International Journal of Research in Medical Sciences
*Babu KH et al. Int J Res Med Sci. 2016 Sep;4(9):3845-3849*
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162837

**Research Article**

# Evaluate all newly diagnosed mild-moderate renal dysfunction patients for primary hypothyroidism

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**Received:** 30 July 2016
**Accepted:** 03 August 2016

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## ABSTRACT

**Background:** Hypothyroidism often presents to nephrologists with elevated serum creatinine which may lead to unnecessary evaluation including renal biopsy.
**Methods:** We retrospectively analysed the data of 24 patients who presented to the department of nephrology at our institute with anasarca/facial puffiness or elevated serum creatinine and diagnosed to have hypothyroidism with TSH >40 µIU/ml.
**Results:** Twelve patients presented with generalised edema, eight patients for evaluation of deranged serum creatinine and four patients with both generalised edema and deranged serum creatinine. Age ($r=0.696$, $p<0.001$) and serum thyroid stimulating hormone ($r=0.504$, $p=0.012$) had significant positive correlation with serum creatinine whereas serum total thyroxine ($r=-0.637$, $p<0.001$) and triiodothyronine ($r=-0.728$, $p<0.001$) had significant negative correlation. Serum sodium was lower (<136 mmol/L) in eight patients. Age ($r=-0.598$, $p<0.001$), serum creatinine ($r=-0.624$, $p<0.001$), and serum thyroid stimulating hormone ($r=-0.728$, $p=0.012$) had significant negative correlation with serum sodium whereas serum total thyroxine ($r=0.869$, $p<0.001$) and triiodothyronine ($r=.845$, $p<0.001$) had significant positive correlation. Serum creatinine and sodium normalised in all after levothyroxine replacement.
**Conclusions:** To conclude, hypothyroidism is not an uncommon cause of mild-moderate renal dysfunction and often presents to nephrologists prompting unnecessary investigations including renal biopsy. Hence, all newly diagnosed mild-moderate renal failure patients should be tested to rule out primary hypothyroidism.

**Keywords:** Hypothyroidism, Elevated creatinine, Hyponatremia, Renal dysfunction

## INTRODUCTION

Hypothyroidism is a common disease (10.95%) with 3 times higher (15.86% vs 5.02%) prevalence in women. Autoimmune hypothyroidism is the most common cause. With increasing prevalence of thyroid autoimmunity (21.85%), the prevalence of hypothyroidism is likely to increase further.[1]

Hypothyroidism has varied presentation. Generalized body swelling (anasarca) or facial puffiness are the common manifestations of overt hypothyroidism which often makes them to consult nephrologist.[2] Up to 55-62.5% of adults with severe hypothyroidism may have elevated creatinine whereas up to 100% may have decreased eGFR.[3,4] Identification of elevated creatinine in these patients often occurs during evaluation for the cause of anasarca or facial puffiness. Sometimes, testing serum creatinine for some other indications (e.g. routine health check) may also reveal high serum creatinine in hypothyroidism patients which prompts consultation with nephrologist.[2] These situations often lead to unnecessary

evaluation for causes of elevated serum creatinine including renal biopsy. Hence, it is very important to keep primary hypothyroidism in the differential diagnosis of all patients with anasarca or elevated creatinine levels.

Some studies have also demonstrated hyponatremia in primary hypothyroidism patients. However, the reports are not consistent and whether hypothyroidism causes hyponatremia is highly debated.[5,6] Few report higher rates of hyponatremia (21%) especially in those with associated elevation of creatinine (45%), whereas others report no or minimal changes in serum sodium levels with severe hypothyroidism.[3,7-11]

It is interesting to know how we started screening all our patients with anasarca and newly-diagnosed renal dysfunction for thyroid dysfunction. The first patient who presented with anasarca was found to have elevated creatinine and since no other cause for elevated creatinine was found, the patient was planned for renal biopsy. However, that patient also had dyslipidaemia for which endocrine opinion was sought. Evaluation by the endocrinologist revealed severe hypothyroidism and replacement with levothyroxine normalised the serum creatinine after one month. After this case, all patients who presented with anasarca/facial puffiness and/or elevated serum creatinine were routinely evaluated with thyroid function tests. Here, we analyse the data of all those patients who were diagnosed to have primary hypothyroidism who presented with TSH >40 µIU/ml when presented for evaluation of anasarca and/or elevated serum creatinine to the department of nephrology.

## METHODS

This retrospective study was conducted at Vydehi Institute of medical sciences and research center. A written informed consent was obtained from all participants.

Patients who consulted the corresponding author with complaints of anasarca or deranged serum creatinine and diagnosed to have primary hypothyroidism during evaluation were included for analysis. The medical case records of these subjects were searched for thyroid function tests, serum creatinine and serum sodium at diagnosis of hypothyroidism and at 3 months of follow-up.

Thyroid function tests, serum creatinine and serum sodium were analysed using Unicel DxC 600 Synchron®, Beckman Coulter Ireland Inc. Normal range for serum sodium was 136-145 mmol/L and hyponatremia was defined as serum sodium <136 mmol/L. Normal range for serum creatinine was 0.61-1.24 mg/dl for men and 0.44-1.0 mg/dl for women. Serum creatinine more than the upper limit of normal for the sex was considered elevated. For the purpose of statistical analysis, TSH>100 µIU/ml was assumed as 100 µIU/ml, total T4<0.5 µg/dl was considered as 0.5 µg/dl and total T3<10 ng/dl was considered as 10 ng/dl.

Data was analysed using SPSS version 20. Continuous variables are mentioned as mean±SD and categorical variables are mentioned as percentages. Comparison between those who had elevated creatinine and those who did not was performed using independent t test. Correlation between variables was estimated using Pearson's correlation coefficient. A p value less than<0.05 was considered significant.

## RESULTS

There were 24 patients who consulted the corresponding author between Jan 2013 and Dec 2015. All except two had elevated anti TPO antibodies. One of the two patients had evidence of Hashimoto's thyroiditis on fine needle aspiration cytology. The other one deferred FNAC.

Twelve patients presented with generalised edema, eight patients for evaluation of deranged serum creatinine and four patients with both generalised edema and deranged serum creatinine. Among twelve patients who presented with elevated serum creatinine with or without anasarca, eight were referred by internists (n=8), general practitioner (n=3) and medical gastroenterologist (n=1) for evaluation of unexplained elevation in serum creatinine and to perform renal biopsy. Subjects with elevated serum creatinine were older and had lower serum total thyroxine and triiodothyronine levels (Table 1). Age (r=0.696, p<0.001) and serum thyroid stimulating hormone (r=0.504, p=0.012) had significant positive correlation with serum creatinine whereas serum total thyroxine (r=-0.637, p<0.001) and triiodothyronine (r=-0.728, p<0.001) had significant negative correlation.

**Table 1: Comparison of parameters between patients with elevated creatinine and normal creatinine.**

| | Elevated serum creatinine | Normal serum creatinine | P value |
|---|---|---|---|
| Age (years) | 44.92±13.32 | 31.58±4.98 | 0.04 |
| Gender (Male:Female) | 7:5 | 5:7 | 0.237 |
| Serum sodium | 131.67±3.86 | 138.08±3.87 | <0.001 |
| Serum thyroid stimulating hormone | 89.67±19.00 | 74.42±19.65 | 0.066 |
| Serum total thyroxine | 1.82±1.32 | 4.6667±1.83 | <0.001 |
| Serum total triiodothyronine | 42.42±19.82 | 76.50±12.78 | <0.001 |

A total of eight (33.33%) subjects had serum sodium below <136 mmol/L. Serum sodium was below 130 mmol/L in two subjects both of whom were older than 60 years and whereas another 6 subjects had serum sodium between 130-136 mEq/L. Serum sodium was

significantly lower in patients with elevated creatinine (<0.001). Age (r=-0.598, p<0.001), serum creatinine (r=-0.624, p<0.001), and serum thyroid stimulating hormone (r=-0.728, p=0.012) had significant negative correlation with serum sodium whereas serum total thyroxine (r=0.869, p<0.001) and triiodothyronine (r=0.845, p<0.001) had significant positive correlation.

There was 23.25% and 27.9% decrease in serum creatinine values at 1 month and 3 months respectively after supplementation with levothyroxine. All patients had normalisation of serum creatinine values.

There was 2.6% and 3.06% increase in serum sodium values at 1 month and 3 months respectively after supplementation with levothyroxine. All patients had normalisation of serum sodium at and 1 month and 3 months.

## DISCUSSION

Our study demonstrates that primary hypothyroidism is commonly associated with elevated serum creatinine and less often with decreased serum sodium levels.

Kreisman et al reported elevation of creatinine in 89.7% episodes iatrogenic severe hypothyroidism and decrease in creatinine after treatment with levothyroxine in 91.7% episodes. However, elevation in the serum creatinine above the upper limit of normal range was seen in only five (6 episodes) of 20 patients.[12] In another large study out of 128 patients with differentiated carcinoma having short term hypothyroidism, 24 (18.8%) had elevated serum creatinine levels whereas in another large study including differentiate thyroid cancer patients, an additional 15% had elevated creatinine during short term iatrogenic hypothyroidism.[5,13] In another small study seven of the 16 patients with primary hypothyroidism had elevated creatinine but all had decreased GFR (<60). Higher rates (55-62.5%) of elevated creatinine have been reported in noniatrogenic severe hypothyroidism which is probably due to prolonged and severe disease.[3,4]

Although in most reports, creatinine levels have been in the range 1.5-2.5 mg/dl, elevated creatinine up to 6 mg/dl has been reported to be associated with hypothyroidism.[14] In our series the highest serum creatinine observed was 2.1 mg/dl. Hence, all those patients who present with mild-moderate renal dysfunction (serum creatinine <2.5 mg/dl) should be tested for hypothyroidism.

Age had a significant correlation with elevated serum creatinine. But, the studies have reported elevation of serum creatinine even in young children suffering from congenital hypothyroidism. Levothyroxine replacement reduced serum creatinine levels by 41.3%.[15] In another study including children with prolonged hypothyroidism, 40% had elevated serum creatinine which reversed in all with levothyroxine treatment.[16] There was no significant correlation between sex and serum creatinine elevation in our study. This is in contrast to a previous study where six of nine episodes in males were associated with elevation of serum creatinine above the upper limit of normal but none of 14 female patients developed such values in 21 episodes.[12]

Elevation in serum creatinine is almost always reversible. All had normalisation of serum creatinine after replaced with oral levothyroxine (100 µg/day). However, in few patients although serum creatinine decreases with levothyroxine therapy, it may not completely normalize.[4]

Hyponatremia is the commonest electrolyte derangement in hypothyroid patients.[17] It is mainly due to a reduction in GFR causing diminished water delivery to the distal tubular segments and inappropriate ADH secretion.[3,18] Previous studies have reported higher incidence of hyponatremia.[3] However, most of the recent studies report no or minimal effect on serum sodium levels in acute iatrogenic hypothyroidism.[7-11] The largest study including 2229 patients reported moderate to severe hyponatremia in 2% of patients and reported old age, female sex, use of thiazide diuretics, and hyponatremia at the initiation of RAI therapy as independent risk factors for the development of hyponatremia.[19]

The study is limited by its retrospective nature. Moreover, the study does not provide the prevalence of renal dysfunction across wide range of thyroid function tests since it included only those patients with TSH >40 µIU/ml.

## CONCLUSION

Overt hypothyroidism is a not an uncommon cause of mild-moderate renal dysfunction and often presents to nephrologists prompting unnecessary investigations including renal biopsy. Hence, all newly diagnosed mild-moderate renal failure patients should be tested to rule out primary hypothyroidism.

*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:** Babu KH, Sarathi V, Boppana R. Evaluate all newly diagnosed mild-moderate renal dysfunction patients for primary hypothyroidism. Int J Res Med Sci 2016;4:3845-9.