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Renal Function Impairment In Hypothyroid Patient: A Study From Eastern India

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Abstract

Objectives: Thyroid hormones are essential for adequate development and maintenance of renal function. Hypothyroidism is associated with decreased glomerular filtration. Present study has been intended to determine the degree of renal impairment in hypothyroid status and its relation with treatment.

Methods: This was a longitudinal & prospective study, involving clinical & diagnostic evaluation and follow up and was conducted on 100 newly diagnosed patient of primary hypothyroidism (TSH value ≥ 6 mIU/ml). Thyroid hormone parameters and renal parameters were analyzed before and 3 months after initiation of supplementation.

Results: The study showed mean serum TSH value before treatment was 44.70±31.59 and after treatment was 2.69±1.06. The difference of TSH level before and after treatment was significant (p=0.000). Mean serum creatinine value before and after treatment were 0.95±0.24 and 0.83±0.18 respectively, which was significant (p=0.000). Mean creatinine clearance level before and after therapy were 77.62±7.01 and 87.45±6.61. The difference between creatinine clearance before and after therapy was significant (p=0.000).

Conclusions: The assessment of thyroid function should be routinely carried out for evaluation of patients presenting with deranged renal function.

Keywords: hypothyroidism; renal impairment.

Abbreviations: Cr- Creatinine; CrCl- Creatinine clearance; GFR- Glomerular filtration rate; ICMA- Immuno chemiluminiscence microparticle assay; SPSS- Standard package for social sciences; TSH – Thyroid stimulating hormone.

Introduction

Hypothyroidism as a clinical syndrome was first described in 1874 by GULL under the name of myxedema in view of the swollen skin (edema) and its excess content of mucin (myx-). Hypothyroidism is the syndrome characterized by the clinical and biochemical manifestations of thyroid hormone deficiency in the target tissue of the thyroid hormone[1]. Reduced production of thyroid hormone is the central feature of the clinical state termed hypothyroidism[2,3]. Primary hypothyroidism is the etiology in approximately 99% of cases of hypothyroidism, with less than 1% being due to TSH deficiency or other causes.

The functional relationship between thyroid and kidneys has been described since the mid-twentieth century[4].

Certain effects of the hypothyroid state on the kidney are well established. Histological changes have been demonstrated in both rats and humans. Physiological effects include changes in water and electrolyte metabolism, notably hyponatremia, and reliable alterations of renal haemodynamics, including decrements in renal blood flow, renal plasma flow, glomerular filtration rate (GFR), and single nephron GFR. In one study GFR failed to reach the levels seen in euthyroid controls following the initiation of thyroid hormone replacement therapy, leaving open the possibility that the effect was not fully reversible. The cause of the decreased renal plasma flow and GFR observed is believed to be principally due to the generalized hypodynamic state of the circulatory system in hypothyroidism[5].

Thyroid disorders cause abnormalities in many locations with the heart and kidneys being the main targets of action of thyroid hormones[6-9]. Primary hypothyroidism is associated with impaired glomerular filtration which is reversible with treatment in approximately 55% of cases[6]. Renal function deterioration secondary to hypothyroidism involves heterogenous mechanisms dominated by hemodynamic abnormalities: a negative inotropic effect on the heart, reduced circulating intravascular volume, and increased peripheral resistance with renal vasoconstriction.

Aims & objectives

The aim of our study was to obtain comprehensive insight into the magnitude of renal function impairment in primary hypothyroid patient and response of levothyroxine therapy on it and to assess the pattern of renal function impairment in primary hypothyroidism.

Materials & methods

Study design & subjects: This was a longitudinal & prospective study, involving clinical & diagnostic evaluation and follow up and was conducted on 100 newly diagnosed patient of primary hypothyroidism (TSH value ≥ 6 mIU/ml) attending endocrinology OPD and inpatient department of Calcutta National Medical College and Hospital, Kolkata over a period of one calendar year (January,2018 to December, 2018).

Inclusion criteria: Newly diagnosed patient of primary hypothyroidism (overt and subclinical).

Exclusion criteria: Patient with congenital or structural kidney diseases, secondary hypothyroidism, myopathies, diabetes, hypertensive and diabetic nephropathies, malignancy or on nephrotoxic medications were excluded.

Ethical clearance

The study proposal was approved by the Ethical Committee of the institution prior to the commencement of the study. During the study ethical issues were dealt rigorously according to revised Helsinki 2000 protocol.

Sample collection

Blood samples were collected by the phlebotomist, from the inner side of the elbow by using disposable syringes of 10 cc. Then samples were incubated at 37°C for 40 minutes. Then serum was centrifuged at 3000 rpm for 20 minutes and stored at -40^0 C till the time of assay.

Methodology used

T_3, T_4 & TSH from the patient were analyzed using the immuno chemiluminiscence microparticle assay (ICMA). Serum urea was measured by kinetic UV test on Olympus AU 400 autoanalyser. Serum creatinine was measured by Jaffe kinetic method.

GFR estimation

Both before & after treatment GFR were calculated using **Cockroft - Gault equation[10]:**

Estimated CrCl = (140-age)×weight(in kg)×0.85(if female)/72× serum creatinine

We did not use the MDRD equation as it has an adjustment factor for african american populations[11], but not for hispanic or asian populations[12,13].

Treatment protocol

The patients were treated with levothyroxine replacement at the dose of 1.5- 1.7 µg/kg/day , orally once in a day, generally results in the prescription of between 75 to 112 µg/day for women and 125-200 µg/day for men[14]. Initially started with 25-50 µg/day[14] and gradually increment of 25-50 µg were made at 1-2 weeks interval until full replacement (1.5-1.7 µg/kg/day) was achieved. In case of high risk elderly patients very slow increment was done according to standard protocol.

Statistical analysis

After collecting all the data, a grand chart was prepared using Microsoft Office Excel 2007 and statistical analysis was performed using SPSS -20 statistical software for analysis of data. P-value of <0.05 was taken as significant.

Results

Our study was comprised of 100 patients of primary hypothyroidism whose serum TSH value was ≥ 6.0 µIU/ml and among them 72 patients were having low GFR.

Demographic profile: In the study population, 91(91%) were female and only 9(9)% were male. Out of them, 66(66%) of were hindu and the rest 34(34%) were muslim. Majority of the patient belongs to the age group 21 to 30 years (28%) , followed by age group 31-40 years (23%). But if we see the presence of renal function impairment , among the primary hypothyroid patients 90% had renal impairment in age group of 41-50 years followed by 77.78% in the age group above 50 years but only 65.5% had renal impairment in the age group 21-30 years and 63.15% in the age group < 20 yrs.

Table 1: Age distribution

Age group (years)	Total number (Percentage)	Patient with low GFR	Percentage of low GFR pt
≤ 20	19 (19%)	12	63.15%
21 - 30	29 (29%)	19	65.5%
31 - 40	23 (23%)	16	69.57%
41 - 50	20 (20%)	18	90%
> 50	9 (9%)	7	77.78%
Total	100	72	

Grading of renal function impairment and hypothyroidism: Renal function was graded based on GFR(ml/min/1.73m^2): normal(≥90), mild impairment(60-89), moderate impairment(30-59) and severe impairment(<30). In our study , 72 patients were having low GFR. 70 patients (70%) had mild renal function impairment and only 2(2%) patients had moderate impairment.

We graded hypothyroid patient based on their TSH level(µIU/ml)- mild (≤ 20), moderate (21-50) and severe(>50). 39 (39%) were suffering from severe degree of hypothyroidism, 37(37%) were from moderate degree of hypothyroidism and 24(24%) were suffering from mild degree of hypothyroidism. Among the patients of mild hypothyroidism 19(79%) had low GFR and 5(21%) had normal GFR. In moderate hypothyroidism group, 29(78%) were suffering from low GFR and in severe hypothyroid group patients with low GFR were 24(62%).

Effects of treatment on renal function: Out of 100 patients, only 72 patients had renal function impairment in the form of low GFR. 31 patients had normalization of GFR after 3 month of levo-thyroxine replacement therapy. Before therapy, average creatinine and GFR were 0.94 mg/dl and 77.62 ml/min respectively. After 3 month of levothyroxine therapy, average creatinine and GFR were 0.83 mg/dl and 87.45 ml/min, respectively.

The study showed mean serum T4 value before treatment was 3.88±1.77 and after treatment was 8.17±1.35. The difference of T4 level before and after treatment was significant (p= 0.000). Mean serum TSH value before treatment was 44.70±31.59 and after treatment was 2.69±1.06. The difference of TSH level before and after treatment was significant (p=0.000). Mean serum creatinine value before and after treatment were 0.95±0.24 and 0.83±0.18 respectively, which was significant (p=0.000). Mean creatinine clearance level before and after therapy were 77.62±7.01 and 87.45±6.61. The difference between creatinine clearance before and after therapy was significant (p=0.000).

Table 2: Relation of T4, TSH, Cr, CrCl- before & after treatment

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair1	T4 - T41	-4.2822222	2.1299165	.2510	-4.7827281	-3.7817164	-17.060	71	.000
Pair2	TSH - TSH	42.013611	31.645203	3.729	34.5773529	49.449869	11.265	71	.000
Pair3	Cr – Cr1	.1177778	.0932243	.0109	.0958711	.1396844	10.720	71	.000
Pair4	CrCl -CrCl1	-9.8334722	6.1430550	.7239	-11.2770194	-8.3899251	-13.583	71	.000

Discussion

Most striking features of hypothyroidism are the marked female preponderance, and the increase occurrence with advancing age[1]. The probability of spontaneous hypothyroidism developing in woman at a particular time increase with age: from 1.4 to 14 per 1000 per year at ages 20-25 and 75-80 years[1]. In this study overall female : male ratio of hypothyroidism was 9:1 . But majority of the patients belong to the age group ≤ 30 years (47%), small sample size may not be sufficient enough to explain this probability.

The present longitudinal and prospective hospital based study evaluated the biochemical markers of renal function in primary hypothyroid subjects and response of levo-thyroxine therapy to the said markers. This study shows that there is significant variation of creatinine and CrCl level before and after therapeutic intervention in hypothyroid patients.

In our study, it is evident that there is significant improvement in creatinine (0.95±0.24 Vs 0.83±0.18) and CrCl level (77.62±7.01 Vs 87.45±6.61) after thyroid hormone replacement therapy, and this is consistent with the study of Chou KM. et al. who has shown decrement of creatinine (0.87±0.22 Vs 0.70±0.17) and increment of CrCl (82±31.08Vs 100.31±31.79) after levo-thyroxine therapy[15].

A 12.63% decrease in serum creatinine was observed after 3 months of thyroxine replacement. Another study done by Tayal et al. reported a 20% decrease in serum creatinine level after 3 months of thyroxine therapy[16]. Asami T., Uchiyama et al. reported 41.3% decrease in serum creatinine levels after 2 months of L-thyroxine substitution[17].

A study conducted by Woodward A et al in a UK hospital among patients with hypo-, eu-, hyperthyroidism showed that there was a mean estimated GFR of 64 ml/min among hypothyroid population[18].

Similarly in a study, in 11 hypothyroid patients the mean creatinine clearance was 66.1ml/min (compared to 98.3 ml/min in controls) and increased to 76.3 ml/min (15.43% increase) after treatment with thyroxine[19]. In our study improvement in mean creatinine clearance is 12.66% (77.62 ml/min vs. 87.45 ml/min).

Primary hypothyroidism is associated with a reversible elevation of serum creatinine in adults. This increase is observed in more than half (~ 55) of adults with hypothyroidism[20]. In our study, out of 100 patients, 72 were suffering from renal function impairment by means of decreased GFR. Among these 72 patients, 31(i.e. 43% approx.) regained normal GFR following 3 months of levothyroxine replacement therapy. Though the remaining patients had significant improvement of renal function, they were beyond the normal range of GFR.

Jayagopal et al. studied the effects of hyperthyroid and hypothyroid state on changes in cystatin C and serum creatinine in 17 patients with hypothyroidism and 19 patients with hyperthyroidism[21]. All patients were newly diagnosed. The hypothyroid patients had a mean serum creatinine of 91µmol/l while the hyperthyroid patients had a mean serum creatinine of 59µmol/l. Creatinine fell by 13% in the hypothyroid patients after treatment, almost similar(12.63%) to our patients .

This study showed, there was significant difference in T4 and TSH levels before and after treatment of the patients with renal function impairment. So there was significant improvement of serum T4 and TSH level with levothyroxine therapy. There was also significant difference in Cr, CrCl before and after levothyroxine therapy.

A reduction in glomerular filtration rate which is not apparent from the plasma creatinine may be more common than expected in patients with hypothyroidism and has obvious implications for drug therapy[22].

Knowledge of reversible association between hypothyroidism and elevated serum creatinine and decreased GFR is important in our day-to-day practice. The assessment of thyroid function should be routinely carried out for evaluation of patients presenting with deranged renal function.

Conclusion

A reduction in glomerular filtration rate which is not apparent from the serum creatinine may be more common than expected in patients with hypothyroidism and has obvious implications for drug therapy. And, the assessment of thyroid function should be routinely carried out for evaluation of patients presenting with deranged renal function.

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