Comparative Study of Lipid Profile, Renal and Muscle Damage in Subclinical and Overt Hypothyroidism

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ABSTRACT

Introduction: Diseases of the thyroid gland is the second most common endocrine diseases worldwide, most common being diabetes. In Indian population the prevalence of subclinical hypothyroidism is 21.9% and that of overt hypothyroidism is 7.4%. This study was done to determine deleterious effects on renal function of subclinical and overt hypothyroidism. Several alterations in muscle function, skeletal muscle abnormalities have been reported in both subclinical and overt hypothyroidism.

Material and Methods: The study group comprised of 90 subjects. The study was performed in duration of one year in the Department of Biochemistry at Rajendra Institute of Medical Sciences Ranchi (Jharkhand).

The lipid profile and the serum creatinine and creatine kinase evaluated in the study with the help of fully automated chemistry analyzer Beckman Coulter AU480.

Results: The study shows statistically highly significant increase in total cholesterol in subclinical hypothyroids (187.033 ± 41.7979 mg/dl) and in overt hypothyroids (253.9 ± 49.4294 mg/dl) compared to controls (157.633 ± 33.2415 mg/dl). Also there was statistically significant increase in serum creatinine in subclinical hypothyroids.

Conclusion: This study showed that subclinical hypothyroids produces lesser damage to tissue as compared to overt hypothyroids. These finding showed that complications of long standing hypothyroidism like hypercholesterolemia, atherosclerosis, acute renal failure, myopathies could be prevented by adequate treatment of hypothyroid disorder with periodic assessment of lipid profile, renal parameters and creatine kinase in hypothyroid patients.

Keywords: Hypothyroidism, Lipid Profile, Serum Creatinine, Creatinine Clearance, Creatine Kinase.

INTRODUCTION

Diseases of the thyroid gland is the second most common endocrine diseases worldwide, most common being diabetes. In Indian population the prevalence of subclinical hypothyroidism is 21.9% and that of overt hypothyroidism is 7.4%.[1]

Lipid disorders associated with hypothyroidism are characterized by increased levels of total cholesterol and LDL- cholesterol with lower HDL- cholesterol.

A study shows that persons meeting the criteria for subclinical hypothyroid had higher rates of elevated cholesterol level than the euthyroid control group, but there were no significant differences in LDL or HDL levels.[2] Another study shows that patients with subclinical hypothyroidism had higher total cholesterol, low LDL cholesterol compared to euthyroid.[3]

Hypothyroidism produces significant reversible alteration in renal function such as decrease in the proximal tubular resorption of Na^+, abnormality in the diluting and concentrating capacities of the distal tubules, and decrease in the renal blood flow and so the GFR. These changes are as a result of hypodynamic state produced as a result of hypothyroidism. In another study serum creatinine was shown to be significantly increased in subclinical and overt hypothyroids as compared to euthyroids with no difference in mean serum urea levels.[4] Another study shows that mean creatinine values of hypothyroid cases were greater than mean creatinine value of euthyroids.[5] Another study shows that the creatinine clearance (eGFR) in a hypothyroid patient increased after treatment with thyroxine.[6]

In the patients of hypothyroidism the serum creatine kinase is elevated due to subnormal body temperature resulting in increased permeability of the muscle cell. As a result of increased permeability there is increased leakage of the enzyme from the muscle cells.

A study shows increased level of serum creatine kinase in hypothyroid and the levels being inversely related with serum T3 concentration.[7] Another study shows that there was no change in muscle enzyme levels in subclinical hypothyroidism.[8]

The results of the above studies are alarming. There is a great need of a similar study in Ranchi, the capital city of newly formed state Jharkhand. The topic is well defined clinically with laboratory support. The outcome of the present study will hopefully help in evaluating current situation, the disease course, its nature of correlation with other component, so that effective preventive strategies could be deployed.

MATERIAL AND METHODS

The present case control study was conducted in the department of Biochemistry, Rajendra Institute of Medical Sciences, Ranchi during one year period from December 2014 to November 2015. Ethical clearance was obtained prior to study by Ethical Committee of Jharkhand. A written informed consent was taken from the patient before collection of the blood sample to participate in the study. 90 out of whom 30 were control having normal thyroid profile, 30 were subclinical hypothyroid and 30 were overt hypothyroid.

Inclusion criteria

1. Patients who were diagnosed as a case of hypothyroid in the department of biochemistry, Rajendra Institute of Medical Sciences, Ranchi, during their hormonal assay.
2. Patients who were diagnosed case of hypothyroid, who visit medicine OPD or Indoors at Rajendra Institute of

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Medical Sciences, Ranchi, for their treatment or follow-up.

Exclusion criteria

1. Patient with acute infections,
2. Patient with hepatobiliary diseases,
3. Patient with renal diseases,
4. Patient with diabetes mellitus,
5. Patient with heart diseases, myopathies,
6. Pregnant females.

On the basis of TSH levels, subjects were classified as;

1. Euthyroid (TSH- 0.34-4.25µIU/ml and FT4- 0.7-1.24ng/dl),
2. Subclinical hypothyroid (TSH- 4.25-10µIU/ml and normal FT4), and
3. Overt hypothyroid (TSH ≥ 10µIU/ml and reduced FT4 levels).[9]

The lipid profile and the serum creatinine and creatine kinase would be evaluated in the study with the help of fully automated chemistry analyzer Beckman Coulter Au480.

The thyroid profile would be evaluated in the study with the help of Chemiluminescence ABBOTT1000 i sr.

STATISTICAL ANALYSIS

The results of the present study were obtained from 90 subjects out of whom 30 were control, 30 were subclinical hypothyroid and 30 were overt hypothyroid. Data was analyzed using Analysis of Variance, Post-hoc tukey test, Kruskar Wallis test, Karl pearson correlation, Mann Whitney test and Chi square test**.** (P value < 0.05 was considered to be statistically significant.)

RESULTS

Comparison of the mean of different parameters of lipid profile in the study groups: Comparison of the mean of different parameters of lipid profile in the study groups shows that the mean of total cholesterol in controls, subclinical and overt hypothyroids were 157.63 ± 33.241 mg/dl, 187.03 ± 41.797 mg/dl and 253.90 ± 49.429 mg/dl respectively. The mean of HDL-cholesterol were 45.06 ± 10.218 mg/dl, 48.13 ± 8.076 mg/dl and 48.80 ± 6.835 mg/dl respectively. The mean of LDL cholesterol were 88.66 ± 26.309 mg/dl, 114.48 ± 41.950 mg/dl and 169.14 ± 43.573 mg/dl respectively. The mean of triglycerides were 122.83 ± 47.106 mg/dl, 136.86 ± 39.535 mg/dl and 185.03 ± 55.83 mg/dl respectively. On comparison of all the parameters in all the three groups, ANOVA F value of total cholesterol was 41.365, of LDL-cholesterol was 34.867, of triglycerides was 13.882 respectively and all were statistically highly significant with p value of 0.000. ANOVA F value of HDL-cholesterol was 1.649 which was not statistically significant with p value of 0.198 (Table 1).

Comparison of the mean of serum creatinine, creatinine clearance, and creatine kinase in the study groups (by using ANOVA F value): Comparison of mean of serum creatinine, creatinine clearance and creatine kinase in the study groups shows that the mean of serum creatinine in controls, subclinical and overt hypothyroids were 0.760 ± .1588 mg/dl, 0.820 ± .1562 mg/dl and 1.023 ± .2622 mg/dl respectively. The mean of creatinine clearance were 96.35 ± 16.77 ml/min/1.73 m2, 86.57± 13.705 ml/min/1.73 m2 and 76.33 ± 20.599 ml/min/1.73 m2 respectively. The mean of creatine kinase were 96.36 ± 50.45 IU/L, 195.96± 182.16 IU/L and 369.16 ± 307.57 IU/L respectively. An ANOVA F value of comparison of each parameter in all three groups was 14.479, 10.093 and 13.235 respectively and was statistically highly significant with p value of 0.000 each (Table 2).

Pair wise comparison of the mean difference of parameters of lipid profile (by using Posthoc-Tukey test): Pair wise comparison of the mean difference of parameters of lipid profile among the study groups (by using Post hoc-Tukey test) shows that the mean difference in total cholesterol between controls and subclinical hypothyroids was -29.400 and was statistically significant with p value of 0.022. The mean difference of -96.266 between controls and overt hypothyroids and of -66.866 between the two groups of hypothyroids was statistically highly significant with p value of 0.000 each. The mean difference of LDL-cholesterol of -26.120 between controls and subclinical hypothyroids was statistically significant with p value of 0.025 and the mean difference of 80.474 between subclinical and overt hypothyroids and of -54.354 between the two groups of hypothyroids were statistically highly significant with p value of 0.000 each. The mean difference of triglycerides of -14.033 was statistically not significant between controls and subclinical hypothyroids with p value of 0.496. The mean differences of -62.200 between subclinical and overt hypothyroids and of -48.166 between the two groups of hypothyroids were

Parameters	Control (n=30)	Subclinical Hypothyroids (n=30)	Overt hypothyroids (n=30)	ANOVA F value	P value
Total cholesterol (mg/dl)	157.63±33.241	187.03±41.797	253.90±49.429	41.365	0.000, HS
HDL-cholesterol (mg/dl)	45.06 ± 10.218	48.13± 8.076	48.80± 6.835	1.649	0.198, NS
LDL-cholesterol (mg/dl)	88.66± 26.309	114.78 ± 41.950	169.141±43.573	34.867	0.000, HS
Triglycerides (mg/dl)	122.83±47.106	136.86 ± 39.535	185.03 ± 58.838	13.882	0.000, HS

Table–1: Comparison of the mean of different parameters of lipid profile in the study groups (by using ANOVA test)

Parameters	Control	Subclinical hypothyroid	Overt hypothyroid	Anova F value	P value
Serum creatinine (mg/dl)	0.760±0.158	0.820±0.156	1.023±0.262	14.479	0.000, HS
Creatinine clearance (ml/min/1.73m^2)	96.350±51.452	85.579±13.705	76.331±20.599	10.093	0.000, HS
Creatine kinase (IU/L)	95.366±51.452	195.966±182.164	369.166±307.572	13.235	0.000, HS

Table–2: Comparison of the mean of serum creatinine, creatinine clearance, and creatine kinase in the study groups (by using ANOVA F value)

Parameters	Groups		Mean difference	P value	significance
Total cholesterol (mg/dl)	Control	SCH	-29.4000	0.022	S
		OH	-96.2666	0.000	HS
	SCH	OH	-66.8666	0.000	HS
HDL cholesterol (mg/dl)	Control	SCH	-3.0666	0.346	NS
		OH	-3.7333	0.210	NS
	SCH	OH	-0.6666	0.950	NS
LDL cholesterol (mg/dl)	Control	SCH	-26.1200	0.025	S
		OH	-80.4746	0.000	HS
	SCH	OH	-54.3546	0.000	HS
Triglyceride (mg/dl)	Control	SCH	-14.0333	0.496	NS
		OH	-62.2000	0.000	HS
	SCH	OH	-48.1666	0.001	HS

Table–3: Pair wise comparison of the mean difference of parameters of lipid profile (by using Posthoc-Tukey test)

Parameter	Group		Mean difference	P value	Significance
Serum creatinine (mg/dl)	Control	SCH	-0.0600	0.474	NS
		OH	0.2633	0.000	HS
	SCH	OH	-0.2033	0.000	HS
Creatinine (clearance ml/min/1.73 m^2	Control	SCH	9.7703	0.078	NS
		OH	20.0186	0.000	HS
	SCH	OH	10.2483	0.061	NS
Creatine kinase(IU/L)	Control	SCH	-100.6000	0.154	NS
		OH	-273.8000	0.000	HS
	SCH	OH	-173.2000	0.005	S

Table–4: Pair wise comparison of the mean difference of serum creatinine, creatinine clearance, and creatine kinase in the study groups (using Post hoc-Tukey test)

	Parameters	r value	P value
FT3	Total cholesterol	-0.409	0.000
	HDL cholesterol	-0.062	0.561
	LDL cholesterol	-0.343	0.001
	Triglyceride	-0.378	0.000
	Serum creatinine	-0.325	0.000
	Creatinine clearance	0.276	0.008
	Creatine kinase	-0.307	0.003
FT4	Total cholesterol	-0.362	0.000
	HDL cholesterol	-0.200	0.059
	LDL cholesterol	-0.286	0.006
	Triglyceride	-0.328	0.002
`	Serum creatinine	-0.316	0.002
	Creatinine clearance	0.211	0.046
	Creatine kinase	-0.311	0.003
TSH	Total cholesterol	0.595	0.000
	HDL cholesterol	0.081	0.450
	LDL cholesterol	0.560	0.000
	Triglyceride	0.491	0.000
	Serum creatinine	0.464	0.000
	Creatine clearance	-0.346	0.001
	Creatine kinase	0.420	0.000

Table–5: Correlation of FT3, FT4 and TSH with other parameters in hypothyroids

statistically highly significant with p value of 0.000 and 0.001 respectively (Table 3).

Pair wise comparison of the mean difference of serum creatinine, creatinine clearance, and creatine kinase in the study groups (using Post hoc-Tukey test): Pair wise comparison of the mean difference of serum creatinine, creatinine clearance and creatine kinase among the study groups shows that the mean difference of serum creatinine of -0.0600 between controls and subclinical hypothyroids and of 0.2633 between controls and overt hypothyroids were statistically not significant with p value of 0.474, but the mean difference of 0.2633 between subclinical and overt hypothyroids and mean difference of 0.2033 between the two groups of hypothyroids were statistically highly significant with p value of 0.000 each. The mean difference of creatine kinase of -100.600 was statistically not significant between controls and subclinical hypothyroids with p value of 0.154. The mean difference of -273.800 between controls and overt hypothyroids and of -173.200 between the two groups of hypothyroids were statistically highly significant with p value of 0.000 and 0.005 respectively (Table 4).

Correlation of FT3, FT4 and TSH with other parameters in hypothyroids: Correlation of FT3, FT4 and TSH with other parameters in hypothyroids shows negative correlation between FT3 and triglyceride (r=-0.378) and positive correlation with creatinine clearance (r=0.276). It shows negative correlation with total cholesterol, LDL cholesterol, HDL cholesterol, serum creatinine and creatine kinase. The table shows positive correlation of FT4 with creatinine clearance and negative correlation with rest others. The table shows positive correlation of TSH with total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, serum creatinine and creatine kinase. TSH shows negative correlation only with creatinine clearance. All correlation (except of HDL) were statistically significant with p value<0.05 (table-5).

DISCUSSION

Comparison of the mean of different parameters of lipid profile in the study groups: In the present study, there was statistically highly significant increase in total cholesterol in subclinical hypothyroids (187.033 ± 41.7979 mg/dl) and

in overt hypothyroids (253.9 ± 49.4294 mg/dl) compared to controls (157.633 ± 33.2415 mg/dl). There was statistically highly significant increase in LDL cholesterol in subclinical hypothyroids (114.7867 ± 41.9502mg/dl) and in overt hypothyroids (169.1413 ± 43.3733 mg/dl) compared to controls (88.666 ± 26.309 mg/dl). There was statistically significant increase in triglycerides in subclinical hypothyroids (136.866 ± 39.535mg/dl) and in overt hypothyroids (185.033 ± 55.838 mg/dl) compared to controls (122.833 ± 47.106 mg/dl); ($p < 0.05$) (Table 1). These findings are in accordance with study by Adrees M et al[10], Costantini F et al[11], Efstathiadou Z et al[12], Hueston W J et al[13] and Sheikh B A et al.[14]

There was no statistically significant increase in HDL cholesterol in subclinical hypothyroids (48.133± 8.076mg/dl) and in overt hypothyroids (48.800± 6.835mg/dl) compared to controls (45.066± 10.218); (Table 1). This finding is in accordance with study of Costantini F et al.[11]

Comparison of the mean of serum creatinine, creatinine clearance, and creatine kinase in the study groups (by using ANOVA F value): The study showed that there was statistically significant increase in serum creatinine in subclinical hypothyroids (0.8200 ± 0.1562mg/dl) and in overt hypothyroids (1.0233 ± 0.2622mg/dl) compared to controls (0.7600 ± .1588mg/dl); ($p < 0.05$, Table 2) in accordance with the study of Tayal D et al[2] which showed that serum creatinine is significantly increased in in subclinical and overt hypothyroid group compared to euthyroid subjects. But there was no statistical significance in the mean difference of serum creatinine (-0.0600) between controls and subclinical hypothyroids (Table 4). This finding is in accordance to a study done by Park YJ et al[15] which states that even after glomerular and tubular function being influenced by thyroid status, it is very unusual to have a significant rise in serum creatinine in patients with subclinical hypothyroidism, but in contrast to study of Adrees M[10] in which serum creatinine was greater and estimated glomerular filration rate was reduced in women with subclinical hypothyroids compared to normal subject.

Another study done by Muhammad A A et al[16] 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, Table 3). The study showed that there was a statistically significant increase in creatine kinase in subclinical hypothyroids (196.966 ± 182.164 IU/L) and in overt hypothyroids (369.166 ± 307.572 IU/L) compared to controls (95.366 ± 54.452IU/L); (p value < 0.05); (Table 2) which is in accordance with study of Prakash A et al[17] and Docherty et al[18] where the mean creatine kinase levels were significantly increased in hypothyroids.

Pair wise comparison of the mean difference of parameters of lipid profile (by using Posthoc-Tukey test): Pair wise comparison of parameters of lipid profile using Post hoc-Tukey test showed that the mean difference of total cholesterol (-66.866), LDL cholesterol (-54.354) and triglycerides (-48.166) between subclinical and overt hypothyroids were statistically significant ($p < 0.05$) (Table 3), which is in accordance with study of Prakash A et al[19] which says that effect of hypothyroidism in the lipid metabolism is more marked in patients with higher serum TSH levels.

Pair wise comparison of the mean difference of serum creatinine, creatinine clearance, and creatine kinase in the study groups (using Post hoc-Tukey test): The study also showed statistical significance in the mean difference of serum creatinine (-0.2033) between the two groups of hypothyroids (p value 0.000, Table 4). This is in accordance with studies of Claus T et al.[20]

Pair wise comparison of the mean difference of creatinine clearance (20.0186) between controls and overt hypothyroids was statistically significant (Table 4, $p < 0.05$). These findings are in accordance with studies of Claus T et al[20] and Rio G et al.[21]

Pair wise comparison of the mean difference of serum creatine kinase using Post hoc-Tukey test showed that it was not statistically significant among both the hypothyroid groups (Table 4), but was significant between control and overt hypothyroid(p value <0.05).

Conclusion:

The study showed that there was increase in the levels of total cholesterol, LDL cholesterol, triglycerides and serum creatinine in hypothyroid cases. The variations in the parameters were more evident in overt hypothyroids with statistically significant difference among subclinical and overt hypothyroids.

Although there was increase in creatine kinase and a decrease in the levels of creatinine clearance in hypothyroid cases, but there was no statistically significant difference in levels of these parameters among subclinical and overt hypothyroids. Also there was no variation in HDL cholesterol.

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