RENAL AND MUSCULAR DYSFUNCTION IN OVERT HYPOTHYROIDISM

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ABSTRACT: BACKGROUND: There is a significant alteration in creatine kinase, creatinine, creatinine clearance and estimated GFR(eGFR) in hypothyroid patients which may be due to renal and muscular damage resulting in renal failure and myopathies. Our study adds to the existing knowledge, the importance of periodic assessment of renal parameters and creatine kinase in hypothyroid patients.

AIM: The aims of this study were to compare parameters of serum creatinine, creatinine clearance, eGFR and serum creatine kinase in patient with overt hypothyroidism.

MATERIALS AND METHODS: This Case control study included twenty eight diagnosed cases of hypothyroidism in the department of Endocrinology, Medicine and Surgery of A J Institute of Medical Sciences & Research Centre, Mangaluru, of age group 15-75 years. Based on T3,T4, TSH levels, subjects were diagnosed as overt hypothyroids. Results were compared with age and sex matched twenty five euthyroids. Serum T_3, T_4 and TSH; Serum creatinine; Creatinine clearance; and Serum creatine kinase were estimated and analysed.

RESULTS: The results of the present study were obtained from 53 subjects out of whom 25 were controls and 28 were overt hypothyroids. Age distribution of study subjects shows that the mean age was 36.30±8.30 for overt hypothyroids. Sex distribution of study subjects shows that majority of overt hypothyroids (78.6%) were females. Pairwise comparison of T_3, T_4 and TSH among euthyroids and overt hypothyroid groups showed that the mean difference of 41.388 between controls and overt hypothyroids. Overt hypothyroids had low T_3 and T_4 levels with high TSH levels. Comparison of mean of creatinine clearance in the study groups shows that the mean in controls, and overt hypothyroids were 96.97±31.90 ml/min/1.73 m^2, and 79.95±25.51 ml/min/1.73 m^2 respectively. The mean of creatinine in the study and control groups were respectively 1.00±0.26 mg/dl and 0.86±0.22 mg/dl. The mean of creatine kinase in the study and control groups were 231(486) IU/L and 94(±22.5) IU/L respectively. The mean of eGFR in the study and control subjects were 70.14±22.55 ml/min/1.73 m^2 and 85.88±30.24 ml/min/1.73 m^2.

CONCLUSION: our study shows that patients with hypothyroidism can gradually end up with renal dysfunction and myopathies. This can be prevented by monitoring thyroid hormones levels along with periodic assessment of renal parameters(creatinine and creatinine clearance) and creatine kinase in hypothyroid patients. This may beneficial in reducing the morbidity of patients.

KEYWORDS: Creatinine; Euthyroids; overt Hypothyroidism; Thyroid hormones.

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INTRODUCTION: Thyroid gland synthesizes two related iodine-containing thyroid hormones thyroxine (T_4, tetraiodothyronine) and triiodothyronine (T_3). Deficiency of thyroid hormone secretion results in hypothyroidism. The onset of primary hypothyroidism is gradual. This is detected when TSH is elevated to compensate for impaired thyroid output. As the thyroid damage continues, TSH levels rise further but T_4 levels fall. The TSH at this stage is usually greater than 10 mU/l, symptoms become apparent, and the patient is said to have overt or clinical hypothyroidism.

Significant reversible changes in the functioning of kidneys and muscle are seen in long standing hypothyroid patients. Hypothyroidism may be associated with low GFR(glomerular filtration rate) because of hypodynamic state. The altered thyroid function causes a decrease in the contractility of the cardiac muscle and thereby decreases the cardiac output. There is increase in peripheral resistance leading to systemic and renal vasoconstriction resulting in decreased renal blood flow causing increase in creatinine and decreased creatinine clearance.[1]

Creatine kinase (CK) is an enzyme that catalyses the formation of ATP from stored phosphocreatine in the muscle. CK is thus an important marker for muscle

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damage. Thyroid hormones cause an alteration in the permeability of the plasma membrane by increasing calcium channel from the sarcoplasmic reticulum. The elevation in serum creatine kinase in patients with hypothyroidism is also due to subnormal body temperature causing enhancement in the permeability of the muscle cell leading to increased leakage of the enzyme from the muscle cells.[2,3,4] Thus long standing hypothyroidism causes significant reversible changes in renal function and muscular function which if left undetected and untreated may result in renal failure and myopathies. The aims of this study were to compare parameters of serum creatinine, creatinine clearance and serum creatine kinase in overt hypothyroid cases.

MATERIALS AND METHODS: This Case control study included twenty eight diagnosed cases of hypothyroidism in the department of Endocrinology, Medicine and Surgery of A J Institute of Medical Sciences & Research Centre, Mangaluru, of age group 15-75 years after Ethical clearance from Institutional Ethical Committee. Based on TSH levels, subjects were diagnosed as overt hypothyroids (TSH ≥20μlU/ml). Results were compared with age and sex matched twenty five euthyroids. Age and sex matched euthyroids (25) taken as control subjects. Patients with acute infections, hepatobiliary diseases, renal diseases, diabetes mellitus, heart diseases, myopathies, pregnant females were excluded from the study.

In all selected individuals about 5ml of blood was collected in plain tube from large peripheral vein with aseptic precautions after obtaining informed consent. Serum was separated after centrifugation at 3000rpm for 10 min and following parameters were estimated:

Serum T_3, T_4 and TSH measured by Chemiluminescence method in Immulite 1000 autoanalyzer.[5,6,7]

Serum creatinine measured by Modified Jaffe's method in semiautoanalyzer using commercially available kit.[8] Creatinine clearance measured using Cockcroft-Gault formula.[9]

$$\text{Creatinine clearance}(\text{ml/min}/1.73\text{m}^2) = \frac{[(140 - \text{age(years)}) \times \text{weight (kg)}]}{72 \times \text{plasma creatinine(mg/dL)}}$$

Correction factor of 0.85 is recommended for females.

Serum creatine kinase was measured by optimized IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) using commercially available kit in semiautoanalyser.[10]

Data was analyzed using Analysis of Variance, Bonferroni test, Kruskar Wallis test, Mann Whitney test, Karl pearsons correlation and Chi square test. P <0.05 was considered to be statistically significant.

RESULTS: The results of the present study were obtained from 53 subjects out of whom 25 were controls and 28 were overt hypothyroids. Age distribution of study subjects shows that the mean age was 36.30±8.30 yrs for overt hypothyroids. Sex distribution of study subjects shows that majority of overt hypothyroids (78.6%) were females.

Comparison of T_3, T_4 and TSH among the study groups shows that the mean of T_3 in controls, and overt hypothyroids were 107.55±29.04 ng/dl, and 60.67±28.93 ng/dl respectively. The mean of T_4 in the control and study groups were 8.36±2.20 μg/dl, and 2.74±1.92 μg/dl respectively. The mean of TSH in the control and study groups were 1.90±1.18μIU/ml, and 55.90±20.98 μIU/ml respectively.

Percentage of individuals studied with altered levels of T_3,T_4 and TSH under each study group shows that there were to 35.7% of overt hypothyroids with normal T_3. There were 60% of overt hypothyroids with below normal T_3. There were 25% of overt hypothyroids with normal T_4.. There were 71.4% of overt hypothyroids with below normal T_4. Almost all patients (100%) under overt hypothyroidism had above normal TSH.

Comparison of mean of creatinine clearance, and creatine kinase in the study groups shows that the mean of creatinine clearance in controls, and overt hypothyroids were 96.97±31.90ml/min/1.73m^2, and 79.95±25.51 ml/min/1.73 m^2 respectively. The mean of creatine kinase were 94(22.5)±and 79.59±316.67 IU/L respectively. Kruskar Wallis test value of comparison of each parameter in all three groups were 22.520, and 46.200 respectively and were statistically highly significant with p value of 0.001 as depicted in Table 1.

DISCUSSION: Our study demonstrated that there was a statistically significant increase in serum creatinine in overt hypothyroids 1.00±0.26 mg/dl compared to controls 0.86± 0.22 mg/dl which is in accordance with the study by Josivan et al.

Prevalence of overt hypothyroidism was high in females with 78.6% under overt hypothyroidism. This is in accordance with studies done with Sheikh BA et al and Ali M N et al.[11,12]

There was a statistically significant decrease of T3 in overt hypothyroids (60.67±28.93ng/dl) compared to the mean in controls (107.55±29.04ng/dl) and a statistically significant decrease in T_4 in overt hypothyroids (2.74±1.92 μg/dl) compared to controls (8.40±2.20μg/dl). TSH in overt hypothyroids (55.90±20.98 μIU/ml) was significantly high compared to controls (1.90±1.18 μIU/ml). These findings are in accordance with study of Tayal Det al.[13]

The study also shows that there was a statistical significance in the mean difference of T_3 (41.388) and of T_4 (5.233) between controls and overt hypothyroids (p<0.05). Majority of overt hypothyroids had below normal T_3 (60.7%) and T_4 (71.4%) and above normal TSH (100%). These findings are in accordance with study of Tayal D et al[11] who claimed that T_3 and T_4 were significantly lower and TSH were higher in overt hypothyroid group as compared to euthyroid group.

Significant increase in the creatinine levels 1.00±0.26 mg/dl in overt hypothyroid patients is seen when compared to the controls 0.86±0.22 mg /dl.

The creatinine clearance was significantly reduced in the study group (79.95±25.51 mg/min/1.73m^2) than the control group (96.97±31.90 mg/min/1.73m^2).

There was a significant decrease in eGFR in study group 70.14±22.55 mg/min/1.73m^2 compared to the control group (85.88±30.24 mg/min/1.73m^2)

According to study of Rodrigo C et al[14] there are several case reports of renal damage in untreated hypothyroidism. The pathogenesis is multifactorial. There is a possible link between thyroid hormones and kidney injury which may be due to reduced cardiac output causing a decreased plasma flow and glomerular filtration rate due to the hypodynamic circulation. The hypodynamic circulatory state causes pre-renal insufficiency which may be aggravated by other multi-systemic effects of hypothyroidism such as reduced cardiac output, low volume state, and increased peripheral resistance due to the arterial wall stiffness.

The study showed that there was statistically significant increase in serum creatinine in overt hypothyroids (1.007± 0.2586mg/dl) compared to controls (0.800±.1472mg/dl) in accordance with the study of Rodrigo C et al[14] which showed a significant increase in serum creatinine in overt hypothyroid group compared to euthyroid subjects. A study by Muhammad A A et al[15] says that renal dysfunction is a recognized finding in overt hypothyroidism. This study showed statistical significance in the mean difference of serum creatinine (-0.2074) between controls and overt hypothyroids (p value 0.001). The study also showed statistical significance in the mean difference of serum creatinine (0.1847) between the two groups of hypothyroids (p value 0.004, Table 7). This is in accordance with studies of Claus T et al[16] and Cristina G et al[17.]

Our findings are also in accordance with the study by DA Mc Growder, YP Fraser et al which showed elevation of CK in hypothyroid patients.[18]

CONCLUSION: This study was undertaken to determine the levels of T_3, T_4 and TSH and their effect on different parameters like serum creatinine, creatinine clearance and creatine kinase in overt hypothyroids. The study showed an increase in the levels of serum creatinine , creatine kinase and a decrease in creatinine clearance in hypothyroid cases.

This shows that the complications of hypothyroidism like renal dysfunction and myopathies can be prevented by monitoring thyroid hormones levels along with periodic assessment of renal parameters and creatine kinase in hypothyroid patients. Although the findings of this study may be utilized for the proper management of hypothyroid cases, further studies on more number of hypothyroid cases along with follow up studies are needed to explore the actual differences in the effects of thyroid hormones in overt hypothyroids.

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Parameter	Control	Overt Hypothyroid	p-value
Age (years)	33±9.4	36.30±8.30	0.081
Serum T3	107.55±29.04	60.67±28.93	<0.001
Serum T4	8.4±2.20	2.74±1.92	<0.001
Serum TSH	1.90±1.18	55.90±20.98	<0.001
Serum Creatinine	0.86±0.22	1.00±0.26	<0.05
Serum Creatine Kinase	94(22.5)	231(486)	<0.001
Creatinine Clearance	96.97±31.90	79.95±25.51	<0.05
eGFR by MDRD	85.88±30.24	70.14±22.55	<0.05

Table 1