT4) ve serbest T3 (fT3) düzeyleri Kemilüminesans ile immünoassay yöntemi kullanılarak incelendi. Glomerüler filtrasyon hızı (eGFH), Renal Hastalıkta Diyet Modifikasyonu (MDRD) formülü kullanılarak hesaplandı. Proteinüri 24 saatlik idrarda ölçüldü.

BULGULAR: Hastaların yaş ortalamaları 49±17 yıldı. Ortalama serum albumine 22±5 (g/L), 24 saatlik idrarda protein 7,8±4,5 (g/gün) ve serum kreatinin 1,32±0,66 (mg/dL)'di. Hastaların TSH ortalaması 3,2±3,1(mIU/mL), serbest T3 ortalaması 2,5±0,6 (pg/mL) ve serbest T4 ortalaması 1,0±0,30 (ng/dL)'dı. Nefrotik sendromlu hastalar kontrol grubuyla kıyaslandığında ortalama TSH düzeyleri daha yüksek, serbest T3 düzeyleri ise daha düşüktü. Nefrotik sendromlu hastalarda serbest T3 düzeyi, serum albumin (r:0,56, p:0,01), ve serbest T4 (r:0,51,p:0,03) ile pozitif, total kolesterol (r: -0,39, p:0,04) ile ise negatif korelasyon göstermekteydi. Hastaların 7 (%21) tanesinde hipotroidi, 3'ünde (%9) hipertroidi ve 11 'inde (%33) ise düşük T3 sendromu vardı.

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SONUÇ: Erişkin nefrotik sendromlu olgularda düşük T3 sendromu başta olmak üzere tiroid disfonksiyonu oldukça fazla görülmektedir. Serbest T3 düzeyi ile nefrotik sendromun ciddiyeti arasında korelasyon bulunmuştur. Düşük T3 sendromunun klinik önemine yönelik ileri incelemeye ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: Tiroid Hormonu, Tiroid disfonksiyonu, Düşük T3 sendromu, Düşük T3, Nefrotik sendrom

INTRODUCTION

The kidneys play a significant role in thyroid hormone metabolism. Deterioration in kidney functions may lead to important alterations in thyroid functions for which a variety of mechanisms have been suggested (1,2). In the nephrotic syndrome, however, loss of thyroid hormones as well as thyroid binding globulin leads to a compensatory increase in serum TSH level ending up with a thyroid dysfunction (3,4). Conversely, hypothyroidism may be an etiological factor in nephrotic syndrome in pediatric patients, and may lead to resistance to treatment (5). In the adult nephrotic syndrome, however, the exact frequency of impaired thyroid function is unclear.

Nephrotic syndrome is characterized by hypoalbuminemia, edema, and dyslipidemia. It is associated with increased oxidative stress, endothelial dysfunction, and atherosclerosis (6,7). The risk for cardiovascular disease is increased in patients with nephrotic syndrome (6-8). The low T3 syndrome commonly accompanies chronic kidney disease (CKD), and its frequency increases with the severity of the disease (9). The low T3 syndrome is now considered to be responsible for increased mortality and morbidity both in patients with CKD and the non-uremic population (10-13). On the other hand, the exact frequency of low T3 as well as its clinical significance in nephrotic syndrome remains unclear.

The aim of this study was to evaluate the frequency of thyroid dysfunction in adult patients with nephrotic syndrome and to investigate the relation between nephrotic syndrome and low T3 syndrome.

MATERIAL and METHOD

Thirty three nephrotic syndrome patients who had presented at our outpatient clinic and 20 healthy controls in two nephrology centers were examined in the study. Inclusion criteria were to be older than 18 years and have all the criteria for the diagnosis of nephrotic syndrome (Proteinuria > 3.5 g/d, hypoalbuminemia, dyslipidemia, and edema). Exclusion criteria were the presence of a positive medical history for thyroid disorder, active infection, or malignancy. Demographical, clinical and laboratory characteristics along with renal biopsy data performed for diagnostic purposes were recorded retrospectively from the patients' charts.

Serum TSH, free T4, and free T3 were measured by chemiluminescent immunoassay. Normal ranges for TSH, fT3 and fT4 were 0.41-4.24 mIU/mL, 2.5-3.9 pg/mL, and 0.61-1.06 ng/dL respectively. Thyroid abnormalities were defined as follows: Overt hypothyroidism: TSH > 4.24 mIU/mL and fT4 < 0.61 ng/dL; subclinical hypothyroidism: TSH >4.24 mIU/mL and fT4 normal; hyperthyroidism: TSH < 0.41 mIU/mL and fT4 > 1.06 ng/dL; subclinical hyperthyroidism: TSH < 0.41 mIU/mL and fT4 normal. The low T3 syndrome was defined as a serum fT3 level below the lower limit of the reference interval (< 2.5 pg/mL) with a TSH level within normal range (0.41–4.24 IU/ml) and fT4 level which is normal or low (normal range: 0.61–1.06 ng/dl) (14). Proteinuria was measured in a 24-hour urine collection. Estimated Glomerular Filtration Rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) Formula (15).

Statistical Analysis

All parameters are expressed as mean ± standard deviation (SD). A p value less than 0.05 was considered as statistically significant. Comparisons between two groups were assessed by independent t-test analysis. Pearson correlation was used to assess correlations of thyroid hormones with other variables. All statistical analyses were performed using SPSS, version 15 (Chicago, IL, USA).

RESULTS

The mean age of the patients was 49±17 years. Twenty three were female and 10 were male. A medical history of diabetes and hypertension was present in 12% and 18% of the patients, respectively. The etiology of nephrotic syndrome was membranous nephropathy in 12 (36%), focal segmental glomerulosclerosis in 6 (18%), AA amyloidosis in 8 (24%), minimal change disease in 4 (13%), membranoproliferative glomerulonephritis in 2 (6%), and IgA nephropathy in 1 (3%). The demographic and laboratory data of the patients are shown in Table I.

The average levels for the parameters measured were as follows: serum albumin, 22±5 (g/L); urinary protein excretion in 24 hour collections, 7.8±4.5 (g/day); serum TSH, 3.2±3.1 (mIU/mL).; fT3, 2.5±0.6 (pg/mL), and fT4, 1.0±0.30 (ng/dL). The serum fT3 level correlated positively with serum albumin (r:0.56, p:0.01), and fT4 (r:0.51,p:0.03) and negatively with total cholesterol (r: -0.39, p: 0.03). These correlations are demonstrated in Figure 1A,B. When the patients were separated into two groups according to the median serum fT3 level, the serum albumin level was observed to be significantly low in the group with lower serum T3 level whereas the levels of both total and LDL cholesterol as well as the amount of proteinuria were higher (Table I).

Table I: Demographic, clinic, and laboratory data of the study patients and correlation of free triiodothyronine (fT3) with clinical laboratory findings.

	All patients (n:33) (Mean±SD)	**Low free T3 (n:17, ≤2.50 pg/mL) (Mean±SD)**	**High free T3 (n:16, >2.50 pg/mL) (Mean±SD)**	**p value**	**Rho (p)**
Age (years)	49±17	47±17	50±16	0.617	0.05 (0.78)
Gender (M/F)	23/10	13/4	10/6	0.372	-0.30 (0.87)
Diabetes Mellitus, (%)	12	5	18	0.116	-0.01 (0.93)
CVD (%)	9	12	6	0.583	-0.49 (0.79)
Hypertension (%)	18	12	25	0.318	-0.11(0.53)
Proteinuria (g/day)	7.8±4.5	9.8±5.4	5.8±2.5	0.015	-0.13 (0.47)
Serum Albumin (g/L)	22±5	19±4	26±4	<0.001	0.56(0.01)
Total Cholesterol (mg/dL)	344±111	383±94	272±89	0.004	-0.39 (0.04)
Triglyceride (mg/dL)	214±114	237±143	172±53	0.107	-0.06 (0.77)
LDL(mg/dL)	249±108	281±87	175±86	0.006	-0.39 (0.05)
HDL(mg/dL)	52±15	55±15	49±15	0.292	-0.31 (0.10)
Serum Creatinine (mg/dl)	1.32±0.66	1.28±0.72	1.33±0.66	0.835	0.19 (0.30)
eGFR (ml/min/ 1.73m^2)	77±48	83±52	75±48	0.649	-0.11 (0.55)
CRP (mg/dl)	1.7±3.7	2.1±4.8	1.2±2.8	0.565	-0.24 (0.27)
Uric Acid (mg/dl)	5.9±1.3	5.8±1.1	5.9±1.2	0.640	-0.98 (0.64)
Sodium (meq/dL)	140±3	139±3	140±3	0.685	-0.78 (0.67)
TSH (μIU/mL)	3.2±3.1	3.4±3.2	3.4±3.3	0.965	-0.86 (0.64)
Free T3 (pg/mL)	2.5±0.6	2.1±0.4	3.0±0.5	<0.001	1
Free T4 (ng/dL)	1.0±0.30	1.0±0.30	1.0±0.40	0.986	0.51(0.003)

LDL: Low-density lipoprotein, **HDL:** High-density lipoprotein, **CRP:** C-reactive protein, **eGFR:** Estimated glomerular filtration rate, **TSH:** Thyroid-stimulating hormone, **T3:** Triiodothyronine, **T4:** Thyroxine.

Six of the patients had subclinical, while 1 had clinical hypothyroidism, 1 had subclinical hyperthyroidism and 2 had clinical hyperthyroidism. Eleven of the patients (33%) had low T3 syndrome. A total of 21 (63.6%) out of 33 patients had a thyroid dysfunction. When compared to others, low T3 syndrome patients had significantly low serum albumin levels (2.4±0.5 g/L, 1.9±0.3 g/L; p:0.008), whereas the amount of proteinuria (6.8±3.5 g/day, 9.6±5.7 g/day; p:0.161), and serum C-reactive protein (CRP) levels (1.2±1.9 mg/dL, 2.6±5.6 mg/dL; p:0.406) tended to be higher in this group.

The mean age of the control group was 44±11 years. Age and sex ratios of the control group were similar to the nephrotic syndrome patients. Thyroid function parameters were as follows: TSH, 1.29±0.68 (0.41-2.90) (mIU/mL).; fT3, 3.24±3.16 (2.51-5.30) (pg/mL), and fT4, 1.06±0.15 (0.80-1.30) (ng/dL). Thyroid dysfunction was not present in this group. Serum TSH (1.29±0.68, 3.24±3.16; p=0.002) and fT3 (3.44±0.63, 2.50±0.61; p<0.001) levels differed significantly between the controls and nephrotic patients whereas serum fT4 levels were similar in both groups (Table II).

DISCUSSION

In this cross- sectional study, we found that alterations in thyroid function parameters are quite frequent in adult nephrotic syndrome patients .We observed low T3 syndrome in one-third of the patients. We found an inverse correlation between tbetween serum free T3 levels and the severity of nephrotic syndrome.

Kidneys have important effects on thyroid hormone metabolism. They play a role in the clearance of iodine, TSH and thyrotropin-releasing hormone (1,2). Alterations in thyroid hormone levels may be observed in nephrotic syndrome (3,4). The loss of thyroid hormones as well as thyroid binding globulin

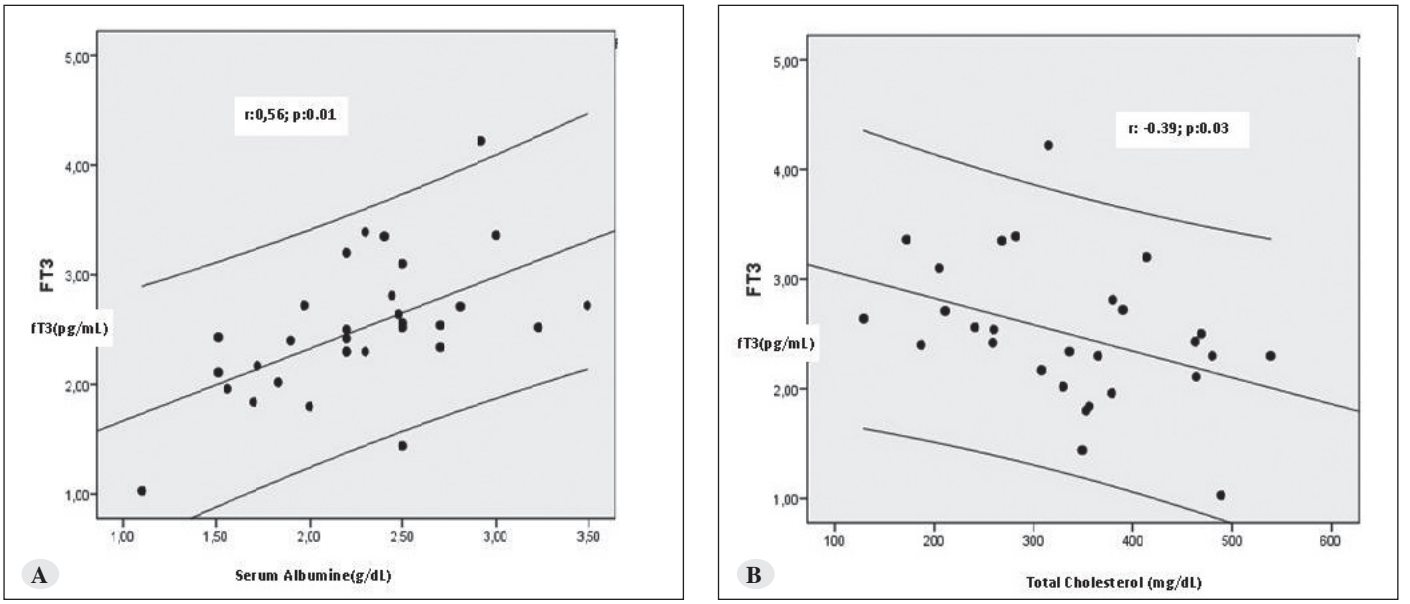

Figure 1: *Correlations of fT3 levels with Serum Albumin* ***(A)*** *and Total Cholesterol* ***(B)***.

Table II: Comparison of thyroid function parameters in patients with nephrotic syndrome and the control group.

	Nephrotic syndrome patients (n:33)	The control groups (n:20)	p value
TSH (mIU/mL) Mean±SD (Range)	3.24±3.16 (0.01-12.45)	1.29±0.68 (0.41-2.90)	0.002
Free T3 (pg/mL) Mean±SD (Range)	2.50±0.61 (1.03-4.22)	3.44±0.63 (2.51-5.30)	<0.001
Free T4 (ng/dL) Mean±SD (Range)	0.95±0.30 (0.37-2.09)	1.06±0.15 (0.80-1.30)	0.159

TSH: Thyroid-stimulating hormone, **T3:** Triiodothyronine, **T4:** Thyroxine.

in nephrotic syndrome leads to a compensatory increase in serum TSH level ending up with thyroid dysfunction (3,4). There are a limited number of studies on this issue. In a study with 159 patients with nephrotic syndrome, Gilles et al.(16) found that 11.3% of the patients had subclinical hypothyroidism and had significantly higher serum TSH levels when compared to the control group. The study emphasized that the frequency of clinical hypothyroidism among nephrotic patients was quite low. In our study, clinical hypothyroidism was found in only 1 patient whereas the frequency of subclinical hypothyroidism was 18%.

On the other hand, experimental and clinical studies have shown that thyroid hormones play an important role in glomerular and tubular function as well as in water and electrolyte homeostasis (17). Both clinical and subclinical hypothyroidism may lead to a decrease in GFR and renal blood flow, ending up with an elevated serum creatinine level (17). Similarly, hypothyroidism is considered to be responsible in the etiology of steroid-resistant pediatric nephrotic syndrome, particularly in patients with end-stage kidney disease (5).

Low T3 syndrome is observed quite commonly in the course of CKD with a frequency range between 20 and 80% (9). In the pathogenesis of low T3 syndrome, proinflammatory mechanisms which lead to inhibition of the 5-deiodinase enzyme and therefore block the peripheral fT4 to fT3 conversion are implicated (18,19). In addition, the low T3 syndrome is associated with endothelial dysfunction, atherosclerosis, and cardiac dysfunction in CKD patients (20-22) and with cardiovascular mortality and morbidity in both uremic and non-uremic populations (10,11,13,21,22). The frequency of the low T3 syndrome in nephrotic patients is

unknown. Serum fT3 has previously been reported to be low in nephrotic patients (5). However, the clinical significance of low T3 in these patients remains unclear. Various mechanisms may be responsible; first, the increased inflammation in nephrotic syndrome may inhibit conversion of fT4 to fT3 due to blockage of 5-deiodinaseand second, serum fT3 levels may be decreased as an adaptive mechanism to minimize energy consumption.

The several limitations of this study include the low number of patients, and the cross-sectional and retrospective nature of the study. Therefore we were not able to find a causal relationship between thyroid hormones and nephrotic syndrome. Other limitations were that serum total T3 and T4 levels were not studied, and the amount of thyroid hormone loss in urine was not measured. However, this study could serve as a model for future investigations as it reports the frequent low T3 syndrome concurrence in nephrotic patients for the first time.

In conclusion, thyroid dysfunction, particularly low T3 syndrome, is frequent in adult patients with nephrotic syndrome. Serum free T3 levels correlate inversely with the severity of nephrotic syndrome. Further studies are necessary regarding the clinical importance of low fT3 levels.

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