Original Article

DOI: 10.7860/JCDR/2016/24046.8974

Nephrotic Syndrome Increases the Need for Levothyroxine Replacement in Patients with Hypothyroidism

Internal Medicine Section

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ABSTRACT

Introduction: Nephrotic syndrome is a known cause of hypothyroidism; however, its effect on replacement doses of L-thyroxine in patients with primary hypothyroidism is not systematically studied.

Aim: The effect of newly diagnosed nephrotic syndrome on the dose of L-thyroxine replacement in previously diagnosed patients with primary hypothyroidism who were on full, stable dose of L-thyroxine replacement for at least one year.

Materials and Methods: Patients with previously diagnosed primary hypothyroidism on stable and full (≥1.6μg/day) replacement dose of L-thyroxine for at least one year who developed newly diagnosed nephrotic syndrome were included in the study. Patients were evaluated with thyroid function tests at diagnosis and every 2-3months. Replacement doses of L-thyroxine were titrated by a single endocrinologist based on serum Thyroid Stimulating Hormone (TSH) level.

Results: The study included nine patients with mean age of 42.77±9.61years. There was significant increase in TSH at diagnosis of nephrotic syndrome (8.16±2.82μIU/ml) when compared to the immediate past visit (2.08±0.7μIU/ml) and needed 17.6% increase in the replacement dose of L-thyroxine. At last follow-up four patients had remission of nephrotic syndrome and in them thyroid function tests improved with reduction in replacement dose of L-thyroxine by 15% whereas patients who did not achieve remission had required further increase in L-thyroxine dose by 19.1%.

Conclusion: Development of nephrotic syndrome significantly increases the need for L-thyroxine replacement dose in previously diagnosed primary hypothyroidism patients on full stable dose of L-thyroxine replacement.

Keywords: Primary hypothyroidism, Proteinuria, Urinary loss of thyroxine

INTRODUCTION

Primary hypothyroidism is a common disorder especially in women. A recent multi-centric Indian study reported a prevalence of hypothyroidism as 10.95% with higher prevalence in women (15.86%) [1]. With increasing availability of thyroid testing facilities, hypothyroidism is often detected at early stages, initially requiring replacement with smaller doses of L-thyroxine (25-50μg/day). In these patients, replacement dose of L-thyroxine increases with progressive damage of thyroid gland and consequent decrease in function of the thyroid. So, increase in need for replacement doses of L-thyroxine over time may be part of the natural history of autoimmune thyroiditis. However, many factors increase the need for replacement dose of L-thyroxine in patients with primary hypothyroidism who are on full replacement doses (≥1.6μg/day). These factors include conditions that increase Thyroxine Binding Globulin (TBG) levels such as use of oral contraceptive pills and chronic active hepatitis, weight gain, development of malabsorption syndromes and initiation of drugs which interfere with absorption of thyroxine etc., [2]. However, it is often forgotten that development of nephrotic syndrome increases the need for L-thyroxine replacement [3-5].

It is well-known that nephrotic syndrome leads to urinary loss of thyroxine and triiodothyronine along with TBG leading to elevation of Thyroid Stimulating Hormone (TSH) [6-9]. The effect of loss of TBG and thyroxine in patients with hypothyroidism who newly develop nephrotic syndrome is not well studied. Here, we have studied the effect of newly diagnosed nephrotic syndrome on the dose of L-thyroxine replacement in previously diagnosed patients with primary hypothyroidism who were on full, stable dose of L-thyroxine replacement for at least one year.

MATERIALS AND 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 from all participants. All adult patients with previously diagnosed primary hypothyroidism and newly diagnosed nephrotic syndrome were screened for the study. Patients who were not on full replacement doses of L-thyroxine (<1.6μg/day) and whose L-thyroxine doses were modified during the previous year were excluded from the study. Patients with hypothyroidism who are not on full dose of LT4 replacement often need increment in replacement doses due to progression of the disease. To avoid the confounding effect of progression of the disease on change in L-thyroxine dose, patients who were not on full stable dose of L-thyroxine were excluded from the study.

Primary hypothyroidism was defined as increase in serum TSH (>10μIU/L) at initial diagnosis. Autoimmune hypothyroidism was defined as primary hypothyroidism with elevated anti-thyroperoxidase antibody (≥9U/ml) or evidence of lymphocytic thyroiditis on fine needle aspiration cytology. Nephrotic syndrome was defined as 24h urinary protein excretion >3.5g/m^2 or spot urinary protein creatinine ratio >2.0.

Data regarding the diagnosis of primary hypothyroidism, immediate past thyroid function tests and dose of L-thyroxine were noted. At diagnosis of nephrotic syndrome all patients were also subjected for serum total protein, albumin and globulin, 24h urinary protein excretion, spot urinary protein creatinine ratio, thyroid function tests including TSH, total thyroxine, total triiodothyronine, free thyroxine, free triiodothyronine and anti-thyroperoxidase antibodies were

performed. Additional investigations such as renal biopsy, serum complement 3, antinuclear antibody, HBsAg, Hepatitis C Virus anti (HCV), anti Human Immunodeficiency Virus (HIV) antibodies etc., were performed as per the standard protocol at our institution to evaluate an adult with new onset nephrotic syndrome.

Among these nine patients, three had minimal change disease, two had focal segmental glomerulonephritis, two had membranous nephropathy, one had membranoproliferative glomerulonephritis and one deferred renal biopsy. All patients received treatment with immunosuppressive drugs as per standard protocols. Patients were followed up every 1-3months with spot urinary protein creatinine ratio, serum creatinine and serum albumin and every 2-3months with thyroid function tests. Patients with spot urinary protein creatinine ratio <2.0 were considered to have remission of nephrotic syndrome. Replacement doses of thyroxine were titrated by a single endocrinologist at diagnosis of nephrotic syndrome and every 2-3months based on serum TSH level. Thyroid function tests, serum creatinine, serum albumin, urinary protein, urinary creatinine were analysed using Unicel DxC 600 Synchron®, Beckman Coulter Ireland Inc.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (SPSS software, Chicago IL, USA). Continuous variables are mentioned as mean ±SD and categorical variables are mentioned as percentages. Continuous variables at diagnosis of nephrotic syndrome and at last follow-up were compared using paired t-test whereas those between two groups with and without remission were analysed using independent t-test. Correlation between two independent variables was estimated using Pearson's correlation coefficient (r). Linear regression analysis was used to analyse independent predictors of increment in L-thyroxine dose with estimation of standardised coefficient (β). A p-value less than < 0.05 were considered significant.

RESULTS

Twelve patients with previously diagnosed primary hypothyroidism on L-thyroxine replacement dose were newly diagnosed with nephrotic syndrome between January 2012 and December 2015. Among these two had normal TSH on <1.6μg/kg/day of L-thyroxine and one had recently increased the dose of L-thyroxine before the diagnosis of nephrotic syndrome. These three subjects were excluded from the analysis. Nine patients who were on stable dose of L-thyroxine of ≥1.6μg/kg/day were included in the analysis. Seven patients were on Thyronorm (Abbott India Ltd) and two patients were on Eltroxin (GlaxoSmithKline Pharmaceuticals India Ltd). The mean age of the study population was 42.77±9.61years. Patients had been diagnosed with primary hypothyroidism for last 5.94±3.71years and were on stable dose of L-thyroxine for last 4.21±1.48years.

At presentation seven patients had an elevated TSH, one had a low T4 and two had low T3 whereas FT3 was low in one whereas none had low FT4. TSH at immediate past visit (9.2±2.one months) before diagnosis of nephrotic syndrome was 2.08±0.7μIU/ml and had significantly increased to 8.16±2.82μIU/ml at diagnosis of nephrotic syndrome (p<0.001).

Patients were followed-up over a period of 15.4±4.8months. At last follow-up four patients had remission of nephrotic syndrome. When compared to that at last follow-up. TSH at diagnosis of nephrotic syndrome was significantly higher (p=0.001) whereas total thyroxine and total triiodothyronine were significantly less (p=0.02 and 0.03 respectively). Free thyroxine and free triiodothyronine at diagnosis of nephrotic syndrome were not significantly different from that at last follow-up (p=0.41 and 0.21 respectively). There was significant reduction in serum creatinine (p=0.001) and spot urinary protein to creatinine ration (p=0.006) and significant increase in serum albumin (p=0.016) at last follow-up [Table/Fig-1].

	At Diagnosis of Nephrotic Syndrome (N=9)	At Last Follow-Up (N=9)	p-value
Total triiodothyronine (ng/dl)	99.11±13.96	115.33±15.62	0.03
Total thyroxine (μg/dl)	7.5±1.46	9.04±1.23	0.02
Free triiodothyronine (pg/ml)	2.87±0.38	3.13±0.47	0.21
Free thyroxine (ng/dl)	0.85±0.21	1.04±0.25	0.41
Thyroid stimulating hormone (μIU/ml)	8.16±2.82	3.24±0.68	0.001
L-thyroxine dose (μg day)	102.88±10.23	125.11±17.67	0.005
Spot urinary protein/creatinine	7.25±3.23	3.38±3.12	0.006
Serum albumin (g/dl)	2.42±0.48	3.11±0.8	0.016
Serum creatinine (mg/dl)	1.61±0.38	1.08±0.29	0.001
Serum sodium (mE q/l)	133.66±8.27	135.11±7.72	0.116

[Table/Fig-1]: Comparison of patient characteristics at diagnosis of nephrotic syndrome and at last visit of follow-up after the diagnosis of nephrotic syndrome.
Variables at diagnosis of nephrotic syndrome and at last follow-up were compared using paired t-test

When patients with remission of nephrotic syndrome at last follow-up were compared with those without remission, there were no significant differences between the two groups at diagnosis of nephrotic syndrome. At last follow-up, urinary spot protein creatinine ratio was significantly lower (p-0.002) and serum albumin (p=<0.001) was significantly higher in the groups who achieved remission of nephrotic syndrome at last follow-up. No significant differences were observed with respect to thyroid function tests [Table/Fig-2].

	At Diagnosis of Nephrotic Syndrome			At Last Follow-Up		
	Remission at Last Follow-Up (N=4)	No Remission at Last Follow-Up (N=5)	p-value	Remission at Last Follow-Up (N=4)	No Remission at Last Follow-Up (N=5)	p-value
Total triiodothyronine (ng/dl)	99.50±13.92	101.12±15.63	0.87	120.13±4.54	111.62±8.96	0.13
Total thyroxine (μg/dl)	7.17±1.59	7.82±1.47	0.91	9.41±1.25	8.76±0.58	0.34
Free triiodothyronine (pg/ml)	2.90±0.35	2.84±0.48	0.82	3.25±0.34	3.08±0.38	0.51
Free thyroxine (ng/dl)	0.83±0.21	0.87±0.18	0.76	1.02±0.14	1.08±0.19	0.61
Thyroid stimulating hormone (μIU/ml)	9.67±1.83	6.96±3.06	0.16	3.47±0.55	3.06±0.78	0.403
L-thyroxine dose (μgday)	109.37±11.9	97.7±5.14	0.145	112.5±6.25	137.5±12.3	0.01
Spot urinary protein/creatinine	6.21±2.21	8.26±2.02	0.15	0.47±0.29	5.72±2.05	0.002
Serum albumin (g/dl)	2.71±0.56	2.19±0.29	0.12	4.02±0.15	2.38±0.22	<0.001
Serum creatinine (mg/dl)	109.37±11.96	97.70±5.14	0.08	109.37±6.25	137.50±12.5	0.005
Serum sodium (mE q/l)	132.75±4.35	134.41±4.56	0.59	135.25±4.78	135.45±3.65	0.931

[Table/Fig-2]: Comparison of characteristics between patients with and without remission of nephrotic syndrome at diagnosis of nephrotic syndrome and at last visit of follow-up after the diagnosis of nephrotic syndrome.
Variables between two groups with and without remission were analysed using independent t-test.

At presentation, the replacement dose of L-thyroxine was increased in seven patients and overall there was a need for significant (17.6%) increase in the dose from that at immediate past visit (102.88±10.23µg to 120.83±16.53µg, p=0.04). In patients who had remission at last follow-up, the dose was reduced from that at 2months after diagnosis of nephrotic syndrome by 15% (128.12±15.72µg/day to 109.37±6.25µg/day) whereas in patients who did not achieve remission it had increased further by another 19.1% (115.00±16.29µg/day to 137.50±12.5µg/day). Overall for those patients who had no remission at last follow-up the dose increment was 41.2% from pre-nephrotic syndrome dose.

At diagnosis of nephrotic syndrome, there was no significant correlation between urine protein creatinine ratio or serum albumin with T3, T4, FT3, FT4 or TSH. There was significant negative correlation of TSH with T4 (r=-0.728, p=0.02) and FT4 (r=0.685, p=0.042). Increment in the dose of L-thyroxine after diagnosis of nephrotic syndrome had significant positive correlation with TSH (r=0.962, p=<0.001) and significant negative correlation with FT4 (r=-0.689, p=0.04). Revised dose of L-thyroxine had significant positive correlation only with TSH (r=0.75, p=0.02). On linear regression analysis, both TSH (β=0.87, p=0.002) and FT4 (β=-0.54, p=0.016) were the independent predictors of need for increment in L-thyroxine dose with onset of nephrotic syndrome.

DISCUSSION

This study reports that onset of nephrotic syndrome is associated with significant increase in TSH. Previous studies have demonstrated that nephrotic syndrome is associated with loss of TBG bound thyroxine and triiodothyronine and also free thyroxine and free triiodothyronine in urine [6,9,10]. This in-turn leads to significant decrease in serum T4 and T3 and demands increased production of thyroxine from the thyroid gland to compensate for the urinary loss of T4 and T3. In patients with previously diagnosed hypothyroidism, however, the hypo-functioning thyroid cannot compensate with increased demand for thyroxine production and should be managed by increasing the dose of L-thyroxine replacement.

At diagnosis of nephrotic syndrome, there was a need for significant increment in L-thyroxine dose. Similar findings have been reported previously in single case reports [5,9,11]. It has been documented in a previously reported patient on thyroxine replacement that as high as 81 µg of thyroxine is lost in urine per day requiring significant increase in L-thyroxine dose from 125µg/day to 225µg/day [9]. In another patient, development of nephrotic syndrome increased the replacement dose of L-thyroxine dose from an initial dose of 75µg (1µg/kg/day) to 200µg (2.6µg/kg/day) daily due to persistent TSH elevation [11]. However, in our study the increment in replacement dose of L-thyroxine was relatively less compared to these reports. It is probably due to bias of case reports where only the most affected cases are reported unlike in our study where all cases of nephrotic syndrome were included irrespective of the need for change in L-thyroxine replacement dose. Our study is the first study that quantitates the increment in L-thyroxine replacement dose due to nephrotic syndrome in patients with previously diagnosed primary hypothyroidism.

The study also evaluated the thyroid functions at last follow-up in all patients and demonstrated that the dose of L-thyroxine was reduced in patients with remission of nephrotic syndrome to the pre-nephrotic syndrome doses. Similar effect of remission of nephrotic syndrome on thyroid functions has been reported previously [7,12]. Studies have also shown that bilateral nephrectomy providing a cure for proteinuria and preventing loss of TBG and thyroxine in urine can also normalise thyroid functions in patients with nephrotic syndrome [13].

LIMITATION

The study had few limitations. Firstly, serum triiodothyronine, thyroxine, free triiodothyronine and free thyroxine data at previous visit before diagnosis of nephrotic syndrome were not available in majority of the patients and hence, change in these parameters from the previous visit to diagnosis of nephrotic syndrome could not be studied. Secondly, the study included small number of subjects.

CONCLUSION

Development of nephrotic syndrome significantly increases the need for L-thyroxine replacement dose in previously diagnosed primary hypothyroidism patients. Hence, all patients with previously diagnosed hypothyroidism should be closely monitored for increase in L-thyroxine dose. We reiterate that nephrotic syndrome should be considered in any hypothyroidism patient on stable and full replacement dose of thyroxine for more than a year, demonstrate a recent increase in TSH.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 09, 2016**
Date of Peer Review: **Sep 20, 2016**
Date of Acceptance: **Oct 20, 2016**
Date of Publishing: **Dec 01, 2016**