RENAL AND MUSCULAR DYSFUNCTION IN SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT: BACKGROUND: Hypothyroidism may result in alteration in renal and muscular functioning resulting in renal failure and myopathies. This study adds to existing literature emphasizing the utility 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 and serum creatine kinase in subclinical hypothyroid cases.

MATERIALS AND METHODS: This case control study included twenty three diagnosed cases of subclinial hypothyroidism in the department of Endocrinology, Medicine and Surgery of A J Institute of Medical Sciences & Research Centre, Mangaluru, of age group 18-45 years. 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 48 subjects out of whom 25 were controls and 22 were subclinical hypothyroids. Age distribution of study subjects shows that the mean age was 35.52±8.60 years for subclinical hypothyroids. Sex distribution of study subjects shows that majority of subclinical hypothyroid cases (81.8%) were females. Elevated levels of serum TSH with normal T_3 & T_4 was significant ($p<0.001$) in subclinical hypothyroid when compared to controls. Serum creatinine was elevated ($p<0.05$) with statistically significant decrease in creatinine clearance ($p<0.001$) in subclinical hypothyroids in comparison with controls. The serum creatine kinase was elevated ($p<0.001$) in subclinical hypothyroid patients.

CONCLUSION: This shows that complications of hypothyroidism like acute renal failure, and myopathies can be prevented by monitoring thyroid hormones levels along with periodic assessment of renal parameters and creatine kinase in subclinical hypothyroid patients..

KEYWORDS: Creatinine; Creatine kinase; Euthyroids; Subclinical hypothyroidism; Thyroid hormones.

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INTRODUCTION: The thyroid is one of the largest of the endocrine organs, weighing approximately 15 to 20 g. The thyroid gland contains spherical follicles (50–500 µm diameter). Follicle cells synthesize the two iodine-containing thyroid hormones thyroxine (T_4, tetraiodothyronine) and triiodothyronine (T_3). Deficiency of thyroid hormone secretion results in hypothyroidism. Impaired production of thyroid hormones is usually due to a primary abnormality of thyroid gland or iodine deficiency; occasionally it is secondary to pituitary or hypothalamic disorders. The onset of primary hypothyroidism is gradual and may be detected when TSH is elevated to compensate for impaired thyroid output and free thyroid hormones are normal. This state is called subclinical hypothyroidism. As 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. Prevalence of Subclinical hypothyroidism is more common (6-8% of women and 3% of men).[1]

Long standing hypothyroidism causes significant reversible changes in renal function such as decrease in sodium reabsorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in urate concentration, and a decrease in renal blood flow and GFR. This is because of hypodynamic state that occurs in hypothyroidism. The altered thyroid function induces a decrease in myocardial contractility and cardiac output. There is increase in peripheral resistance leading to systemic and renal vasoconstriction. This results in decreased renal blood flow causing decrease in GFR, increase in creatinine and a decrease in creatinine clearance. There is thickening of basement membrane which again causes reduced blood flow to the kidneys, so there is decreased creatinine clearance.[2]

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Thyroid hormones influence the maturation of renin angiotensin system, thus increasing concentration of renin and angiotensinogen in the serum. T_3 causes relaxation of blood vessels. There is vasoconstriction and increased peripheral resistance in hypothyroidism leading to reduced blood flow in the renal arteries. Thus serum creatinine is influenced by a decrease in T_3 and T_4 and increase in TSH.[3] The elevation in serum creatine kinase in patients with hypothyroidism is 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.[4,5,6]

The aim of this study was to compare parameters of serum creatinine, creatinine clearance and serum creatine kinase in subclinical hypothyroid cases.

MATERIALS AND METHODS: This Case control study included 48 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 18-45 years after Ethical clearance from Institutional Ethical Copmmittee. Based on TSH levels, subjects were classified as subclinical hypothyroids (TSH 6.1-10μlU/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, and women on oral contraceptive pills 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.[7,8,9]

Serum creatinine measured by Modified Jaffe's method in semiautoanalyzer using commercially available kit.[10] Creatinine clearance measured using Cockcroft-Gault formula.[11]

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

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.[12]

Data was analyzed using SPSS v.17. Independent sample t test was applied to compare the parameters in both the groups. Data is represented as Mean and standard deviation.

P-value <0.05 was considered to be statistically significant.

RESULTS: The results of the present study were obtained from 48 subjects out of whom 25 were controls and 23 were subclinical hypothyroids. Age distribution of study subjects shows that the mean age was 35.52±8.60 years for subclinical hypothyroids.

Comparison of T_3, T_4 and TSH among the study groups shows that the mean of T_3 in controls, and subclinical hypothyroids were 107.56±29.1 ng/dl and 104.91±27.67 ng/dl. The mean of T_4 in the two groups were 8.39±2.12μg/dl and 8.6±1.21μg/dl. The mean of TSH in the two groups were 1.92±1.19μIU/ml and 7.24±1.10μIU/ml respectively. On comparison of all three parameters in controls, and subclinical hypothyroid groups, only serum TSH values were significant with p value of <0.001. (Table 1)

Comparison of mean of serum creatinine, creatinine clearance, and creatine kinase in the study groups is depicted in Table 1. The mean serum creatinine value was slightly elevated in subclinical hypothyroids compared to controls but was statistically significant t(46) = -2.45; p=0.018. There was significant effect in creatinine clearance, t(46) = 4.35; p<0.001, with decrease in the subclinical hypothyroid group. The serum creatine kinase levels were significantly elevated t(46) = -17.60; p<0.001, when compared to controls.

DISCUSSION: Hypothyroidism is a graded phenomenon, ranging from very mild cases in which biochemical abnormalities are present but the individual hardly notices symptoms and signs of thyroid hormone deficiency, to very serious cases of life threatening myxodema coma. The transition from the euthyroid to the hypothyroid state is first detected by a slightly elevated serum TSH, caused by a minor decrease in thyroidal secretion of T_4 which does not give rise to subnormal serum T4 concentration. A further decline in T_4 secretion results in T_4 value below the lower normal limit and even higher TSH, but serum T_3 concentrations remain within the reference range. It is only in the last stage that subnormal serum T_3 concentrations are found, when serum T_4 has fallen to very low levels associated with markedly elevated serum TSH concentrations. In hypothyroidism, the first stage of subclinical hypothyroidism may progress towards overt hypothyroidism.

This study showed that the mean age group of subclinical hypothyroids was 35.52±8.60 years. This is in accordance with a study done by Tayal D et al which showed the age group of patients in the study group as 43.4 ± 2.67 years and in the control group as 44.1 ± 3.2 years.[3]

Prevalence of subclinical hypothyroids was high amongst females (81.8%). This is in accordance with studies done with Sheikh BA et al[13] and Ali M N et al.[14]

Majority of subclinical hypothyroids had normal T_3 (81.8%) and normal T_4 (72.7%). The serum T_3 & T_4 levels in the controls and patients with subclinical hypothyroid was comparable (p>0.05), and were within the normal reference range. These findings are in accordance with

study of Nananda F et al.[15] There was a statistically significant increase in TSH in subclinical hypothyroids (7.24±1.10 µIU/ml) compared to controls (1.92±1.19 µIU/ml); (p value <0.001). These findings are in accordance with study of Tayal D et al.[3] and consistent with the inclusion criteria for subclinical hypothyroidism.

According to study of Rodrigo C et al there are several case reports of acute renal failure in untreated hypothyroidism.[16] The exact pathogenesis is still unclear and thought to be multifactorial. The predominant mode of kidney injury is thought to be reduced plasma flow and glomerular filtration rate due to the hypodynamic circulation. The hypodynamic circulatory state results in a pre-renal insufficiency and this may be aggravated by other multi-systemic effects of hypothyroidism such as reduced cardiac output, low volume state, hyponatraemia with associated hemodynamic changes and increased peripheral resistance due to arterial wall stiffness. Primary glomerular and tubular dysfunction in hypothyroidism has been observed with supportive histological evidence from biopsy specimens with thickening of glomerular and tubular basement membranes and inclusions in cell cytoplasm. Rhabdomyolysis, another rare manifestation of hypothyroidism can also result in acute kidney injury. These are reversible with thyroxine treatment.

The study showed that there was statistically significant increase in serum creatinine in subclinical hypothyroids (0.96±0.15 mg/dl) compared to controls (0.83±0.22 mg/dl); ($p < 0.05$) in accordance with the study of Tayal D et al[3] which showed a significant increase in serum creatinine in subclinical compared to euthyroid subjects. There was a significant decrease in the creatinine clearance in subclinical hypothyroids ($p<0.001$). This finding is in accordance to a study done by Adrees M et al[17] in which serum creatinine was greater and estimated glomerular filtration rate was reduced in women with subclinical hypothyroids compared to normal subjects. The decrease in creatinine clearance ($p < 0.001$) in subclinical hypothyroids corroborates the findings putforth in a study by Muhammad A et al[18] which illustrates that renal dysfunction can be seen across the whole spectrum of severity of hypothyroidism including subclinical hypothyroidism.

CONCLUSION: This study was undertaken to study the levels of T_3, T_4 and TSH and their effect on different parameters like serum creatinine and creatinine clearance and creatine kinase in subclinical hypothyroids. The study showed that in both cases of hypothyroidism TSH levels were increased, but the levels of T_3 and T_4 in majority of subclinical hypothyroids were normal. The study showed that there was increase in the levels of serum creatinine in subclinical hypothyroid cases. There was a significant increase in creatine kinase and a decrease in the levels of creatinine clearance in subclinical hypothyroid cases. This study shows that the minor alterations in the levels of thyroid hormones might be associated with lesser degree of damage to tissues in subclinical hypothyroids. This shows that complications of hypothyroidism like acute renal failure, and myopathies can be prevented by monitoring thyroid hormones levels along with periodic assessment of renal parameters and creatine kinase in subclinical hypothyroid patients. Although the findings of this study may be utilized for the proper management of hypothyroid cases, further studies on more number of cases along with follow up studies are needed to explore the actual differences in the effects of thyroid hormones in subclinical hypothyroids.

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Parameter	Control (n=25)	Subclinical Hypothyroid (n=23)	p-value
Age (in years)	32±9.32	35.52±8.60	0.181
Females; n (%)	23 (92%)	19 (82.6%)	
Serum T3 (ng/dL)	107.56±29.1	104.91±27.67	0.748
Serum T4 (µg/dL)	8.39±2.12	8.6±1.21	0.673
Serum TSH (µIU/mL)	1.92±1.19	7.24±1.10	<0.001
Serum creatinine (mg/dL)	0.83±0.22	0.96±0.15	0.018
Creatinine clearance (ml/min/1.73m^2)	95.36±9.98	82.56±10.38	<0.001
Serum Creatine Kinase (IU/L)	94.92±16.93	275.34±48.15	<0.001

Table 1: Baseline characteristics of the controls and subclinical hypothyroid cases