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Original Article

Evaluation of kidney function in children with Hashimoto's Thyroiditis

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Abstract

Aim: Thyroid hormones have various effects on kidney function and both hypothyroidism and hyperthyroidism may result in clinically important alterations in kidney function. Therefore, we evaluated kidney functions and changes in kidney functions over time in children with Hashimoto thyroiditis (HT) who treated or not treated with thyroid hormone replacement therapy.

Materials and Methods: The patients were divided into three groups. Group 1 included patients who had hypotroidism and received treatment, group 2 included patients who had euthyroid goiter and received treatment and group 3 consisted of patients who were clinically euthyroid and not received any treatment. All participants were followed prospectively. Serum creatinine (Cr), albumin and serum cystatin C (CysC) levels, estimated glomerular filtration rate eGFR, and urine protein to creatinine ratio (PCR) were measured at the time of diagnosis and one and six months after diagnosis

Results: There were significant differences between baseline and follow-up characteristics of the group 1 in terms of serum Cr, urine PCR, CysC and eGFR. The baseline and follow-up characteristics of groups 2 and 3 were not statistically significant.

Conclusion: Children with HT may present with kidney dysfunction and proteinuria, which improve with thyroid hormone replacement. We think that clinicians who follow children with HT should pay attention to this issue.

Keywords: Children; hashimoto's thyroiditis; kidney disease; proteinuria

INTRODUCTION

The most common thyroid disorder in childhood is Hashimoto's thyroiditis (HT). Patients with HT may present with clinical and laboratory findings of hypothyroidism, euthyroidism or hyperthyroidism (1-3). Kidney involvement in HT is not rare and different renal pathologies, such as membranous nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, acute kidney injury and renal tubular acidosis, can emerge during the course of the disease (4-8).

Thyroid dysfunctions can cause kidney diseases by affecting kidney physiology and development. Thyroid hormones affect renal functions via both pre-renal and renal factors. Pre-renal effects occur through effects on renal blood flow and the cardiovascular system. Direct renal effects take place through the effects of thyroid hormones on glomerular filtration rate (GFR), tubular secretion and reabsorption, as well as through effects on renal tubular physiology (9-11).

Hypothyroidism may decrease GFR and subsequently cause elevation of serum creatinine. It is shown that thyroid hormone replacement in patients with overt or subclinical hypothyroidism improves renal function and proteinuria (12). The aim of this study is to evaluate kidney functions and changes in kidney functions over time in children with Hashimoto thyroiditis (HT) who treated or not treated with thyroid hormone replacement therapy.

MATERIALS and METHODS

Forty-one children who referred to the department of pediatric endocrinology and who were diagnosed with HT were included in the study. Patients who had known kidney disease were excluded from the study. Hypothyroidism is defined as a deficiency of circulating thyroid hormones. Euthyroid goiter is defined as a normal thyroid hormone level and thyroid tissue greater than normal (2,13). Age, sex, weight, height, blood pressure, body mass index (BMI) and laboratory findings of all cases were recorded. Cut of values were obtained for TSH and fT4 levels according to

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age and gender. Patients with euthyroid goiter had normal thyroid hormone levels and high thyroid autoantibodies. In addition, ultrasonography hashimoto thyroiditis findings and physical examination had goiter. HT diagnoses were made based on high anti-thyroglobulin (anti-TG) and/or anti-peroxidase (anti-TPO) autoantibody levels. The patients were subdivided into three groups. Group 1 included patients who had hypotroidism and received treatment, group 2 included patients who had euthyroid goiter and received treatment and group 3 consisted of patients who were clinically euthyroid and not received any treatment. All participants were followed prospectively. Serum creatinine (Cr), albumin and serum cystatin C (CysC) levels, estimated glomerular filtration rate (eGFR), and urine protein to creatinine ratio (PCR) were measured at the time of diagnosis and one and six months after diagnosis. Estimated glomerular filtration rate (eGFR) were calculated with the Schwartz formula (14). The first urine sample was taken in the morning. Abnormal proteinuria was described if urine PCR> 0.2 g/gr Cr (15). L-thyroxine therapy (1 µg/kg/day) was given in patients in group 1 and 2.

This study conformed to the Declaration of Helsinki and was approved by the Erciyes University Ethics Committee (2014/581). Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

Data were evaluated with IBM SPSS 24.0 (Chicago, USA) statistical program. In the analysis of categorical variables, Chi-Square and Fisher's Exact Tests were used. In the analysis of continuous variables, Mann-Whitney U and Kruskal Wallis tests were used. Data with normal distribution were expressed as mean±standard deviation (SD), and the parameters with abnormal distribution were expressed as median [interquartile range (IQR)]. Means of the groups at different time points were compared by Wilcoxon test, followed by Bonferroni post hoc test to determine significant differences between groups and p < 0.017 was set as the level of significance for Wilcoxon test. A p value less than 0.05 was considered as statistically significant. The relationship between fT4, TSH levels and PCR, GFR at the time of diagnosis was evaluated by Spearman correlation analysis. A p value of <0.01 was considered statistically significant.

RESULTS

A total of 41 cases, 34 (83%) were girls and 7 (17%) were boys. The average age at diagnosis was 11.1 (8-14.8) years. There were 28 patients in Group 1, 6 patients in Group 2, and 7 patients in Group 3. Demographic characteristics, clinical and laboratory findings at the time of diagnosis were given in Table 1. There was no significant difference between three groups in terms of age, gender, BMI, blood pressure and anti-TG levels (p >0.05). TSH levels were higher and free T4 levels were lower in group 1 compared to group 2 and 3. Both achieved statistical significance (p<0.001). There was no difference between group 2 and group 3 (p>0.05) for TSH and free T4 levels. Anti-TPO levels were significantly higher in group 1 than group 2 and group 3 (p=0.006 and p=0.001, respectively).

Serum Cr, urine PCR, CysC and GFR levels of the patients at the beginning of treatment, at the first month of the treatment, and at the sixth month of the treatment were given in Table 2.

In group 1, Cys C and eGFR levels were significantly increased at the first and six months of the treatment compared to onset of the treatment. The mean Cys C levels were 0.68 mg/L at onset and 0.86 mg/L at sixth month of treatment. The mean eGFR levels were 94 at onset and 130 ml/min/1.73 m^2 at sixth month of treatment. Baseline serum Cr levels and urine PCR were significantly higher compared to the first and six months of the treatment. There was also a significant difference between the first and six months of the treatment for urine PCR (Table 2). However, there was no statistical significance among the three periods in terms of serum albumin levels.

Comparison of baseline serum Cr, PCR, CysC and eGFR levels between groups are given in Table 3. The baseline serum Cr levels were significantly higher in group 1 than in group 2 (p=0.001) and group 3 (p=0.001). The baseline PCR was significantly higher in group 1 than in group 2 (p=0.047) and group 3 (p=0.006). Moreover, eGFR levels were significantly lower in group 1 than group 2 (p=0.043) and group 3 (p<0.001).

Table 1. Demographic characteristics, clinical and laboratory findings at the time of diagnosis

	Group 1 (n:28)	Group 2 (n:6)	Group 3 (n:7)	p value
Age (years)*	11(9.3-13.4)	10.2(9-13.7)	11.2(8.5-12.8)	p=0.876
Gender (female, %)	82	83	86	p=0.975
BMI (kg/m²)*	16.2(15.5-18.4)	16.6(15.6-19.9)	16.8(15.3-17.2)	p=0.955
T4 (ng/dL)*&	0.44(0.23-0.67)	1,15(1.09-1.55)	1,12(0.48-1.19)	**p<0.001**
TSH (µIU/mL)*&	50 (37.25-64.0)	4.11 (3.10-4.42)	3.84 (3.60-4.56)	**p<0.001**
anti-TPO (IU/mL)*&	631(430-948)	228(150-280)	281(198-432)	**p=0.001**
anti-TG (IU/mL)*	98 (31.5-138.25)	82.5 (19.1-437.0)	117 (21-234)	p=0.979

n=number of cases, *:Median (25^{th}-75^{th} percentile), BMI: Body mass index, p<0.05 statisticaly significant, &: Group 1 was significantly different from groups 2 and 3

Table 2. Comparison of serum Cr, Urine PCR, CysC, and eGFR at baseline, at first and sixth months of treatment

Groups	Onset (a)	1st month (b)	6th month (c)	p value
Group 1 (n=28)				
Cr (mg/dL)	0.90(0.76-1.08)	0.70(0.62-0.80)	0.70(0.66-0.70)	**a vs b p<0.001**
				b vs c p=0.038
				a vs c p<0.001
Urine PCR (mg/mg)	0.41(0.28-0.61)	0.17(0.14-0.21)	0.12(0.10-0.14)	**a vs b p<0.001**
				b vs c p<0.001
				a vs c p<0.001
CysC (mg/L)*	0.68(0.64-0.76)	0.82(0.71-0.84)	0.86(0.83-0.88)	**a vs b p<0.001**
				b vs c p=0.002
				a vs c p<0.001
GFR (ml/min/1.73 m²)	94(82-112)	128(124-141)	130(124-148)	**a vs b p<0.001**
				b vs c p=0.008
				a vs c p<0.001
Group 2 (n=6)				
Cr (mg/dL)	0.57(0.51-0.66)	0.61(0.58-0.63)	0.61(0.56-0.66)	p=0.538
Urine PCR (mg/mg)	0.31(0.19-0.51)	0.21(0.17-0.25)	0.15(0.12-0.16)	p=0.046
CysC (mg/L)	0.70(0.61-0.75)	0.80(0.75-0.85)	0.87(0.73-0.92)	p=0.069
eGFR (ml/min/1.73 m²)	117(108-127)	119(110-134)	126(109-130)	p=0.223
Group 3 (n=7)				
Cr (mg/dL)	0.60(0.58-0.64)	0.64(0.60-0.65)	0.66(0.60-0.66)	p=0.061
Urine PCR (mg/mg)	0.14(0.12-0.18)	0.16(0.14-0.17)	0.14(0.13-0.15)	p=0.717
CysC (mg/L)	0.76(0.69-0.84)	0.84(0.78-0.86)	0.80(0.69-0.82)	p=0.180
eGFR (ml/min/1.73 m²)	132(124-146)	128(122-138)	124(119-148)	p=0.050

PCR, protein to creatinine ratio; CysC, cystatin C; Cr, creatinine; eGFR, estimated glomerular filtration rate
All parameters are shown as median (25th-75th percentile). p<0.017 statisticaly significant

Table 3. Comparison of laboratory values between groups at onset

Variables	Group 1 (n=28)	Group 2 (n=6)	Group 3 (n=7)	p value
Cr (mg/dL)	0.90(0.60-1.50)	0.57(0.50-0.70)	0.60(0.45-0.66)	**1 vs 2 p=0.001**
				1 vs 3 p=0.001
				2 vs 3 p=0.998
Urine PCR (mg/mg)	0.41(0.16-1.21)	0.31(0.15-0.65)	0.14(0.12-0.21)	**1 vs 2 p=0.047**
				1 vs 3 p=0.006
				2 vs 3 p=0.884
CysC (mg/L)	0.68(0.43-1.22)	0.70(0.53-0.75)	0.76(0.62-0.90)	1 vs 2 p=0.434
				1 vs 3 p=0.303
				2 vs 3 p=0.991
GFR (ml/min/1.73 m²)	94(72-134)	117(108-132)	132(114-166)	**1 vs 2 p=0.043**
				1 vs 3 p<0.001
				2 vs 3 p=0.186

PCR, protein to creatinine ratio; CysC, cystatin C; Cr, creatinine; eGFR, estimated glomerular filtration rate
All parameters are shown as median (25th-75th percentile). p<0.05 statisticaly significant

In Group 1, while the eGFR levels of 12 patients were between 60 and 89 ml/min/1.73 m^2 at the beginning, none of the patients had a GFR lower than 60 ml/min/1.73 m^2.

In the correlation analysis, fT4 level was negatively correlated with PCR level and positively correlated with GFR level. TSH level was positively correlated with PCR level and negatively correlated with GFR level at the time of diagnosis (Table 4).

Table 4. The relationship between fT4, TSH levels and PCR, GFR at the time of diagnosis

	PCR		GFR	
	r	p	r	p
fT4	-0.449	0.003	0.515	0.001
TSH	0.439	0.004	-0.556	0.000

PCR, protein to creatinine ratio; eGFR, estimated glomerular filtration rate

DISCUSSION

This study demonstrates that hypothyroidism in children with HT are associated with impaired kidney functions which is improved after thyroid hormone replacement therapy. HT is a disease that is more common in girls and is the most common cause of hypothyroidism in childhood (16). Because of the autoimmune nature of the disease, girls were more in our study (83%; n=34). In HT, the clinical picture can differ from euthyroid to hypothyroidism or hyperthyroidism; however, hypothyroidism is more common in children (16). In our study, 68% of the cases had hypothyroidism at the time of diagnosis. L-thyroxine therapy is recommended for children with hypothyroidism, as well as children with goiter without a hypothyroidism (17). As recommended, we used L-throxine treatment in group 1 (hypothyroidism) and group 2 (goiter without hypothyroidism).

Thyroid hormones, especially triiodothyronine, affect the cardiovascular system by altering heart rate, heart contraction and vascular resistance. In cases of hypothyroidism, cardiac contractility is disrupted, ventricular filling decreases, and cardiac output decreases due to bradycardia. Hypothyroidism also has significant effects on renal hemodynamics, including GFR and effective renal blood flow. In hypothyroidism, the decrease in GFR which occurs as a result of the extensive hypodynamic state of the circulatory system has been reported to return to normal following thyroid hormone replacement (18-20). In our study, eGFR values of patients in group 1 increased after treatment. In this group, twelve patients (42.8%) had GFR between 60 and 89 ml/min/1.73 m^2 at baseline. At the six months of treatment, eGFR levels were greater than 90 ml/min/1.73 m^2.

It has been reported that glomerular diseases can be seen in patients with HT. The most common glomerular disease is minimal change disease followed by membranous glomerulonephritis, immunoglobulin A nephritis, membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis (4,21-24). Thickening of the glomerular and tubular basement membrane and increase in the mesangial matrix have been reported in hypothyroidism (25). The most common urinary finding in patients with HT is proteinuria, which can range from mild to nephrotic range proteinuria. The increased transcapillary escape of plasma proteins is considered as main reason of proteinuria. Different mechanisms for explaining the association between glomerular diseases and HT have been implemented. It has been shown that the subendothelial accumulation of circulating immune complexes against to thyroglobulin, called anti-thyroglobulin, result in increased glomerular permeability. However, it is unclear to define the relation of HT with renal pathologies only by immunological abnormalities (25-28). Weerakkody et al demonstrated the improvement of proteinuria associated with hypothyroidism, with treatment (29). In line with previous study, we showed the reversibility of proteinuria with treatment in patients with hypothyroidism. L-thyroxine treatment for euthyroid patients with goiter is still controversial (17). In our study, although proteinuria was decreased with treatment, we still do not know whether the follow-up of these patients without L-thyroxine treatment lead to permanent renal damage.

Hypothyroidism may deteriorate kidney functions with hemodynamic changes characterized by decreased sensivity to β-adrenergic stimulus, renin release and RAS activity, erythropoietin production and atrial natriurec factor levels, and increased mean arterial pressure, with glomerular changes characterized by decreased renal blood flow, GFR, expression of renal vasodilators and cytatin C, and increased serum creatinine and glomerular capillary permeability and with tubular changes characterized by increased sensivity to vasopressin and Na excretion, and decreased activity of Na/K ATPase and Na-H exchanger (11).

In this study, anti-TPO levels were significantly higher in group 1 than in the other groups. However, there was no significant difference between the groups in terms of anti-TG levels. We think that these findings are not sufficient to establish relationship between antibody levels and renal involvement.

In some studies, CysC has been found to be better than serum creatinine in the assessment of renal functions. However, it is not recommended to use CysC level in the evaluation of renal functions in hypothyroid patients. Because, thyroid hormones may influence serum CysC levels by altering CysC production and consumption rates. When compared with euthyroid status, CysC level has been found to decrease significantly in hypothyroidism status. Therefore assessment of kidney functions with CysC should be avoided in patients with thyroid dysfunction (30,31). As expected, in our study, CysC levels decreased in Group 1 at the time of diagnosis and increased after treatment ($p<0.001$, Table 2).

LIMITATIONS

One of the important limitations of our study is the small number of cases and due to the nature of the disease; the number of patients between the groups was not equal. Therefore we think that further studies including more cases should be conducted on this field.

CONCLUSION

In conclusion, renal involvement associated with HT was found as proteinuria and decreased glomerular filtration rates in our study. Patients with proteinuria or renal failure were found to recover with thyroid hormone replacement therapy. Since L-thyroxine treatment decreases proteinuria in patients with euthyroid goiter, we recommend that these patients should be monitored carefully in terms of kidney involvement. Patients with HT should also be evaluated for kidney involvement.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study conformed to the Declaration of Helsinki and was approved by the Erciyes University Ethics Committee (2014/581).

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