International Journal of Research in Medical Sciences
Karethimmaiah H et al. Int J Res Med Sci. 2016 Oct;4(10):4300-4304
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20163192

Research Article

Abnormalities of thyroid function tests in adult patients with nephrotic syndrome

Hareeshababu Karethimmaiah[1]*, Vijaya Sarathi[2]

[1]Department of Nephrology, Vydehi Institute of Medical Sciences and Research Center, Bangalore, India
[2]Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, Bangalore, India

Received: 09 September 2016
Accepted: 14 September 2016

***Correspondence:**
Dr. Hareeshababu Karethimmaiah,
E-mail: drharri@yahoo.com

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ABSTRACT

Background: Nephrotic syndrome is well-known cause of thyroid dysfunction in children; however, there is limited data on this issue in adults, especially regarding natural course of thyroid abnormalities.
Methods: Patients with nondiabetic nephropathies were included in the study and evaluated with thyroid function tests at diagnosis and every 2-3 monthly. Age and sex matched healthy volunteers constituted the control group.
Results: The study included 39 patients with newly diagnosed nephrotic syndrome and 39 controls. When compared to the control group, patients with nephrotic syndrome had significantly higher thyroid stimulating hormone and significantly lower total thyroxine, total triiodothyronine, free thyroxine and free triiodothyronine levels. Eighteen patients had remission at last follow-up (18.3±3.4 months) and those with remission had improvement in thyroid function tests. Anti thyroperoxidase antibody tended to be more common in nephrotic syndrome patients and among patients with remission, elevated antibodies was associated with persistence of hypothyroidism.
Conclusions: Nephrotic syndrome in adult patients is significantly associated with abnormalities in thyroid function tests. All these abnormalities improve with remission of nephrotic syndrome. Patients with elevated thyroid stimulating hormone and anti-thyroperoxidase antibody levels are more likely to progress to overt hypothyroidism and should be closely followed-up or replaced with levothyroxine.

Keywords: Nephrotic syndrome, Proteinuria, Hypothyroidism, Anti thyroperoxidase antibodies

INTRODUCTION

Nephrotic syndrome (NS) is a common cause of massive proteinuria and is associated with loss of multiple binding proteins like thyroid binding globulin (TBG), corticosteroid binding globulin and vitamin D binding globulin.[1,2] Urinary loss of thyroid binding globulin is accompanied with loss of thyroxine (T4) and triiodothyronine (T3).[3-6] This leads to decrease in serum total thyroxine (TT4) and serum total triiodothyronine (TT4) concentrations and increases the demand on thyroid gland to produce more T4. This increased demand is reflected by increase in the elevation of thyroid stimulating hormone (TSH), although not always above the upper limit of normal.[4,5]

Many studies have documented thyroid abnormalities in children with NS.[4-7] In children, association of thyroid abnormalities with NS may help to identify the latter condition at an earlier stage. Elevation of TSH in new-born screening programs often leads to diagnosis of congenital NS.[8,9] However, there is limited data on thyroid abnormalities in adults with NS. More importantly, the natural history of thyroid abnormalities in adult patients with NS is not well studied. It has been documented that abnormalities in thyroid functions could be normalised by LT4 replacement. On the other hand, few studies have concluded that thyroid abnormalities are transient and does not require replacement with LT4.[4,11]

Hence, it is not clear whether patients with NS with subclinical hypothyroidism should receive replacement with L-thyroxine. It would be important to know the course of thyroid functions in adult patients with NS and identify any predictors of persistence of hypothyroidism in them. Hence, we have studied the thyroid function abnormalities and predictors of persistence of thyroid abnormalities in adults with NS.

METHODS

The study was conducted between January 2012 and December 2015 at department of Nephrology in a tertiary health care center at Bangalore. The study was approved by institutional ethics committee and a written informed consent was obtained by all participants. All patients aged more than 18 years, who presented with nephrotic syndrome, were included in the study. Nephrotic syndrome was defined as 24-h urinary protein excretion >3.5 g/1.73m^2 or spot urinary protein creatinine ratio >2.0. Patients with acute sickness, pregnancy, lactation, diabetes mellitus and previously diagnosed patients with hypothyroidism were excluded from the study. Age and sex matched healthy volunteers constituted the control group.

At diagnosis of NS, all participants were subjected for serum total protein, albumin and globulin, 24-h urinary protein excretion, spot urinary protein creatinine ratio, thyroid function tests including TSH, TT4, TT3, FT3, FT4 and anti-thyroperoxidase antibody (anti-TPO) level. Additional investigations such as renal biopsy, serum complement 3, antinuclear antibody, HBsAg, anti HCV and anti HIV etc were performed as per the standard protocol at our institution to evaluate an adult with new onset NS.

Among 39 patients, fifteen had focal segmental glomerulonephritis, thirteen had minimal change disease, five had membranous nephropathy and one had membraneoproliferative glomerulonephritis whereas in the rest renal biopsy was not done since patients deferred the procedure. All patients received treatment with immunosuppressive drugs as per the standard protocols. Patients were followed up every 1-3 monthly with spot urinary protein creatinine ratio, serum creatinine and serum albumin and 2-3 monthly with thyroid function tests. Patients with spot urinary protein creatinine ratio <2.0 were considered to have remission of NS. Partial remission was defined as spot urinary protein creatinine ratio 0.2-2.0 and complete remission as <0.2. Patients were replaced with LT4 only if TSH ≥20 µIU/ml.

Thyroid function tests, serum creatinine, serum albumin, urinary protein, urinary creatinine were analysed using Unicel DxC 600 Synchron®, Beckman Coulter Ireland Inc. Normal reference range for TSH, TT4, TT3, FT3, FT4 and anti TPO were 0.4-4.2µIU/ml, 5.5-11.0 µg/dl, 0.94-180 ng/ml, 2.5-3.9 pg/ml, 0.61-1.12 ng/dl and 9 IU/ml.

Statistical analysis was performed using SPSS version 20 (SPSS software, Chicago IL, USA). Continuous variables are mentioned as mean ±SD and categorical variables are mentioned as percentages. Continuous variables between two groups were analysed using independent t test and categorical variables using chi-square test. Variables at diagnosis of NS and at last follow-up we compared using paired t test. A p value less than <0.05 was considered significant.

RESULTS

Thirty nine patients presented with newly diagnosed NS. The mean age of the study population was 34.89±9.14 years and was not significantly different from that of controls (n=39).

When compared to the age and sex matched control group, patients with NS had significantly higher TSH and significantly lower TT4, TT3, FT3 and FT4 (Table 1). In NS group, sixteen (41.02%) patients had normal TSH (0.4-4.2 µIU/ml), four (10.25%) had more than 10 µIU/ml whereas the rest (19, 48.71%) had TSH between 4.2 and 10 µIU/ml. Fourteen (35.89%) patients had a low TT4 and nine (23.07%) had low TT3 whereas FT3 was low in four (10.25%) and FT4 was low in three (7.6%) at presentation. In healthy volunteer group, none of the patients had abnormal thyroid function tests. Among NS group, eight patients had elevated anti-TPO whereas only two subjects in the control group had positive anti-TPO (p=0.3). None of the patients had TSH >15 µIU/ml and none were replaced with thyroxine.

Table 1: Comparison of thyroid function tests between patients with nephrotic syndrome at diagnosis and healthy volunteers.

	Nephrotic syndrome patients at diagnosis (n=39)	Controls (n=39)	P value
Thyroid stimulating hormone (µIU/ml)	7.03±4.21	2.58±0.98	<0.001
Total triiodothyronine (ng/dl)	97.46±10.89	141.28±18.63	<0.001
Total thyroxine (µg/dl)	7.37±1.26	10.09±1.42	<0.001
Free triiodothyronine (pg/ml)	2.69±0.32	3.29±0.36	<0.001
Free thyroxine (ng/dl)	0.85±0.21	1.07±0.12	<0.001
Age (years)	34.89±9.14	34.97±8.31	0.9
Male: Female	18:21	19:20	0.5

Patients with NS were followed-up over a period of 18.3±3.4 months. Eighteen patients had remission of NS at last follow-up whereas the rest had persistence of NS. At last follow-up, TSH was significantly lower whereas TT4, TT3, FT3 and FT4 were significantly higher when compared to that at diagnosis of NS. There was significant reduction in serum creatinine and spot urinary protein to creatinine ratio and significant increase in serum albumin in patients with remission of NS (Table 2).

When patients with remission of NS were compared with those without remission, none of the characteristics at diagnosis of NS differed significantly between the two groups. When compared to characteristics at diagnosis of NS, patients with remission had significant decrease in spot urine protein creatinine ratio, serum creatinine and significant increase in serum albumin. At last follow-up, patients with remission had significantly lower TSH (p=<0.0001) and higher TT4 (p=<0.0001), TT3 (p=<0.0001), FT4 (p=0.0012) and FT3 (p=<0.0001) than those at diagnosis of NS. Among 18 patients with remission at last follow-up, five had elevated anti-TPO, three of whom continued to have TSH >10 µIU/ml whereas none among those with normal anti-TPO had TSH > 10 µIU/ml (p=0.012).

Table 2: Comparison of patient characteristics at diagnosis of nephrotic syndrome and at last follow-up.

	At diagnosis of nephrotic syndrome	At last follow-up	P value
Total triiodothyronine (ng/dl)	97.46±10.89	125.33±15.62	<0.0001
Total thyroxine (µg/dl)	7.37±1.26	8.54±1.93	0.002
Free triiodothyronine (pg/ml)	2.69±0.32	2.89±0.37	0.01
Free thyroxine (ng/dl)	0.85±0.21	0.94±0.25	0.01
Thyroid stimulating hormone (µIU/ml)	7.03±4.21	4.34±3.68	0.003
Spot urinary protein/creatinine	7.25±3.23	3.38±3.12	<0.0001
Serum albumin (g/dl)	2.02±0.48	3.11±0.8	<0.0001
Serum creatinine (mg/dl)	1.61±0.38	1.18±0.41	<0.0001
Serum sodium (mEq/l)	133.66±8.27	135.11±7.72	0.42

Table 3: Comparison of characteristics between patients who achieved remission of nephrotic syndrome with those who did not.

	At diagnosis of nephrotic syndrome			At last follow-up		
	Remission at last follow-up (n=18)	**No remission at last follow-up (n=21)**	**P value***	**Remission at last follow-up (n=18)**	**No remission at last follow-up (n=21)**	**P value***
Total triiodothyronine (ng/dl)	95.50±10.92	99.12±11.63	0.33	139.13±14.54	108.62±16.96	<0.0001
Total thyroxine (µg/dl)	7.17±1.29	7.82±1.37	0.14	9.81±1.25	7.96±1.58	0.0003
Free triiodothyronine (pg/ml)	2.60±0.35	2.64±0.28	0.7	3.15±0.34	2.85±0.38	0.014
Free thyroxine (ng/dl)	0.83±0.21	0.87±0.22	0.57	1.04±0.14	0.89±0.19	0.008
Thyroid stimulating hormone (µIU/ml)	7.67±3.83	6.96±4.06	0.58	3.47±3.55	6.06±3.78	<0.0001
Spot urinary protein/creatinine	7.11±2.21	7.36±2.02	0.6	0.47±0.29	5.72±2.05	0.002
Serum albumin (g/dl)	2.01±0.56	2.19±0.29	0.07	4.02±0.15	2.38±0.22	<0.001
Serum creatinine (mg/dl)	1.55±0.36	1.65±0.40	0.4	0.99±0.39	1.22±0.29	0.004
Serum sodium (mEq/l)	132.75±4.35	134.41±4.56	0.59	135.25±4.78	135.45±3.65	0.931

* p value is for comparison between patients with and without remission at last follow-up

DISCUSSION

This study reports significantly lower concentration of serum TT4, TT3, FT3 and FT4 and significantly higher concentration of serum TSH in patients with NS when compared with age and sex matched healthy volunteers. Previous studies have demonstrated similar findings.[4-7] Studies have also documented significant reduction in serum TBG levels.[12] Decrease in concentration of serum

TT4, TT3, FT3, FT4 and TBG levels in patients with NS is due to excessive urinary loss of these substances.[3-6]

Urinary loss of serum T4, T3 and TBG levels in-turn lead to significant decrease in serum TT3 and TT4 and demands increased production of T4 from the thyroid gland to compensate for the urinary loss of T4 and T3.[4,5] This in turn increases serum TSH level. In milder cases, increase in TSH compensates to maintain serum FT3 and FT4 level. However, in severe urinary T4 loss, thyroid gland may not be able to meet for the increasing demand and FT4 level may fall below the normal range. In agreement with this, 58.97% of our patients had elevated TSH whereas only 7.6% of patients had low FT4. However, a larger number of patients demonstrate low serum TT4 level. Compared to 7.2% patients who had lower FT4, higher number (35.89%) of patients had low serum TT4, which is due to concomitant loss of TBG.

The study also evaluated the thyroid functions at last follow-up in all patients and demonstrated that the abnormalities in thyroid function improved in most of the patients with remission of NS. Similar effect of remission of NS on thyroid functions has been reported previously.[3-5,10] Improvement in thyroid functions of NS patients has also been documented with bilateral nephrectomy which provides a cure for proteinuria and prevents loss of TBG and T4 in urine.[13]

Anti-TPO antibodies tended to be more common in NS patients than in control group. It may be a reflection of underlying autoimmune etiology of NS in these patients. Coexistence of autoimmune hypothyroidism has been described previously with various histological types of nephrotic syndrome, especially with membranous nephropathy.[14-18] In our study, four of 15 patients with membranous nephropathy had elevated anti-TPO antibodies.

Among patients with remission elevated anti-TPO antibody was associated with persistence of hypothyroidism at last follow-up and these patients were initiated on LT4 replacement. Higher rate of progression to overt hypothyroidism in patients with positive anti microsomal antibodies has been proven previously.[19] Hence, patients with elevated anti-TPO should be closely followed-up for progression of hypothyroidism or initiated on LT4 replacement.

CONCLUSION

The study confirms that significant number of adult patients with NS have abnormalities in thyroid function tests. Most of these abnormalities improve with remission of NS. Anti-TPO antibodies tend to be more common in adult NS patients than control group and those with elevated anti-TPO are more likely to progress to overt hypothyroidism. Hence, all patients with NS who have elevated TSH should be evaluated for anti-TPO and those with elevated anti-TPO should be closely followed-up or replaced with LT4.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Karethimmaiah H, Sarathi V. Abnormalities of thyroid function tests in adult patients with nephrotic syndrome. Int J Res Med Sci 2016;4:4300-4.