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Original Research Article

A study of serum uric acid levels and serum creatinine levels in hypothyroidism

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ABSTRACT

Background: 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.
Materials and Methods: Study included 60 patients of newly diagnosed hypothyroidism, of which 30 were subclinical and 30 were overt cases. 80 age sex matched healthy controls were taken. Venous blood was used for estimation of serum fT3, fT4, TSH, uric acid and creatinine levels. Statistical analysis was done using unpaired t' test. Correlation between creatinine, thyroid parameters and uric acid was done.
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.

1. Introduction

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones leading to generalized slowing down of metabolic processes. Hypothyroidism is most common hormonal deficiency, the diagnosis can be made quickly, confirmed or excluded and treatment is straight forward with excellent prognosis.

Creatinine is formed in muscle from creatine phosphate by irreversible non enzymatic degradation and loss of phosphate. Creatine phosphate is the high energy buffer in skeletal muscle and brain. Creatinine phosphate prevents rapid depletion of ATP by providing a readily available high energy phosphate that can be used to regenerate ATP from ADP. Both subclinical and overt hypothyroidism cases are associated with elevated serum creatinine and uric acid levels. The gold standard test for screening hypothyroidism is the estimation of serum TSH. Further, blood testing of T_3 and T_4 will diagnose the type of hypothyroidism. These biochemical testing is used for the treatment of hypothyroidism.

2. Aims and Objective

To estimate serum uric acid and serum creatinine levels and calculates e GFR in hypothyroid patients (study group) and euthyroid controls (control group).

1. To compare the serum uric acid levels among the study and control group.
2. To compare the serum creatinine levels among the study and control group.
3. To compare e GFR values among the study and control group.
4. To find the correlation between Thyroid profile (T3, T4, TSH) and serum uric acid, serum creatinine and e

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GFR value in study group.

3. Materials and Methods

3.1. Place of Study

Study was conducted in the Department of Biochemistry, Rajeev Gandhi College and General Hospital Bhopal for a period of six months January 2020 to July 2020.

The experimental protocol includes

1. Recording of a detailed history including history of cardiovascular disease, diabetes mellitus, hypertension, and surgery or any drug intake and family history of renal, muscular, liver disorders.
2. Measurement of Anthropometric Indices:

The subjects were asked to stand erect, with their arms relaxed at their side and feet together.

The following were measured:

1. Weight (in kilograms) was recorded using a portable standard weighing machine.
2. Height (in centimeters) was measured to the nearest 0.5 cm using a stadiometer.
3. Body Mass Index (BMI) was calculated using Quetelet's Index.

BMI = Weight (Kg)/ Height (m^2).

1. Recording of vital signs viz. pulse rate, respiratory rate and measurement of blood pressure were done and documented.
2. Blood investigations: The investigations include
   (a) Serum Uric acid by Uricase –Trinder – Enzymatic and colorimetric methoddd.
   (b) Serum Creatinine by Modified Jaffe's method (Alkaline Picrate Method.

4. Comparison of Results

The serum uric acid levels and serum creatinine levels, e GFR values in hypothyroid patients and euthyroid controls was analysed using unpaired student t test, correlation between thyroid profile (T3,T4,TSH) and serum uric acid, serum creatinine, e GFR value in hypothyroid patients were analysed using Pearson's correlation coefficient test and Prevalence of Hyperuricemia among study group and control group, staging of e GFR among study group and control group is analysed by chi square test. By means of SPSS (Statistical Package for Social Sciences) software version 16, analysis of statistics was performed. The statistical significance was drawn at 'p' value < 0.05.

When comparing the BMI between cases and controls it was found that there was no statistical significance in the values between them. Results analysed using student T test showed a statistically insignificant 'p' value.

Table 1: Age distribution

Age (in years)	Case	Control	Total
21 – 30	15	30	45
31 – 40	25	12	37
41 – 45	10	8	18
Total	50	50	100
Mean	34.14	29.92	
Standard deviation	6.95	7.33	
p value	0.00396	Significant	

Table 2: Gender distribution

Gender	Case	Control	Total
Male	5	4	9
Female	45	46	91
Total	50	50	100

5. Discussion

Present study evaluated the effect of hypothyroidism on parameters of renal function and to compare it with euthyroid subjects and also to study the correlation of (TSH, T4 and T3) with uric acid, creatinine and e GFR. Person with age group 21–45 years were included in this study. Mean age of this study and control group were 34.14 (years) and 29.92 (years) respectively. Most of the people in study group belonged to the age group of 31 to 40 years and that of control group belonged to age group 21-30 years.

In a study conducted by Chandhury H.S. et al., 2013, the most common age group 30-39 years. The mean age of hypothyroid and controls were nearly same. However, hypothyroidism was found more common in 25-35 years age group. Mean BMI of the study and control group were 25.49(kg/m^2) and 25.32 (kg/m^2) respectively.[1]

Another study done by Qahtan A. Rashead et al. 2015, the highest percentage of people were in age group 26-45 years.[2]

Tejomani M et al. 2013 also observed the prevalence of hypothyroidism was higher among females. The increased predisposition of females is observed in overt and subclinical hypothyroids.[3] Also in Qahtan A. Rashead et al. 2015 study- distribution of study population had more percentage rate of females than the percentage rate of males.[2]

In this study, the mean value of T3 among study group and control group is 0.854(ng/ml) and 1.5(ng/ml) respectively and that of T4 among study group and control group is 6.42 (μg/dL) and 9.57 (μg/dL) respectively. It is seen that the (T3, T4) level significantly decreased in study group when compared to control the finding is very similar to Singh et al. 2006, Nagarajappa et al. 2014.[4,5]

Very similar results were found in subsequent studies like Nagarajappa et al. 2014 showed increase in uric

Table 3: Thyroid profile (T3, T4, TSH)

Thyroid hormones	Case		Control		p value
	Mean	Standard deviation	Mean	Standard deviation	
T3 (ng/ml)	0.854	0.377	1.5	0.35	<0.00001 (Significant)
T4 (μg/dL)	6.42	3.1	9.57	1.84	<0.00001 (Significant)
TSH (μIU/ml)	32.02	16.6	2.25	1.04	<0.00001 (Significant)

Table 4: Serum uric acid analysis

Name of the substance	Case		Control		p value
	Mean	Standard Deviation	Mean	Standard Deviation	
URIC ACID (mg/dl)	6.87	1.16	5.41	1.07	<0.00001 Significant

Table 5: Correlation between thyroid profile and serum uric acid levels in hypothyroid patients

Thyroid hormones	Serum uric acid (mg/dl) 'r' value	'p' value
T3(ng/ml)	- 0.079	0.585 (Not Significant)
T4 (μg/dL)	- 0.3915	**0.004 (Significant)**
TSH (μIU/ml)	0.2505	1.79 ot Significant)

Table 6: Correlation between thyroid profile and serum creatinine levels in hypothyroid patients

Thyroid hormones	Serum Creatinine(mg/dl) 'r' value	'p' value
T3(ng/ml)	0.0621	0.668 (Not Significant)
T4 (μg/dL)	- 0.0645	0.658 (Not Significant)
TSH (μIU/ml)	0.1631	0.258 (Not Significant)

Table 7: Correlation between thyroid profile and e GFR in hypothyroid patients

Thyroid hormones	e GFR (ml/min/1.73m^2) 'r' value	'p' value
T3(ng/ml)	-0.055	0.704 (Not Significant)
T4 (μg/dL)	0.2096	0.144 (Not Significant)
TSH (μIU/ml)	-0.1543	0.285 (Not Significant)

acid levels in cases as compared to controls and the increase is statistically highly significant, the hyperuricemia is secondary to decreased renal plasma flow and urate excretion.[5]

In this study, mean TSH value among study group and control group is 32.02(μIU/ml) and 2.25(μIU/ml) respectively. There is a significant difference in TSH value among study and control group which is very similar to study conducted by VI Indrajith.[6]

Indrajith 2016 which showed decreased level of T3 and T4 and increased TSH in the study when compared to that of control group. This is due to decreased synthesis of thyroid hormones and loss of negative feedback control when compared to healthy individuals.[6]

A study done by Devika Tayal et al. 2009 showed an significant increase in serum uric acid levels in hypothyroid patients as compared to euthyroid subjects. In a case-control study done by Khan et al. 2010 showed serum uric acid level significantly higher in cases compared to controls.[7]

Another study done by Sarika Arora et al. 2009 showed that there is significant increase in uric acid levels in hypothyroid patients as compared to euthyroid subjects. The changes in biochemical marker of renal function were found to be reversible after thyroxine replacement therapy.[8] A study done by Ajaykumar et al 2013, also showed increase in uric acid levels in newly diagnosed hypothyroid patients, which decreased with 6 months of thyroxine replacement therapy. These studies suggest that increase in uric acid level is because of hypothyroid effect on kidneys leading to impaired urate excretion and once thyroxine supplementation is done it is reversible.[9]

Gagandeep Sidhu et al 2016, Vijayapriya I Indrajith 2016 these studies also showed serum uric acid level was significantly increased in hypothyroid patients than controls and hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration.since 75% of uric acid is eliminated through kidneys, in patients with hypothyroidism impaired renal function is one of the etiology for hyperuricemia.[6,10]

In this study, uric acid showed negative correlation with T3 (-0.079) and T4 (- 0.3915), positive correlation with TSH (0.2505), but correlation with T4 is alone statistically significant and with T3, TSH were very weak. This finding indicates that uric acid levels are negatively regulated by thyroid hormones, especially T4 and they tend to increase in overt hypothyroid cases where T4 levels are low.

In Tayal et al 2009 study uric acid showed a significant negative correlation only with T3 levels in overt hypothyroid group and weak negative correlation with T4 and positive correlation with TSH. [7]

In Sarika Arora et al. 2009 study uric acid showed a significant negative correlation with T3 levels. [8]

Lai-Chu See et al. 2014 study there was no significant correlation between TSH and serum uric acid levels. In Jia D et al 2015 study TSH showed no correlation with serum uric acid, Free T4 and Free T3 showed negative correlations with serum uric acid. [11,12]

Gulab Kanwar et al. 2014 showed TSH is positively correlated with uric acid is statistically significant. In this study the prevalence of hyperuricemia is high among hypothyroid group than euthyroid control group. In study group it is 44% as compared to 8% in control group. The results are very similar to previous studies suggesting hyperuricemia occurring more common in hypothyroidism and is due to impaired renal function. [13]

Erickson et al. 1994 evaluated 54 patients with a documented gouty arthritis for the presence of hypothyroidism. The prevalence of hypothyroidism was significantly higher in patients with gouty arthritis. Overall, 15% of these patients, 25% of women and 12% of men, had hypothyroidism. These rates were 2.5-fold greater in women and sixfold greater in men than found in the controls. [14]

Study done by Giordano et al 2001 showed 33.3% prevalence of hyperuricemia in patients with hypothyroidism as compared to 10% prevalence in general population. [15] Similar studies were found hyperuricemia in patients with hypothyroidism. There is high prevalence of hyperuricemia and gout in hypothyroidism. In hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration. Giordano et al 2001 found a significant increase in the incidence of both hyperuricaemia and gout in the hypothyroid patients. Hyperuricemia leading to gout had been reported in Hypothyroid subjects in a few studies done around the world. In present Study though showed high prevalence of hyperuricemia but there was no case of gout reported. This is similar to study done by Tayal D et al 2009 which showed that no case of gout was reported despite the presence of Hyperuricemia in overtly hypothyroid cases. [7]

Jayagopal et al. 2003 studied the effects of the hypothyroid state on changes in serum creatinine in 17 patients with hypothyroidism. All patients were newly diagnosed. The hypothyroid patients had a mean serum creatinine of 1.02mg/dl. It had been confirmed that the rise in creatinine levels in hypothyroid patients did not relate to abnormalities in other renal functions or creatine kinase levels suggesting that neither hypothyroid myopathy nor intrinsic renal disease contributed to the changes seen in creatinine levels. [16]

In Sukrella Khalid et al. 2006 study, mean serum creatinine levels increased in hypothyroidism as compared to the control group. Tayal et al. 2009 found that mean serum creatinine concentrations were significantly increased in both patient groups i.e. sub-clinical and overt hypothyroid as compared to euthyroid subjects. [17]

Similar findings were seen in subsequent studies Chaudary et al 2013 ; Tejomani M et al 2013 ; Khan et al 2013 ; Nagarajappa et al 2014; Mamantha et al 2016. All these Studies say that the elevated serum creatinine levels in hypothyroid patients are due to physiological effects including alterations in renal hemodynamics, decrease in GFR and reduced clearance of creatinine. Some argue that serum creatinine level may also be increased due to hypothyroid myopathy. [1,3,5]

Sarika Arora et al. 2009 The levels of serum creatinine in hypothyroid subjects were within normal range (< 1.4 mg/dl) but significantly higher than in the euthyroid subjects ($p<0.001$). A significant decrease was observed in serum Creatinine, after 6 weeks of thyroxine replacement therapy. After 6 weeks of thyroxine replacement, the value of creatintine was comparable to euthyroid group. [8] A study done by Ajaykumar et al 2013 also showed increase in serum creatinine levels in newly diagnosed hypothyroid patients which decreased with 6 months of thyroxine replacement therapy. [9]

Thus, the increase in creatinine in hypothyroid patients, though on the higher side of physiological range is high then the controls and is statistically significant and is mainly because of alterations in renal hemodynamics leading to decrease in GFR, reduced creatinine secretion, thus decreased creatinine excretion. In this study, serum creatinine has positive correlation with T3 (0.0621) and TSH(0.1631), negative correlation with T4(- 0.0645). But all were weak and statistically not significant.

Jia D et al 2015 TSH showed weak negative correlation with creatinine, FT3 and FT4 showed significant negative correlation with creatinine. Vaneet Kaur et al 2015 TSH showed a significant positive correlation with serum creatinine levels whereas fT4 and fT3 did not show any significant correlation with creatinine. This studies are showing mixed observations. [12]

Lippi G et al 2008 - indicated a mutual relationship between kidneys and thyroid status where TSH >2.5mIU/L were associated with decreased estimated glomerular filtration rate (e-GFR). [18]

In Anne et al 2008 study, eGFR was calculated using the simplified Modification of Diet in Renal Disease Study equation and it was found that the mean e GFR value is low in hypothyroid as compared to euthyroid and stated that in hypothyroidism, decreased eGFR probably reflects a true reduction in GFR. The mechanism of this is thought to be the decreased cardiac output caused by the reduced cardiac heart rate, stroke volume and contractibility all of which are caused by low thyroid hormone status.[19] Although there is an increased systemic vascular resistance, overall there is a decrease in systemic blood volume and consequently a reduction in GFR. When a low eGFR is encountered, hypothyroidism should be considered as a possible cause.

Sukrella Khalid et al 2006, in hypothyroid patients mean estimated GFR was decreased as compared to mean estimated GFR control group and the difference is statistically significant.[17]

In this study the e GFR value has negative correlation with T3(-0.055) and TSH (-0.1543) but positive correlation with T4 (0.2096). The correlation was weak and statistically not significant.

6. Conclusion

Present study shows that there is increased uric acid levels and creatinine levels and decreased e GFR levels in study group as compared to control group. The prevalence of hyperuricemia is high in hypothyroidism. These changes in the biochemical values is because of the renal dysfunction evident by decrease in mean e GFR level as compared to mean e GFR level in control group.

Thus, these findings are helpful in understanding the interaction between thyroid gland and kidney showing the detrimental effect of hypothyroid state on renal functioning. This renal impairment is often overlooked but is readily reversible by prompt treatment leading to normalization of biochemical markers.

Hence, it is suggested to assess the renal status of the patient at the time of diagnosis of Hypothyroidism. To have strict observation of these parameters in follow up phase especially in person having risk factors for developing kidney disease eg-hypertension, diabetes mellitus To do Thyroid screening in person presenting with these biochemical abnormalities and patients has worsening chronic renal failure without any cause.

7. Limitations

Further studies can be planned with the larger sample size and multiple measurements of serum uric acid, serum creatinine, TSH levels to study the biochemical values in same patients.

8. Source of Funding

None.

9. Conflict of Interest

The authors declare no conflict of interest.

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