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Original Article

Biochemistry Section

Estimation of Serum Electrolytes and Renal Profile in Hypothyroidism: A Cross-Sectional Study

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ABSTRACT

Introduction: Kidneys has important role in the metabolism and removal of thyroid hormones. The water and electrolyte balance in the body was influenced by thyroid hormone. Thyroid dysfunction is usually related with disturbances of calcium and phosphorous homeostasis. It causes significant changes in tubular and glomerular functions of water and electrolyte homeostasis. Both hypothalamus-pituitary-thyroid axis and thyroid hormone peripheral metabolism were affected in Chronic Kidney Disease (CKD).

Aim: To assess the renal parameters and electrolytes in well-defined hypothyroid patients and in age matched apparently healthy controls.

Materials and Methods: The present cross-sectional study was carried in department of endocrinology and internal medicine at SRM Hospital, Tamil Nadu, India from July 2015 to July 2016. A total of 65 aged 35-50 years known hypothyroid patients both males and females were included in this study which forms the study group and 65 age matched controls were also recruited. Serum Urea, Creatinine, Uric acid and electrolytes were estimated by Ion Selective Electrodes (ISE) in the Beckman Coulter (California, USA) AU480 auto analyser. Free Tri iodotyronine (FT3), Free Tyroxine (FT4) and Thyroid Stimulating Hormone (TSH) was done by Fluorometric Enzyme Immunocapture Assay (FEIA) method in TOSOH AIA 360 (Japan) hormone analyser were measured. Estimated Glomerular Filtration (eGFR) was calculated by using MDRD (Modification of diet in renal disease) formula. Statistical analysis was done by using Student t-test and Pearson correlation analysis.

Results: Hypothyroid patients showed significant elevation of serum creatinine, urea and potassium levels (1.39±0.33, 36.7±5.4, 4.78±0.40,p<0.005) when compared to controls. eGFR was decreased significantly in study group (66.8±1.29) when compared to control (96.2±4.69) and (p<0.005).

Conclusion: Hypothyroidism is associated with decreased renal function. Hypothyroid patients should be monitored regularly for renal parameters to prevent chronic kidney diseases.

Keywords: Chronic kidney diseases, Thyroid dysfunction, Thyroid stimulating harmone

INTRODUCTION

Thyroid hormones are required for normal growth, development and function of all tissues with major effect on oxygen consumption and for the maintenance of water and electrolyte homeostasis [1]. T3 and T4 hormones act through receptors Alpha (α) and Beta (β), and play a critical role in cell differentiation during development and it helps to regulate thermogenic and metabolic homeostasis in adults [2]. Thyroid hormones are metabolised and eliminated from circulation through kidneys. Dysfunction in thyroid leads to significant changes in glomerular and tubular functions and by this method it affects water and electrolyte homeostasis. Hypothyroidism causes decrease in glomerular filtration, renal blood flow and this may bring in changes in serum electrolytes [3]. Hypothyroidism decreases cardiac output caused by the reduced heart rate, stroke volume and myocardial contractility and this contributes to decreased GFR. Electrolytes plays an important role in controlling fluid levels, acid-base balance (pH), nerve conduction, blood clotting and muscle contraction [4].

Sodium and potassium are important components of the enzyme Na+/K+ ATPase, present on cell membrane, helps in water and nutrients transport. The activity of sodium-potassium pump is regulated by thyroid hormone in most of the tissue. Hypo and hypernatremia are the most common electrolyte abnormalities, due to defect in enzyme (Na+/K+ ATPase) [5]. Hypothyroidism is accompanied by alterations in kidney functions and impairs water and electrolyte balance. Several studies have focussed on thyroid status in chronic kidney diseases but not much data is available about effect of hypothyroidism on renal functions [6-9]. Several studies have also reported that thyroid hormones especially T3 can serve as a marker of longevity in patients with chronic kidney diseases [10-12]. Only single research article was available about the effect of thyroid hormones on kidney diseases [13]. Hence, the present study was conducted with an aim to assess renal parameters and electrolytes in well-defined hypothyroid patients based on FT3, FT4 and TSH levels.

MATERIALS AND METHODS

The cross-sectional study was conducted from July 2015 to June 2016, at SRM Medical college Hospital and Research centre, Chennai, Tamil Nadu, India. The study protocol was approved by the Institution Ethics Committee of (867/IEC/2015) and informed written consent was obtained from all the subjects. Based on the prevalence of Hypothyroidism in India, sample size was calculated using formula n=4pq/ L2 [14]. The participants both females and males in the age group of 35-50 were included. The study consists of two group, study group comprises of 65 hypothyroid patients who are on treatment. Another group with 65 age matched, healthy individuals who attended master health check-up formed the control group.

Inclusion Criteria

Male and Female patients with Hypothyroidism.

Exclusion Criteria

People diagnosed with Diabetes, Hypertension and Chronic illness, Heart failure, Pregnancy were excluded.

Sample Collection

After an overnight fasting, 5 mL of venous blood sample was collected from all the participants. Estimation of TSH, FT3 and FT4 was done by Fluorometric Enzyme Immuno-capture Assay (FEIA) method in TOSOH AIA 360 (Japan) hormone analyser. Sodium (Na+), Potassium (K+) and Chloride (Cl-) were estimated by Ion Selective Electrodes (ISE) in the Beckman Coulter (California, USA) AU480 auto-analyser. Creatinine by modified Jaffe's method, Urea by GLDH- Urease method, Uric acid by Uricase method, in the Beckman Coulter (California, USA) AU480 chemistry auto-analyser. Creatinine clearance is calculated by using Cockcroft Gault Formula [15].

An eGFR was calculated, using MDRD (Modification of Diet in Renal Disease) Formula Estimated eGFR (mL/min/1.73 m^2)

=186 × (Scr)-1.154 × (Aged) × -0.203× (0.742 if females × (1.210 if African – American)

=exp (5.228-1.154× ln (Scr)-0.203× ln (Age)-(0.299 if females) + (0.192 if African -American)

eGFR greater than 90 mL/min/1.73 m^2 were considered to be normal.

The eGFRCKD-EPI {Equation for eGFR from serum creatinine by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)} was calculated as described by Van den Brand JA et al., [16].

STATISTICAL ANALYSIS

Data was analysed using Statistical Package for Social Sciences (SPSS) version 16. The data collected from the study was expressed as the mean and standard deviation. Statistical significance for study group and control was analysed using Student's t-test. The p-value <0.05 was considered statistically significant. Pearson's correlation test was used for correlation analysis between the variables.

RESULTS

Among the 130 Participant, 65 hypothyroid subject (24 males and 41 females) with average age 42.93±3.39 years and 65 Healthy Control (19 males and 46 females) with average age of 41.30±3.82.

Significant increase in serum creatinine levels in hypothyroid subjects (1.39±0.33 mg/dL) was observed as compared to controls (0.74±0.20 mg/dL). The mean levels of urea and serum potassium were found to be significantly elevated in hypothyroid subjects when compared to controls. However, no significant difference was observed between the uric acid levels between the two groups [Table/Fig-1].

Parameter	Controls (n=65)	Hypothyroid subjects (n=65)	p-value
Age	41.30±3.82	42.93±3.39	0.2654
Free Tri iodotyronine (pg/dL)	3.71±0.39	1.19±0.33	<0.001*
Free Tyroxine (ng/dL)	1.12±0.30	1.02±0.33	0.091
TSH (µIU/mL)	3.13±1.07	10.70±3.5	<0.001*
Urea (mg/dL)	22.6±4.15	36.7±5.4	<0.001*
Creatinine (mg/dL)	0.74±0.20	1.39±0.33	<0.001*
Uric acid (mg/dL)	4.24±0.54	4.09±0.31	0.043
Sodium (mEq/L)	137.4±1.78	136.7±1.95	0.046
Potassium (mEq/L)	3.97±0.41	4.78±0.40	<0.001*
Chloride (mmol/L)	100.7±12.36	97.4±2.32	<0.001*
Estimated glomerular filtration (mL/min/1.73 m^2)	96.2±4.69	66.8±1.29	<0.001*

[Table/Fig-1]: Mean distribution of biochemical parameters in hypothyroid subjects and controls.
Values are expressed in mean±standard deviation; * Statistically significant; Students t-test was used; TSH: Thyroid stimulating hormone

There was significant negative correlation (-0.25) between FT3 and urea levels in hypothyroid subjects. Uric acid showed positive correlation significantly with FT3 in subjects with r-value (0.29). Positive correlation between serum sodium and FT3 (r=0.2) and a negative correlation between serum potassium and FT3 (r=-0.29) was observed in hypothyroid subjects [Table/Fig-2].

Parameter	Mean±SD	r-value	p-value
TSH	10.70±3.5 µIU/mL	r=-0.0542	<0.05*
Urea	36.7±5.4 mg/dL	r=-0.25	<0.05*
Creatinine	1.39±0.33 mg/dL	r=-0.3	<0.05*
Uric acid	4.09±0.31 mg/dL	r=0.29	<0.05*
Sodium	136.7±1.95 mlEq/L	r=0.2	<0.05*
Potassium	4.78±0.40 mlEq/L	r=-0.29	<0.05*
eGFR	66.8±1.29 mL/ min/1.73 m^2	r=0.31	<0.05*

[Table/Fig-2]: The Pearson's correlation analysis between FT3 (1.19±0.33 pg/dL) with TSH, Urea, Creatinine, Uric acid, Sodium, Potassium and eGFR.
Values are expressed in mean±standard deviation; * Statistically significant

A significant negative correlation observed between FT4 and urea levels (r=-0.001) in hypothyroid subjects. Uric acid showed a positive correlation significantly with FT4 in subjects with r-value (0.1126). Positive correlation between serum sodium and FT4 (r=0.1797) and a negative correlation between serum potassium and FT4 (r=-0.0402) was observed in hypothyroid subjects [Table/Fig-3].

Parameter	Mean±SD	r-value	p-value
TSH	10.70±3.5 µIU/mL	r=-0.1356	<0.05*
Urea	36.7±5.4 mg/dL	r=-0.001	<0.05*
Creatinine	1.39±0.33 mg/dL	r=-0.1283	<0.05*
Uric acid	4.09±0.31 mg/dL	r=0.1126	<0.05*
Sodium	136.7±1.95 mlEq/L	r=0.1797	<0.05*
Potassium	4.78±0.40 mlEq/L	r=-0.0403	<0.05*
eGFR	66.8±1.29 mL/ min/1.73 m^2	r=0.0885	<0.05*

[Table/Fig-3]: The Pearson's correlation analysis between FT4 (1.027±0.330 ng/dL) with TSH, Urea, Creatinine, Uric acid, Sodium, Potassium and eGFR.
Values are expressed in mean±standard deviation; * Statistically significant

A significant positive correlation observed between TSH and urea levels (r=0.3444) in hypothyroid subjects. Uric acid showed negative correlation significantly with TSH in hypothyroid subjects r-value (-0.401). A negative correlation between serum sodium and TSH (r=-0.3326) and a positive correlation between serum potassium and TSH (r=0.4189) was observed in hypothyroid subjects [Table/Fig-4].

Parameter	Mean±SD	r-value	p-value
FT3	1.19±0.33 pg/dL	r=-0.0542	<0.05*
FT4	1.027±0.330 ng/dL	r=-0.1356	<0.05*
Urea	36.7±5.4 mg/dL	r=0.3444	<0.05*
Creatinine	1.39±0.33 mg/dL	r=0.3774	<0.05*
Uric acid	4.09±0.31 mg/dL	r=-0.401	<0.05*
Sodium	136.7±1.95 mlEq/L	r=-0.3326	<0.05*
Potassium	4.78±0.40 mlEq/L	r=0.4189	<0.05*
eGFR	66.8±1.29 mL/ min/1.73 m^2	r=-0.3876	<0.05*

[Table/Fig-4]: The pearson's correlation analysis between TSH (10.70±3.5 µIU/mL) with FT3, FT4, urea, creatinine, uric acid, sodium, potassium and eGFR.
Values are expressed in mean±standard deviation; * statistically significant

DISCUSSION

The present study shows that there is a significant increase in serum creatinine levels (1.39±0.33) in hypothyroid subjects when compared to controls (0.74±0.20). de Castro AV et al., in their study, observed similar increase in serum creatinine levels

in hypothyroid subjects [17]. A significant negative correlation was observed between FT3 and urea, creatinine and uric acid [18]. Study by Kreisman SH and Hennessey JV stated that hypo-thyroid state is linked with a steady rise in the serum creatinine level, most probably due to a reduction in the GFR, and demonstrates that it is a reversible change that develops quickly [19]. Kaur V et al., also observed similar changes in serum urea and creatinine levels and stated that increasing degree of hypothyroidism is associated with deteriorating renal function [20]. The consistency of elevation in serum creatinine levels was explained and it is attributed to balance between renal clearance and creatinine generation. Several case studies and case reports show increased levels of serum creatinine in patients of hypothyroidism [21-23].

Gouty arthritis with inflammed phalangeal and knee joints in one of the patients with chronic hypothyroidism was observed during the present study. The serum uric acid levels are elevated which may support that possibly nucleotide metabolism may also be affected in hypothyroidism [24]. This was supported by findings from Giordano N et al., who have shown that there is an increased uric acid levels and gout in hypothyroid patients [25]. Bharti A et al., also reported similar changes in urea and creatinine levels [26]. The serum creatinine, urea, uric acid levels are elevated which can be due to reduction in glomerular filtration rate, renal plasma flow, altered haemodynamic circulation and decreased cardiac output [27]. The electrolytes Na^+, k^+ & cl^- were analysed in hypothyroid subjects where there was a significant increase in k+ and cl- levels compared to controls. eGFR was estimated in the present study to know the functioning status of kidneys. A significant decrease in eGFR was observed in hypothyroid patients (66.8±1.29 mL/min/1.73 m^2) when compared to control (96.2±4.69 mL/min/1.73 m^2). eGFR was positively correlated with FT3. This can be explained as due to decrease in cardiac output caused by decrease in heart rate and myocardial contractility which in turn decreases stroke volume and increases peripheral vascular resistance [28]. Hypothyroidism affects cardiac and renal function by altering the haemodynamic and endothelial function. Decrease in renal plasma flow also cause imbalance in sodium and K+ levels. In the present study, we observed a marginal decrease in sodium levels and increase in k^+ levels. Hypothyroidism leads to hyponatremia and hyperkalemia as observed in several publications and reports [29,30]. There was a slight increase in uric acids levels which can be a cause for gouty arthritis. This can be due to myopathy in hypothyroid subjects with decrease in renal clearance of uric acid [31].

Limitation(s)

Present study is limited by small group of patients and shorter duration. Investigations like creatinine clearance can also be studied for better understanding.

CONCLUSION(S)

Hypothyroidism is associated with decreased renal function. There was a significant increase in urea, creatinine levels with significant decrease in eGFR. Serum electrolytes, especially K+ levels were increased. It is emphasised that there should be regular monitoring of renal function in patients with hypothyroidism which can prevent further damage to kidneys.

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