A Comparative Study of Serum Creatinine and Uric Acid Levels in Subclinical and Overt Hypothyroidism Patients

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ABSTRACT

BACKGROUND

Thyroid hormones are essential for normal growth, tissue differentiation, general development and metabolism. Thyroid stimulating hormone (TSH) secreted by thyrotrope cells of anterior pituitary, plays a very important role in the control of thyroid axis and serves as the most important marker of thyroid hormone action. TSH is a very sensitive and specific parameter for determining thyroid function and is important in early detection or exclusion of thyroid disorders. Hypothyroidism is an endocrine disease, which presents with decreased synthesis of thyroid hormones and their diminished action resulting in decreased metabolic processes and is associated with biochemical dysfunction which includes raised serum creatinine and uric acid levels. This study was undertaken to estimate the serum creatinine and uric acid levels in subclinical, overt hypothyroid cases and healthy controls and correlate these parameters with TSH in hypothyroid cases.

METHODS

Study included 90 patients of newly diagnosed hypothyroidism, of which 60 were subclinical and 30 were overt cases. 80 age sex matched healthy controls were taken. Venous blood was used for estimation of serum fT_3, fT_4, TSH, uric acid and creatinine levels. Statistical analysis was done using unpaired t' test. Correlation between creatinine, thyroid parameters and uric acid was done by Pearson's correlation method. All three parameters were compared using ANOVA test.

RESULTS

There was significant elevation in serum levels of creatinine and uric acid in subclinical and overt hypothyroidism cases when compared to controls. Overt cases had significantly higher creatinine and uric acid levels in comparison to subclinical hypothyroid cases. Significant positive correlation with TSH was shown by both creatinine and uric acid.

CONCLUSIONS

Both subclinical and overt hypothyroidism cases are associated with elevated serum creatinine and uric acid levels.

KEYWORDS

Hypothyroidism, Creatinine, Uric Acid, Gout

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BACKGROUND

Hypothyroidism is the 2nd most common endocrine disorder seen in females in India. This condition presents with low production of thyroid hormones, affecting 2-15% of population worldwide. Thyroid gland fails to synthesize adequate hormones resulting in primary hypothyroidism. Secondary hypothyroidism is characterized by insufficient functioning of the hypothalamic-pituitary–thyroid axis.[1] Subclinical hypothyroidism is characterized by increased serum TSH and normal free triiodothyronine (fT_3), free tetraiodothyronine (fT_4) levels. Overt is characterized by increased TSH and decreased fT_3, fT_4 levels.[2] Hypothyroidism affects every tissue in the body resulting in declination of physical and mental activities. Long standing hypothyroidism causes reversible changes in the metabolic parameters such as elevation in serum creatinine and uric acid levels. There is reduction in glomerular filtration, which leads to derangement of serum creatinine and uric acid levels. Studies suggests that in hypothyroidism there is decreased myocardial contractility and stroke volume with increased peripheral vascular resistance, which reduces the effective renal plasma flow and GFR, causing decreased clearance of creatinine and uric acid. This leads to elevation of serum creatinine and uric acid levels in hypothyroidism.[3,4] The serum creatinine concentration increases in hypothyroid patients due to reduction of glomerular filtration rate because of hemodynamic changes in severe hypothyroidism. Serum creatinine level may also be increased due to hypothyroid myopathy. In hypothyroidism, associated autoimmune diseases may also play the role in modifying the underlying renal problem. Hypothyroidism, although rare, has been reported as a definite and authentic cause of rhabdomyolysis.[5]

Kreisman Stuart (1999) in his study concluded that there is consistent and reversible elevation of serum creatinine in hypothyroid cases. Creatinine elevation was presumed to be due to reduction in GFR and decreased renal blood flow and decreased clearance of creatinine.[6] The significant increase of both hyperuricemia and gout was found in the hypothyroid patients, and of hyperuricemia in the hyperthyroid patients. In hyperthyroidism the hyperuricemia is due to the increased urate production, while in hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration.[7] Therefore this study was undertaken to evaluate the serum levels of creatinine and uric acid in newly diagnosed hypothyroidism cases and to see the correlation of these parameters with TSH in hypothyroid cases.

METHODS

Source of Data

This was a comparative study. The study was conducted on 90 randomly selected, clinically newly diagnosed and confirmed cases of hypothyroidism, attending the medicine outpatient department at Hanagal Shri Kumareshwar Hospital and Research Centre, Navanagar, Bagalkot and 80 age and sex matched healthy controls. Duration of study was from January to November 2014. Detailed history and clinical examination of the selected subjects were carried out. 90 newly diagnosed hypothyroid cases were involved. Of which 60 subclinical and 30 overt hypothyroid cases were taken

Inclusion Criteria

Patients with newly diagnosed hypothyroidism. Age group between 19- 59 years. Patients were sub grouped into subclinical and overt hypothyroid cases based on fT3, fT4 and TSH values. Controls: Healthy euthyroid age and sex matched individuals without any major illness and not on any medications.

Exclusion Criteria

Patients with chronic kidney diseases, gout, diabetes mellitus, hypertension, hypothyroid patients on treatment, hyperthyroid patients, muscular dystrophies, pregnant and lactating women. Patients on hypolipidaemics, antiepileptic drugs and women on oral contraceptives were excluded from the study.

After a thorough history taking and clinical examination**,** the procedure was explained to the subjects and informed written consent was obtained. A sample of 5 ml venous blood was collected and was allowed to clot. After clotting it was centrifuged. fT3, fT4, TSH were estimated by using Maglumi SNIBE 1000 machine using CLIA method.[8] Normal ranges for fT3 (1.2 - 4.1 pg/ml), fT4 (8.9-17.8 pg/ml), TSH (0.45-5.0 µIU/ml). Serum creatinine (0.6-1.4 mg/dL) and uric acid (2.7-6.5 mg/dL) were measured by auto-analyser Biosystem using their own kits. Creatinine was estimated by alkaline picrate method[9] and uric acid by uricase peroxidase method.[10]

Statistical Analysis

USI Statistical analysis was done by unpaired 't' test for comparison of two groups and a 'p' value of <0.05 is considered statistically significant. Correlation between study variables was done using Pearson's correlation. All three parameters were compared using ANOVA test.

RESULTS

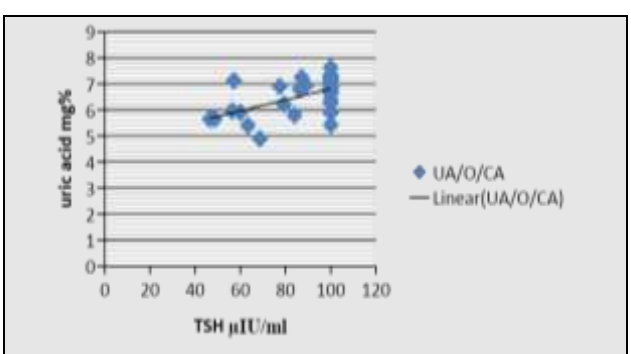

Figure 1. Positive Correlation of Uric Acid with TSH

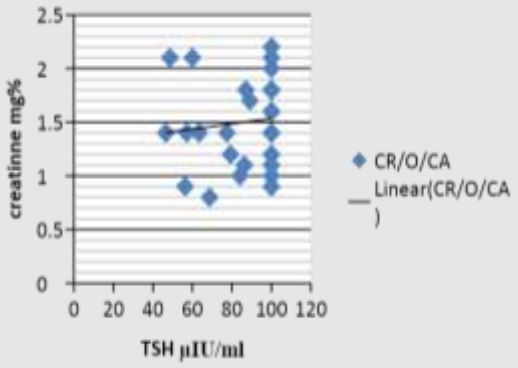

Figure 2. Positive Correlation of Creatinine with TSH

Thyroid Parameters	Cases (90)	Controls (80)	p Value
fT_3 (pg/ml)	1.72 ± 0.79	2.13 ± 0.53	< 0.001**
fT_4 (pg/ml)	9.29 ± 3.40	12.28 ± 2.08	< 0.001**
TSH (µIU/ml)	41.88 ± 34.86	2.07 ± 0.95	< 0.001**

Table 1. Comparison of Thyroid Parameters in Hypothyroid Cases and Controls (Mean ± SD)

**Statistically highly significant p<0.05, fT_3: Free triiodothyronine, fT_4: Free tetraiodothyronine, TSH: Thyroid stimulating hormone

Thyroid Parameters	Subclinical (60)	Overt (30)	p Value
fT_3 (pg/ml)	2.11 ± 0.43	0.94 ± 0.18	<0.001**
fT_4 (pg/ml)	10.5 ± 1.55	5.05 ± 1.66	<0.001**
TSH (µIU/ml)	21.65 ± 12.07	84.21 ± 18.05	<0.001**

Table 2. Thyroid Parameters in Subclinical and Overt Hypothyroidism Cases Expressed as Mean ± SD

**Statistically highly significant p<0.05

Study Parameters	Controls (80)	Subclinical Hypothyroid (60)	Overt-Hypothyroid (30)	F Value	Significance between Each Group. p Value		
					Sub-Clinical Controls	Overt Controls	Sub-Clinical Overt
Creatinine (mg/dL)	0.77 ± 0.10	0.98 ± 0.21	1.44 ± 0.39	171.60	<0.001**	<0.001**	<0.001**
Uric acid (mg/dL)	4.08 ± 0.65	4.87 ± 0.70	6.43 ± 0.69	139.68	<0.001**	<0.001**	<0.001**

Table 3. Comparison of Serum Creatinine and Uric Acid Levels in All the Three Groups (ANOVA)

**Statistically highly significant p<0.05

Significant difference in serum levels of fT_3, fT_4, TSH, creatinine and uric acid between the cases and controls were observed. Subclinical and overt hypothyroid cases had significant elevation of serum creatinine and uric acid levels compared to euthyroid subjects which was statistically highly significant (p<0.001). Positive correlation was seen between creatinine and uric acid levels with TSH. Table shows Comparison of thyroid parameters between controls and hypothyroid cases with p value <0.001**.

Similarly, table 2 showed statistically significant difference (p<0.001**) in fT_3, fT_4 and TSH levels between two groups of hypothyroid cases. All three groups comparison was done in table 3. There was statistically significant difference in these parameters showing increased serum creatinine and uric acid levels in subclinical and overt cases compared to controls. Comparison of subclinical with controls, overt with controls and subclinical with overt cases was done. There was highly significant difference in serum levels of creatinine and uric acid with p value <0.001**. Figure 1 and 2 displays the positive correlation of uric acid & creatinine with TSH levels.

DISCUSSION

Thyroid disorders result in considerable changes in renal function and the most common disturbance associated with hypothyroidism is increase in the serum levels of creatinine and uric acid due to decrease in glomerular filtration rate and renal plasma flow. There is a reversible elevation of serum creatinine in both adults and children in primary subclinical hypothyroidism.[3] In this case control study, we have compared the above two biochemical parameters in 90 cases of hypothyroidism, who were newly diagnosed and 80 cases of age and sex matched, healthy controls. The significance of both parameters between the groups, their diagnostic value and correlation with thyroid hormones were analysed and discussed. The present study showed a significant increase in mean serum creatinine levels in both subclinical (0.95 ± 0.21) and overt hypothyroid cases (1.48 ± 0.39) in comparison to controls (0.67 ± 0.10) with p<0.001**. Serum creatinine levels in overt hypothyroid cases were significantly higher in comparison to subclinical cases with p <0.001**. This case control study showed a significant increase in serum uric acid in both subclinical (4.67 ± 0.70) and overt hypothyroid cases (6.53 ± 0.69) in comparison to controls (4.18 ± 0.65) with p<0.001**. Serum uric acid levels in overt hypothyroid cases were significantly higher when compared to subclinical cases with p <0.001**, our findings are in accordance to the following studies.

Hypothyroidism leads to considerable changes in renal function which results in decreased renal blood flow, decrease in GFR and decrease in sodium reabsorption in proximal convoluted tubules. Changes in water and electrolyte metabolism together with hyponatremia and alterations of renal hemodynamic is also seen in hypothyroidism.[11,12] Ajaykumar and co-workers (2013) in their open label, single centre, randomized prospective study carried out in the Outpatient Department of Endocrinology, Govt. Rajaji hospital, Madurai, for a period of 6 months showed an increase in serum creatinine with a mean of 1.12, increase in serum uric acid with a mean of 7.358 and increase in serum cholesterol with a mean of levels 226.19 along with decrease in Hb levels with a mean of 9.50. These patients were treated with L- thyroxine and the same patients were evaluated at the end of six months. The changes in the metabolic parameters were found to be reversible after thyroxine replacement therapy. The increase in serum uric acid and creatinine may be either due to increased production or decreased renal clearance due to the generalized hypodynamic circulation in hypothyroid patients.[13]

Another study done by Arora S and co-workers in 2009 evaluated the changes in kidney function in hypothyroid subjects before and after treatment and correlated these values with thyroid profile of the patients. Their results showed hypothyroid subjects had significantly higher levels of serum TSH, creatinine and serum uric acid as compared to euthyroid subjects (p<0.001). All the patients with moderate and overt hypothyroidism had hyperuricemia (uric

acid levels >7 mg/dL). TSH showed significant positive correlation with uric acid levels. Uric acid levels were significantly negatively correlated only with T3 levels. A significant decrease in serum uric acid was seen after 6 weeks of thyroxine replacement and these values were comparable to euthyroid group.[14]

Nagrajappa K. 2014 in his study determined the levels of serum creatinine in hypothyroid cases and controls. Serum creatinine is increased in case of hypothyroid cases (1.8 ± 0.03) which was significant when compared to controls (0.86 ± 0.24) and also they found elevated serum Triglyceride and total cholesterol levels in hypothyroid cases.[15] Our study is in accordance with A Khan[5] studies which showed increased serum uric acid levels in hypothyroid cases due to decreased renal clearance. Iglesias study on thyroid dysfunction and kidney disease shows elevation of serum creatinine levels due to decreased glomerular filtration rate and due to decreased renal plasma flow.[3] N Giardonain his study, observed high prevalence of hyperuricemia in both hypothyroid and hyperthyroid patients. In hypothyroidism, hyperuricemia is secondary to a reduction in renal plasma flow and glomerular filtration and concluded that hyperthyroidism can cause a significant increase in serum uric acid, as well, although lower than the hyperuricemia due to thyroid hormone deficiency.[7]

Mohammed in 2012, conducted a case control study on Sudanese patients attending the Khartoum Hospital at Khartoum state, in the period from April 2012 to December 2012. The study showed significant increase in the level of uric acid in both hyper and hypothyroidism test groups when compared with control group (6.7 ± 1.69 mg/dL and 6.5 ± 1.66 mg/dL versus 4.0 ± 0.87 mg/dL respectively), ($p<0.05$). These changes in uric acid among patients with thyroid dysfunction are reversed upon therapy ($p <0.05$). There is insignificant correlation between serum uric acid level with duration of both hypo and hyperthyroidism ($r=0.036$, $p=0.805$) and ($r=0.087$, $p=0.547$) respectively. Also, there is no significant correlation between serum uric acid level with the age in both hypo and hyperthyroidism patients ($r=-0.137$, $p=0.343$) and ($r=-0.239$, $p=0.095$) respectively.[16]

Sinisa et al, observed elevation of serum creatinine in hypothyroid subjects 115 ± 12 µmol/L which decreased after treatment to 95 ± 14 µmol/L. Diminished creatinine tubular secretion together with the increased creatinine release from muscle cells results in higher values of serum creatinine in hypothyroid cases.[17] In view of this, the present study was undertaken to assess the clinical utility of some of the biochemical markers like creatinine, uric acid. These are inexpensive and can be used as screening markers to diagnose hypothyroidism.

CONCLUSIONS

In our study, serum creatinine and uric acid levels have been found to be significantly higher in both subclinical and overt hypothyroidism cases, in comparison to controls. Both parameters were found to be at higher levels in overt cases, compared to subclinical hypothyroid cases. Creatinine and uric acid showed positive correlation with TSH in hypothyroid cases. Hence hypothyroidism should be taken into account in patients presenting with chronic kidney diseases. On the other hand, kidney disease also affects thyroid function in many ways leading to decreased T_3 and T_4 levels.

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