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"A STUDY OF CREATINE KINASE LACTATE DEHYDROGENASE ACTIVITY IN THYROID DISORDERS CASES AND IN HEALTHY CONTROLS."

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Abstract

Background: Thyroid function plays a crucial role in regulating various metabolic processes, including lipoprotein metabolism and cardiovascular disease (CVD) risk factors, ultimately influencing overall CVD risk. Hypothyroidism can lead to a decline in muscle creatine levels, contributing to thyroid myopathy. This condition is characterized by primary muscle involvement, resulting in slowed muscle contraction and relaxation, muscle pain, and proximal muscle weakness.

Aim: The present study was aimed to evaluate creatine kinase and lactate dehydrogenase activity in thyroid disorders and control subjects.

Materials & Methods: A hospital-based case-control study was conducted over a period of one year to investigate the relationship between thyroid disorders and muscle enzyme activity. The study included 200 cases of thyroid disorders (100 cases of Hypothyroidism and 100 cases of Hyperthyroidism), aged 20-60 years, and 100 healthy controls. Serum creatine kinase and lactate dehydrogenase activity were measured in all participants, and the results were compared and analysed using SPSS software 23.0 version.

Results: The study revealed significant differences in weight and BMI, with the hyperthyroidism group having higher values compared to the hypothyroidism and control groups ($p<0.05$). Additionally, overt hypothyroidism was characterized by elevated TSH levels and LDH activity, while subclinical hypothyroidism showed increased T3, T4, and CK levels. The thyroid profile (TSH, T3, and T4) differed significantly between subclinical and overt hypothyroidism ($p<0.05$), whereas CK and LDH activity showed no significant differences ($p>0.05$).

Conclusion: It can be concluded that elevated levels of CK and LDH enzymes can serve as indicators of cellular necrosis and tissue damage, warranting consideration of hypothyroidism in patients with myopathy and unexplained elevation of serum muscle enzymes. The study also reveals that hypothyroidism commonly affects individuals in their third and fourth decades of life, with a higher prevalence among females. Furthermore, CK and LDH activity may be useful as supplemental diagnostic tools and prognostic metrics for hypothyroid diseases, and their considerable increase suggests potential utility in screening for thyroid dysfunction.

Key words: Thyroid Disorder, Creatine Kinase, Lactate Dehydrogenase

Introduction

Thyroid function regulates a wide array of metabolic parameters. Thyroid function significantly affects lipoprotein metabolism as well as some cardiovascular disease (CVD) risk factors, thus influencing overall CDV risk.[1] Indeed, even within the normal range of thyroid-stimulating hormone (TSH) values, a linear increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs) and a linear decrease in high-density lipoprotein cholesterol (HDL-C) levels has been observed with increasing TSH.[2]

Apart from classical risk factors like dyslipidemia, exceedingly high HbA1c has now been regarded as an autonomous threat for vascular disease in cardiac patients.[3] Studies in man have also demonstrated increased MDA with progressive hyperlipidaemia.[4] Studies also reported that induction of the acute hyperlipidaemia increases oxidative stress marker.[5] Macrovascular and microvascular complications have been shown to be mainly,[6,7] or partly[8,9] dependent on hyperglycaemia, that can induce tissue damage through different pathways: (1) enhanced polyol activity, causing sorbitol and fructose accumulation; (2) increased formation of the advanced glycation end products (AGEs)' (3) activation of the protein kinase C (PKC) and (4) increased hexosamine pathway flux[10]. There is significant evidence that these bio-chemical pathways, that are activated by hyperglycaemia, are related with generation of the reactive oxygen species (ROS), ultimately leading to the increased oxidative stress[10,11] Dyslipidemia, an established risk factor for the CVD, is common strikingly in patients having type 2 diabetes, affecting almost 50.0% of this population.[12] In addition to hyperglycaemia, and hypertension, the dyslipidemia is modifiable CVD risk-factor that remains uncontrolled largely in diabetic patients.[12]

Deficiency of thyroid hormones in hypothyroidism slows down the metabolic functions. In muscle, reduction in mitochondrial oxidative capacity and beta-adrenergic receptors in addition to induction of an insulin–resistant state may be seen.[13] Histologically the muscle fibres show enlargement, focal myofibrillar degeneration, increase in central nuclei, glycogen accumulation and mitochondrial aggregations and type II fibre atrophy.[13,14] These metabolic disturbances results in change in distribution of muscle fibers from fast twitch fibers to slow twitch fibers causing delayed muscle contraction and relaxation which is seen in myopathy. Decrease in muscle carnitine in hypothyroidism may also contribute to thyroid myopathy.[15] True myopathy is a primary muscle involvement characterized by slowed muscle contraction and relaxation, muscle pain, proximal muscle weakness, sluggish ankle jerks and absence of sensory involvement.[16] Pain on muscle exertion is due to defective carbohydrate metabolism.[17]

Thus, in addition to the characteristic clinical picture, hypothyroidism may be associated with a wide range of muscle disturbances varying from myalgia to a true myopathy. Muscular symptoms like weakness, myalgia, stiffness, cramps and easy fatigability are seen 30-80.0% of patients.[14]

To assess the muscular involvement in these patients, biochemical tests such as Creatine Kinase (CK) or Creatine phosphokinase (CPK) and Lactate Dehydrogenase (LDH) can be used. Of these, CK is the most sensitive indicator and measure of muscle damage and LDH is a general indicator of tissue damage. CK is an enzyme found mainly in the heart, brain, and skeletal muscle. When total CK (CK MM isoenzyme is 80.0% of total CK level) is very high, it usually means there has been injury or stress to the skeletal muscle tissue. High CK levels might be seen in stroke cases, dermatomyositis or polymyositis, heart attack, myocarditis, muscular dystrophies and myopathy. Other conditions that may cause elevated CK levels are hypothyroidism, hyperthyroidism and pericarditis following a heart attack. Lactate Dehydrogenase (LDH) is an intracellular enzyme found in heart, blood cells, lungs, kidney, placenta, pancreas, liver and skeletal muscles. LDH is general indicator of existence, and the severity of acute, or the chronic tissue damage.[18]

Aim:

The aim of the present study to evaluate analyze creatine kinase and lactate dehydrogenase activity in diagnosed case of thyroid and control subjects.

Materials and Methods:
The present case- control study conducted in Department of General Medicine and Department of Biochemistry at Gautam Buddha Chikitsa, Mahavidyalaya, RBB Subharti University, Dehradun, Uttarakhand; evaluate a study of thyroid function test, CK and LDH in thyroids dysfunction and controls subjects. The study included 200 cases of thyroid disorders (100 cases of Hypothyroidism and 100 cases of Hyperthyroidism), aged 20-60 years, and 100 healthy controls.

Collection of Data
A detailed clinical history including age, sex, occupation, socio – economic status and any associated risk factors contributing for the illness will be elicited from the case and controls. the anthropometric measurements like height, and weight, were taken. Height was calculated to the closest 0.1 cm with subject standing barefoot. Body-weight was measured to nearest 0.1 kg on the balanced scale. BMI was calculated by weight (kg) divided by height (m) square.
Under aseptic condition, 3ml of venous blood was collected from the subjects in a plain vial. For measuring T3, TSH the ELISA kit from Phoenix Pharmaceuticals (Burlingame, CA, USA) was used. Estimation of serum creatine kinase (CK) by IFCC method. Estimation of serum lactate dehydrogenase (LDH) by UV - Kinetic method.

Statistical analysis
Data were analysed using the Statistical Package of the Social Sciences (SPSS version 23.0). Data are presented as mean ± standard deviation. Independent sample t-test/One Way ANOVA t test and Chi-square test, were used to compare different parameters. Pearson correlations were used to find the Correlation of Thyroid profile, CK, LDH activity and serum creatinine level. The differences among the means (Mean ± SD) were considered significant if $P < 0.01$ & 0.05.

Result:
The age group distribution showed a significant difference ($p=0.009$), with the highest proportion of participants in the 51–60-year age group among hyperthyroidism patients. The sex distribution also showed a significant difference ($p<0.001$), with a higher proportion of males in the control group and a higher proportion of females in the hypothyroidism group. However, there was no significant difference in dietary habits ($p=0.844$) among the three groups. Notably, a significant difference was observed in family history ($p<0.001$), with a higher proportion of participants with a positive family history in both the hypothyroidism and hyperthyroidism groups compared to the control group. [Table 1]

The hypothyroidism group had significantly higher TSH levels (17.67±31.60 IU/L) and lower T3 levels (0.88±0.45 ng/ml) compared to the hyperthyroidism and control groups ($p<0.001$). In contrast, the hyperthyroidism group had significantly higher T3 levels (1.79±1.63 ng/ml) compared to the hypothyroidism and control groups ($p<0.001$). Additionally, the hypothyroidism group had significantly higher CK (198.63±43.92 U/L) and LDH (232.44±56.55 U/L) levels compared to the hyperthyroidism and control groups ($p<0.001$). Serum creatinine levels were also significantly higher in the hypothyroidism group (1.11±0.96 mg/dl) compared to the control group (0.82±0.31 mg/dl) ($p<0.001$). [Table 2]

TSH levels were negatively correlated with T3 ($r=-0.211$, $p<0.001$) and T4 ($r=-0.274$, $p<0.001$), and positively correlated with CK ($r=0.287$, $p<0.001$) and LDH ($r=0.304$, $p<0.001$). T3 levels were positively correlated with T4 ($r=0.321$, $p<0.001$) and negatively correlated with CK ($r=-0.244$, $p<0.001$) and LDH ($r=-0.237$, $p<0.001$). CK and LDH activity were strongly positively correlated ($r=0.811$, $p<0.001$).[Table 3]

Table 1: Distribution of demographic variables in among studied groups

		Group			Chi Square value	P value
		Hypothyroidism (n=100)	Hyperthyroidism (n=100)	Control (n=100)		
Age Group (Years)	21-30	32 (32.0%)	12 (12.0%)	20 (20.0%)	17.177	0.009
	31-40	21 (21.0%)	21 (21.0%)	26 (26.0%)		
	41-50	28 (28.0%)	30 (30.0%)	31 (31.0%)		
	51-60	19 (19.0%)	37 (37.0%)	23 (23.0%)		
Sex	Male	39 (39.0%)	54 (54.0%)	67 (67.0%)	15.777	<0.001
	Female	61 (61.0%)	46 (46.0%)	33 (33.0%)		
Dietary habit	Veg.	75 (75.0%)	78 (78.0%)	78 (78.0%)	0.339	0.844
	Non-veg.	25 (25.0%)	22 (22.0%)	22 (22.0%)		
Family History	Yes	35 (35.0%)	36 (36.0%)	10 (10.0%)	22.019	<0.001
	No	65 (65.0%)	64 (64.0%)	90 (90.0%)		

Table No. 2: Thyroid profile, CK, and LDH levels in Hypothyroidism, Hyperthyroidism and Control group

	Hypothyroidism (n=100)	Hyperthyroidism (n=100)	Control (n=100)	F value	P value
TSH (mlU/L)	17.67±31.60	0.17±0.15	1.49±1.90	19.436	<0.001
T3 (ng/ml)	0.88±0.45	1.79±1.63	1.29±0.43	27.673	<0.001
T4 (ug/dl)	6.96±2.67	7.78±3.13	7.61±1.33	4.123	0.008
CK (U/L)	198.63±43.92	105.33±25.95	97.76±22.78	280.879	<0.001
LDH (U/L)	232.44±56.55	141.94±29.87	129.59±25.38	218.097	<0.001
Serum Creatinine (mg/dl)	1.11±0.96	1.19±0.67	0.82±0.31	7. 364	<0.001

* One Way ANOVA t test

Table No. 3: Correlation of Thyroid profile, CK and LDH activity

Correlations							
Pearson's Correlation Coefficient		TSH	T3	T4	CK	LDH	Serum Creatinine
TSH	R	1.000	-0.211**	-0.274**	0.287**	0.304**	0.021
	P value	--	<0.001	<0.001	<0.001	<0.001	0.758
T3	R	-0.211**	1.000	0.321**	-0.244**	-0.237**	0.033
	P value	<0.001	--	<0.001	<0.001	<0.001	0.587
T4	R	-0.274**	0.321**	1.000	-0.113	-0.135*	0.036
	P value	<0.001	0.321**	--	0.067	0.020	0.563
CK	R	0.287**	-0.244**	-0.113	1.000	0.811**	0.051
	P value	<0.001	<0.001	0.067	--	<0.001	0.405
LDH	R	0.304**	-0.237**	-0.135	0.811**	1.000	0.112
	P value	<0.001	<0.001	-0.135	<0.001	--	0.061
Serum Creatinine		0.021	0.033	0.036	0.051	0.112	1.000
		0.758	0.587	0.563	0.405	0.061	--
**. Correlation is significant at the 0.01 level (2-tailed).							
*. Correlation is significant at the 0.05 level (2-tailed).							

* Bivariate analysis (Pearson's correlation coefficient)

DISCUSSION

This is a case-control, hospital-based study conducted in Department of General Medicine and Department of Biochemistry at Gautam Buddha Chikitsa, Mahavidyalaya, RBB Subharti University, Dehradun, Uttarakhand; and analyse creatine kinase, lactate dehydrogenase activity and serum creatinine in diagnosed case of thyroid and control subjects.

In this study majority of the studied cases were fallen in age group 41 – 50 years. We noted that the average age of Hypothyroidism, Hyperthyroidism and control group was 39.62±11.39, 45.57±10.81 and 42.87±11.16 years respectively. There were statistically significant higher older age population in Hyperthyroidism group and younger age population in Hypothyroidism distribution in compare to control group (P<0.05). **Shanti R et al[19]** reported that majority of the cases was belonging to 31-40 years; with mean age 35.4±9.2 years in hypothyroids and 36.2±9.8 years in control group. Contrast to our study **Tejomani M et al[20]** reported the average age of Hypothyroidism was 33.96±10.17 and Euthyroid Controls 33.96±10.17 years. **McGrowder et al[21]** reported the patient groups (overt hypothyroidism and subclinical hypothyroidism; overt hyperthyroidism and subclinical hyperthyroidism) and control groups were similar in regard to age (60.67 ± 17.96 and 59.16 ± 21.16; 58.38±18.33 and 58.65 ± 17.91 years) and 52.75 ± 16.44 years, respectively.

In our study case groups, Hypothyroidism 61.0% and Hyperthyroidism 46.0% were female and rest were male; but in control groups 67.0% were male and 33.0% were female patients. By using the chi square test, we find insignificant distribution in both groups (P<0.05). Greater than 75.0% cases were married in present study. We noted that there was marital status distribution was statistically insignificant distribution in among groups (P>0.05). **Shanti R et al**[19] reported that gender distribution among the study subjects. Of the 50 subjects with overt hypothyroidism, 36 were females and 14 were males. In the euthyroid control group, there were 31 females and 19 males. It is evident that hypothyroidism is more predominant in females. **Tejomani M et al**[20] reported the prevalence of hypothyroidism was higher among females as is observed worldwide. **McGrowder DA et al**[21] reported the patient groups (overt hypothyroidism and subclinical hypothyroidism; overt hyperthyroidism and subclinical hyperthyroidism) and control groups were 16/4 and 34/16; 26/5 and 46/15) and 64/25, female/male, respectively.

In this present study greater than 75.0% cases in studied population were vegetarian and rest were non-vegetarian dietary habit. We observed the dietary habit distribution was statistically insignificant distribution in among groups (P>0.05). And 35.0% cases were having family history of Hypothyroidism and 36.0% cases were Hyperthyroidism; but only 10.0% cases were having family history of thyroid disfunction in control group. We found the statistically significant family history of thyroid disfunction distribution in among groups (P<0.05). In our studied population the statistically significant higher weight and BMI in Hyperthyroidism group in compare to Hypothyroidism and control group (P<0.05). But height was almost equal in both groups.

In our study we noted the TSH level and LDH activity were higher in overt hypothyroidism; while T3, T4 and DK were higher in Subclinical hypothyroidism. The difference between Subclinical and over**t** hypothyroidism in thyroid profile (TSH, T3 & T4) was found to be statistically significant (p<0.05); but CK and LDH activity were found to be statistically insignificant differences (p>0.05). On applying the bivariate analysis (Pearson's correlation) we noted a positive significant association of thyroid profile TSH with CK and LDH activity. T3 and T4 was negative significant associated. While serum creatinine was positively insignificant correlated with thyroid profile TSH, T3 and T4. **Reena R et al**[18] observed that the significant difference in serum CK and LDH activities were observed in these seven cases compared to rest of the forty-three cases. Even though there was no significant difference among the study groups (cases and controls), a weak positive correlation of CK, LDH with TSH levels and weak negative correlation with T3 and T4 levels were observed. **Koner S & Chaudhuri A[22]** observed the hypothyroid patients had increased Serum CPK level (25%). Mean TSH and mean FT4 levels were significantly different between hypothyroid and control patients (P 0.0001 and P 0.0001, respectively). as well as mean CPK (P 0.0001). TSH levels and serum CPK levels were positively associated (r=0.761, P0.0001), while serum CPK was adversely connected (r=-0.328, P0.00001) with senior FT4. This finding is in accordance with the studies by **Tejomani M et al**[20] and **Panag et al[23]**. **Shanti R et al**[19] reported that moderate positive association found between CK activity, and TSH (r=0.517, p=0.001), and weak positive association between the TSH activity, and LDH (r=0.331, p=0.018). **McGrowder DA et al**[21] reported that positive association between CK activity, and TSH (r=0.292, P=0.015), and negative association between CK activity, and FT4 (r= -0.325, P=0.007); and between FT4, and TSH (r= -0.371, P=0.002). **Tayal D et al[24]** reported that

creatinine showed significant negative association with T3, &T4 in overt group (r= -0.372 and r= -0.371), whereas positive association with TSH (r=0.283).

Various mechanisms have been proposed as causing elevated CK activity in hypothyroidism, although these mechanisms may have varying influence at different stages of the disease.[25,26] The hypo-metabolic state of hypothyroidism can cause a reduction in glycolysis and oxidative phosphorylation and thus reducing adenosine triphosphate (ATP) concentrations beyond critical limit. The alteration in the sarcolemmal membranes could cause increased cell-permeability and leakage of the CK from cells.[27,28] Another possibility is reduced turnover of CK because of hypothyroidism, allowing serum activities to rise generating a marked release of CK through the altered sarcolemnal membranes.[29]

Our finding of lower CK activity in hyperthyroidism, is in accordance with other reports and suggests that in the hypermetabolic state there may be increased enzyme degradation which may have contributed to these low CK activity.[30] That the muscle cell is less permeable than normal to efflux of CK in hyperthyroidism is unlikely, although possibly in these circumstances the muscle cell might reflect loss of muscle bulk.[30]

Studies have shown that LDH activity was increased and decreased in the hypo- and hyperthyroid states, respectively.[31,32] The study found increase in LDH activity in patients with hypothyroidism which correlates with the degree of hypothyroidsm. LDH activity have been reported to be increased in primary hypothyroidism[31,33] and in one study, 37.0% of hypothyroid patients had elevated LDH.[34] In another study of six untreated primary hypothyroid patients, LDH activities from 473 to 1885 U/L was reported;[34] and in a latter study 27 of 45 hypothyroid patients had elevated total LDH levels.[35] Further isoenzme analysis showed a normal pattern of LDH isozyme in 12 patients, while in the remaining ten, three showed increased LDH1 levels, one showed an increased lactate dehydrogenase isozyme 3 level (LDH3), and six showed elevated lactate dehydrogenase isozyme 5 (LDH5) levels.[35] Studies of LDH isozymes in myxedema heart disease have shown that LDH isozyme1 (LDH1) may be elevated in this disorder and gradually fade with thyroid replacement therapy.[36] The elevations of LDH levels could reflect increased release and/or decreased clearance from the liver.[37] In addition, lactate dehydrogenase values were inversely related to both them thyroxine and triiodothyronine concentrations. The finding of the latter study differs from others in that the LDH levels was statistically significantly higher than the control group in both patients with subclinical and over hyperthyroidism as significant number of these patients had normal LDH. Strasberg reported no association of hyperthyroidism with elevated levels of the LDH isozyme.[38]

Strengths: The study identified significant correlations between thyroid function tests and muscle enzyme activity, which may have important implications for the diagnosis and management of thyroid disorders.

Limitations: The study was conducted in a hospital setting, which may introduce selection bias and limit the generalizability of the findings.

Conclusion

In conclusion, this study demonstrates significant differences in demographic and biochemical profiles between hypothyroidism, hyperthyroidism, and control groups. The findings suggest that hypothyroidism is more prevalent in females and is associated with higher levels of TSH, CK, and LDH, as well as lower levels of T3. In contrast, hyperthyroidism is characterized by higher levels of T3. The study also reveals significant correlations between thyroid hormones, CK, and LDH activity, indicating interrelated roles in the pathophysiology of thyroid disorders. These findings have important implications for the diagnosis and management of thyroid disorders, highlighting the need for careful consideration of demographic and biochemical profiles in clinical practice. Additionally, the study suggests that CK and LDH may be useful biomarkers for thyroid dysfunction, particularly in hypothyroidism.

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