

# Thyroid dysfunctions and renal status: implications in hyponatremia



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## ABSTRACT

**Background:** Hypothyroidism is a common endocrine disorder which has been linked to the development of hyponatremia. However, the data supporting the development of hyponatremia is inadequate and confusing. **Aims and Objectives:** Therefore this study was conducted to investigate an association between hypothyroidism and hyponatremia and to correlate it with other related parameters like renal function status. **Materials and Methods:** Retrospective analysis of laboratory records of one hundred fifty individuals with TSH level above the normal served as cases and one hundred fifty one individuals with normal TSH served as controls. **Results:** Hyponatremia (< 135 mEq/L) was observed in only twenty-one percent of cases of hypothyroidism. Although patients of hypothyroidism had a significantly lower sodium levels than controls, this was not evident with severity of disease. A high creatinine level evident in the overt cases did not affect the sodium level, although the chloride level was reduced. **Conclusion:** The present study showed that hyponatremia is not commonly associated with hypothyroidism and screening for hyponatremia is not essential in such patients.

**Key words:** Hypothyroidism, Hyponatremia, eGFR, Creatinine

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## INTRODUCTION

Measurement of electrolytes is a common diagnostic procedure using ion selective electrodes performed in a clinical chemistry laboratory. Electrolyte homeostasis is regulated by hormones such as antidiuretic hormones, aldosterone and thyroid hormones. Hyponatremia is the most common electrolyte abnormality and to evaluate its underlying cause is often questionable.<sup>1</sup> All these require extensive laboratory investigations and clinical correlations. The interpretation of these values is somewhat meaningless without analysis of the clinical history and is often impossible without parallel measurements of renal function. Alterations of thyroid hormone, particularly hypothyroidism has historically been linked to the development of hyponatremia. However, though there is evidence to suggest that short term uncomplicated hypothyroidism, can result in reduction in glomerular filtration rate (GFR) and subsequent increase in serum creatinine,<sup>2,3</sup> the data supporting the development of hyponatremia in this setting is limited and

confusing. Moreover, the link between hypothyroidism and hyponatremia as mentioned in standard text books of internal medicine needs to be re-established due to the conflicting sets of previously published data.<sup>4</sup>

The current study was therefore conducted to investigate the association between hypothyroidism and the occurrence of hyponatremia and also to establish if there was any correlation between the severity of hypothyroidism with electrolytes and other renal parameters.

## MATERIALS AND METHODS

Retrograde data analysis was done after screening of laboratory records of samples which were assayed for TSH in the clinical biochemistry lab between December 2015 to March 2017.

All demographic details and other clinical investigations like plasma glucose, renal function tests, which included urea, creatinine, and electrolytes like sodium, potassium

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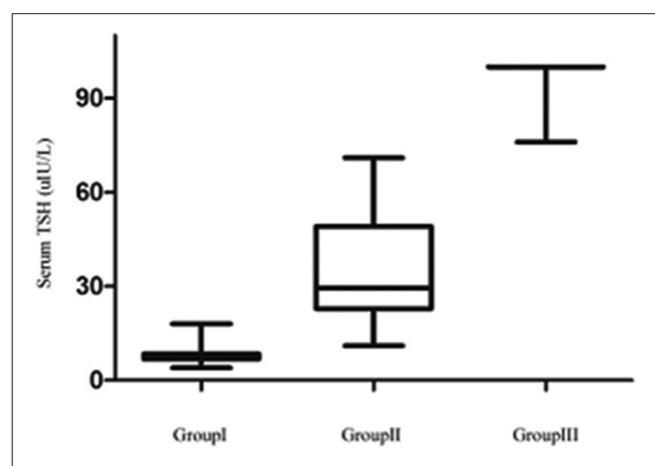
and chloride were noted from records. Calculated parameters included estimated glomerular filtration rate (eGFR) by Cockcroft and Gault<sup>5</sup> and serum osmolality.<sup>6</sup> Data of patients who had elevated TSH levels without taking any medications were included as cases. Data of patients who had come to the hospital for other ailments without hypothyroidism, but had their TSH investigated, which was found to be normal served as controls. Data from a total of 301 samples was collected of which 151 were age and sex matched euthyroid individuals and the rest 150 samples had serum TSH above the normal limits. The cases were further divided into three subgroups<sup>7</sup> (Figure 1) namely,

- i) Mildly high or subclinical hypothyroidism (4-10  $\mu$ IU/L) – Group I
- ii) Moderately high TSH (10 -75  $\mu$ IU/L) – Group II and
- iii) Very high TSH or overt hypothyroidism (>75  $\mu$ IU/L) – Group III.

TSH was measured by electrochemiluminescence immunoassay (Cobas e411) and electrolyte analysis was measured by direct ion selective electrodes (Combi Line electrolyte analyser). Fasting plasma glucose (FPG), serum urea and creatinine, were estimated in clinical chemistry autoanalyser (Biosystem BA400) using standard protocol. Hyponatremia was defined as serum sodium concentration less than 135 mEq/L.

### Statistical analysis

Statistical analysis was carried by Graph pad prism 5 software. Student t test was performed to compare parameters between the euthyroid group and the hypothyroid population. Analysis between the control euthyroid group and the three sub groups of hypothyroid subjects was done using one way ANOVA. Correlation analysis using regression was done between electrolytes and



**Figure 1:** Box plot graph of serum TSH in the stratified hypothyroid population

renal parameters with serum TSH. The p-value of <0.05 was accounted for statistically significant.

## RESULTS AND DISCUSSION

Table 1 depicted the demographic and biochemical investigations (measured and calculated) in the study population. With 62% of the patients being females, the mean age of the hypothyroid patients was  $39.6 \pm 11.9$  years.

The mean values of FPG in all the three groups of hypothyroidism were within the normal clinical limits. However the glucose values were found to be significantly high in hypothyroid cases ( $98 \pm 18$  mg/dl) than in the euthyroid population ( $84 \pm 12$  mg/dl). The role of TSH on glucose metabolism is still under debate. Studies have reported increased insulin resistance<sup>8,9,10</sup> in hypothyroidism while others have shown decreased insulin resistance<sup>11,12</sup> or no change.<sup>13</sup> The reason hypothesized for increased resistance is that peripheral muscles become less responsive in a state of hypothyroidism. Although not properly explained a possible role of poor synchronization of leptin has been also implicated.<sup>10</sup>

The most common parameter on renal function, serum urea, showed a marginal non significant increase in hypothyroid patients, while serum creatinine showed a significant rise in hypothyroidism patients. However, both these values were within the normal reference range. Such elevation of urea and creatinine levels in hypothyroidism have been shown previously by few researchers,<sup>14,15</sup> thereby concluding that renal function may be altered and should be regularly monitored in hypothyroid patients.

Serum sodium and chloride documented a significant decline in hypothyroid patients, however the serum potassium showed no change from euthyroid persons. The mean sodium level in hypothyroid cases was in the normal range but few authors have documented presence of hyponatremia in patients of hypothyroidism.<sup>16-19</sup> The eGFR although normal, was significantly lowered in hypothyroid patients, and is a reflection of serum creatinine.<sup>20</sup> A similar change was also observed in osmolality in hypothyroid patients.

To compare the biochemical parameters of the stratified hypothyroid subjects, one way ANOVA was used which is shown in Table 2. As observed the plasma glucose level shows a gradual significant rise with increase in state of hypothyroidism. Hypothyroidism in all degrees whether subclinical, moderately elevated or overt have been associated with disorders of glucose metabolism.<sup>21,22</sup> However, the exact mechanism connecting hypothyroidism

**Table 1: Demographic and biochemical parameters (mean±SD) of controls and cases**

Parameters	Euthyroid (n=151)	Hypothyroid (n=150)	p value
Age (Years)	39±13	39.6±11.9	0.67
Male: Female(%)	97:54 (64.2:35.8)	93:57 (62:38)	0.84
Fasting plasma glucose (mg/dl)	84±12	98±18	0.0001
Serum Urea (mg/dl)	21±5.8	24.06±9.3	0.08
Serum Creatinine (mg/dl)	0.78±0.2	0.85±0.2	0.002
Serum Sodium (mEq/L)	139±3.4	137.8±4.8	0.01
Serum Potassium (mEq/L)	4.6±0.4	4.7±0.5	0.80
Serum Chloride (mEq/L)	106.2±3.7	105.3±3.6	0.03
eGRF ( ml/min)	116±36.4	103±24.3	0.001
Serum Osmolality (mOsm/kg)	287±6.6	284.7±9.5	0.01

**Table 2: Comparison of biochemical parameters (mean±SD) in stratified patient population according to TSH levels**

TSH Range (µIU/L)	Group I 4-10 (n=50)	Group II 10-75 (n=50)	Group III>75 (n=50)	p value
Parameters				
Fasting plasma glucose (mg/dl)	91.5±10.53	93.3±10.01	108.3±24.07*	<0.0001
Serum Urea (mg/dl)	21.7±7.5	22.5±6.7	23.50±11.75	0.77
Serum Creatinine (mg/dl)*	0.74±0.12	0.78±0.13	0.88±0.21*	0.004
Serum Sodium (mEq/L)	138.1±4.8	137.7±3.7	136.6±5.5	0.28
Serum Potassium (mEq/L)	4.5±0.44	4.54±0.34	4.68±0.58	0.78
Serum Chloride (mEq/L)*	106.2±3.5	106.2±2.56	104.4±4.09*	<0.01
eGRF (ml/min)	108.2±3.26	107.8±25.31	105.6±30.9	0.55
Serum Osmolality (mOsm/kg)	284.9±9.39	283.8±7.8	283.1±11.1	0.69

Post hoc Tukey's test (HSD) \*p < 0.01 (III Vs I, II)

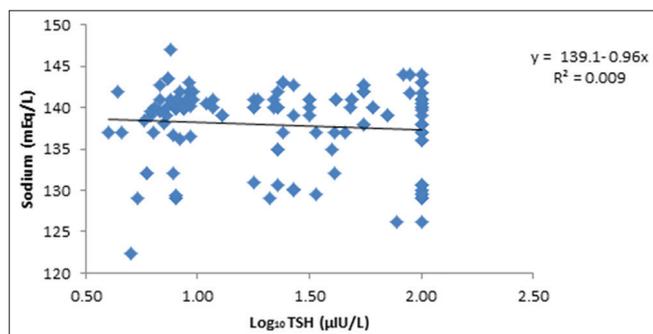
to insulin resistance is still unclear. In these patients, the change was significant ( $p < 0.01$ ) in the overt group in comparison with the subclinical and moderately hypothyroid group. A gradual rise in serum urea and serum creatinine was observed along with a parallel rise in TSH levels in patients of hypothyroidism. The reduction in renal blood flow and GFR could be responsible for reduced clearance of urea and creatinine and thus its elevation.<sup>23</sup> The serum creatinine in overt hypothyroidism was significantly elevated ( $p < 0.01$ ) as compared to the other two groups of patients.

Apart from serum chloride, which was significantly lowered in overt group in comparison to the other two groups, there was no significant change in serum sodium and potassium. Although it has been shown that hyponatremia was more common in patients with impaired renal functions,<sup>2,14</sup> our observation was that even with declining renal function the change in sodium level was not significant. Thirty-two (21.3%) cases had serum sodium less than 135 mEq/L, the value defined for hyponatremia, however there was no case with sodium less than 120 mEq/L. Sixteen (50%) of the hyponatremic patients were in the group of overt hypothyroidism. A Fischer's exact test showed no significant difference between the three groups in proportions of sample that had a serum sodium below 135 mEq/L ( $p = 0.06$ ). A linear regression between the hypothyroid patients ( $n = 32$ ) and creatinine documented

no association between these parameters ( $R^2 = 0.028$ ,  $p = 0.35$ ). Thyroid dysfunction has been shown to cause remarkable changes in glomerular and tubular functions resulting in poor electrolyte and water homeostasis.<sup>24</sup> The increased systemic vascular resistance, reduced GFR and renal blood flow associated with hypothyroidism results in reduced excretion of water by the kidneys.<sup>25</sup> However, this was not the case in our study population as the eGFR and osmolality were insignificantly changed. However, although the sodium declined, because of low osmolality, the chloride was reduced much in degree.

The correlation coefficient as depicted in Table 3, shows a negative correlation of TSH only with sodium, whereas a positive correlation with potassium, chloride, eGFR and osmolality.

Regression analysis after logarithmic transformation of TSH revealed, no significant correlation with serum sodium concentration ( $R^2 = 0.009$ ) (Figure 2) or chloride concentration ( $R^2 = 0.089$ ). Studies where an association between hypothyroidism and sodium have been described are generally in myxedemic population or in acute or chronic illness and hospitalized patients.<sup>26,27</sup> Although the reason of hyponatremia in myxedemic coma is multifactorial, renal tubular function gets affected due to decline in GFR to cause hyponatremia.<sup>28</sup> A finding similar to ours have been documented by authors who



**Figure 2:** Linear regression of log transformed TSH with serum sodium in hypothyroid patients

**Table 3: Correlation coefficient of electrolytes and calculated parameters in patients of hypothyroidism**

Parameters	Sodium	Potassium	Chloride	eGFR	Osmolality
TSH	-0.13	0.10	0.44	0.25	0.06

found weak or no relationship between hypothyroidism and hyponatremia.<sup>17,29-31</sup>

The negative correlation between serum sodium levels and serum TSH was not statistically significant, the level of sodium were not clinically significant in any group and did not necessitate any treatment. Although a small number (21%), the reason of hyponatremia could not be elicited as the study was an analysis of database. The biggest limitation of this study was that it was a retrospective analysis, and many other clinical parameters could not be collected for laboratory records which could have been correlated. Because the population under study was less than 40 years, electrolyte homeostasis may have been maintained inherently by the body even with alteration in TSH level. Therefore while choosing population different age groups must be studied.

## CONCLUSION

This study found that although sodium levels declined, hyponatremia was not a prominent finding of hypothyroidism. With a lot of cross sectional studies being published what is now needed is a systematic review with meta-analysis for a satisfactory appreciation of hyponatremia in hypothyroidism.

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**SS**– Collected data, review literature manuscript preparation, statistical analysis and interpretation; **SP** – Preparing first draft of manuscript, statistical analysis and interpretation; **AG** - Collected data, manuscript preparation, statistical analysis and interpretation; **RN** – Concept and design of study, interpretation, helped in preparing first draft of manuscript and critical revision of manuscript; **EM** – Interpretation, helped in preparing first draft of manuscript and critical revision of manuscript.

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