Section A-Research paper
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A Study of Creatine Kinase Lactate Dehydrogenase Activity in Thyroid Disorders: A prospective Case-control study

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Abstract

Background : 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. Decrease in muscle creatine in hypothyroidism may also contribute to thyroid myopathy. 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. Pain on muscle exertion is due to defective carbohydrate metabolism. The present study was designed to evaluate creatine kinase and lactate dehydrogenase activity in thyroid disorders and control subjects.

Materials & Methods:A hospital based case control study was done for 3 years. Serum creatine kinase and lactate dehydrogenase activity were measured in 100 cases in age group of 20-60 years of thyroid disorders and the results obtained were compared with 100 healthy controls. Assessment of the results was done using SPSS software.

Results: The statistically significant higher weight and BMI in Hyperthyroidism group in compare to Hypothyroidism and control group ($P<0.05$). The TSH level and LDH activity were higher in overt hypothyroidism. T3, T4 and CK were higher in Subclinical hypothyroidism. The difference between Subclinical and overt hypothyroidism in thyroid profile (TSH, T3 & T4) was found to be statistically significant ($p<0.05$); CK and LDH activity were found to be statistically insignificant differences ($p>0.05$).

Conclusion: It can be concluded from the present study that there are elevated levels of CK and LDH enzymes levels represents an indicator of cellular necrosis and tissue damage Hence Hypothyroidism should be considered in patients with myopathy and unexplained elevation of serum muscle enzymes. According to this study, hypothyroidism is common in the third & fourth decade of life. Female is more affected than the male. Therefore, it may be inferred that CPK and aldolase readings may serve as a supplemental diagnostic tool for the identification of hypothyroid diseases and may also suggest as a useful prognostic metric.

The considerable increase in CK, and LDH activity suggests that these markers can be utilized to screen people with thyroid dysfunction..

Key words: Thyroid Disorder, Creatine Kinase, Lactate Dehydrogenase

Introduction

Thyroid hormones are essential for metabolism and energy homeostasis and participate in insulin action and glucose regulation.[i] Previous studies reported higher prevalence rates of thyroid disorders in diabetic patients compared with nondiabetic individuals, and overt hypothyroidism was frequently observed in type-2 diabetes mellitus (T2DM).[ii] Moreover, subclinical hypothyroidism (SCH), a pathological status defined as an elevated serum thyroid stimulating hormone (TSH) value with normal concentrations of free thyroid hormones,[iii] Thyroid disease refers to a class of common disorders that are among that most prevalent medical afflictions .These disorders affect approximately 6.6% of the world population, with females being 5-10 times more likely than males to develop some kind of abnormality in the thyroid gland.[iv] 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.[v] Macrovascular and microvascular complications have been shown to be mainly[vi,vii] or partly[viii,ix] dependent on hyperglycemia, 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[x]. 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,[xi] Dyslipidemia, an established risk factor for the CVD, is common strikingly in patients having type 2 diabetes, affecting almost 50.0% of this population.[xii] 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.[xiii] Histologically the muscle fibres show enlargement, focal myofibrillar degeneration, increase in central nuclei, glycogen accumulation and mitochondrial aggregations and type II fibre atrophy.[xiv] 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

creatine in hypothyroidism may also contribute to thyroid myopathy.[xv] 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.[xvi] Pain on muscle exertion is due to defective carbohydrate metabolism.[xvii]

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. 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.[xviii]

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 **c**ase- control study conducted evaluate a study of thyroid function test, CK and LDH in thyroids dysfunction and controls subjects. The total sample size=200 (100 cases and 100 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.. 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: Microsoft Excel was used in creating the database and producing graphs,

while the data were analysed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows.

Results :

Table 1: Age and sex distribution

Age Group (Years)	Group			Chi Square value	P value
	Hypothyroidism (n=100)	Hyperthyroidism (n=100)	Control (n=100)		
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%)		
Male	39 (39.0%)	54 (54.0%)	67 (67.0%)	15.777	**<0.001**
Female	61 (61.0%)	46 (46.0%)	33 (33.0%)		

Majority of the studied cases were fallen in age group 41 – 50 years. We found that the statistically significant higher older age population in Hyperthyroidism group but younger age population in Hypothyroidism distribution in compare to control group (P<0.05). In 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).

Table 2: Thyroid profile, CK, and LDH levels in Hypothyroidism, Hyperthyroidism and Control group

		Frequency	Mean	Std. Deviation	F value	P value
TSH	**Hypothyroidism**	100	17.77	34.06	21.338	**<0.001**

(mlU/L)	**Hyperthyroidism**	100	0.14	0.13		
	Control group	100	1.94	1.09		
T3 (ng/ml)	**Hypothyroidism**	100	0.86	0.41	31.736	**<0.001**
	Hyperthyroidism	100	1.81	1.36		
	Control group	100	1.27	0.34		
T4 (ug/dl)	**Hypothyroidism**	100	6.92	2.76	4.020	**0.019**
	Hyperthyroidism	100	7.87	3.31		
	Control group	100	7.66	1.38		
CK (U/L)	**Hypothyroidism**	100	201.51	47.29	302.978	**<0.001**
	Hyperthyroidism	100	103.23	23.59		
	Control group	100	98.11	23.87		
LDH (U/L)	**Hypothyroidism**	100	243.44	60.56	223.970	**<0.001**
	Hyperthyroidism	100	144.29	27.28		
	Control group	100	133.19	22.89		

* One Way ANOVA t test

Table 3: Thyroid profile, CK, and LDH activity distribution in various thyroid dysfunction and control groups

		Frequency	**Mean**	**Std. Deviation**	**F value**	**P value**
TSH (mlU/L)	Subclinical hypothyroidism	72	9.87	2.39	27.902	**<0.001**
	Overt hypothyroidism	26	40.41	62.10		

	Subclinical hyperthyroidism	81	0.33	1.24		
	Overt hyperthyroidism	19	0.14	0.11		
	Control	100	1.94	1.09		
T3 (ng/ml)	Subclinical hypothyroidism	72	1.03	0.33	36.624	**<0.001**
	Overt hypothyroidism	26	0.38	0.17		
	Subclinical hyperthyroidism	81	1.53	0.95		
	Overt hyperthyroidism	19	2.98	2.07		
	Control	100	1.27	0.34		
T4 (ug/dl)	Subclinical hypothyroidism	72	8.45	0.95	145.728	**<0.001**
	Overt hypothyroidism	26	2.59	1.14		
	Subclinical hyperthyroidism	81	6.64	1.35		
	Overt hyperthyroidism	19	13.24	3.83		
	Control	100	7.66	1.38		
CK (U/L)	Subclinical hypothyroidism	72	203.02	43.82	141.113	**<0.001**
	Overt hypothyroidism	26	198.51	57.97		
	Subclinical hyperthyroidism	81	104.05	22.80		
	Overt hyperthyroidism	19	110.21	24.64		
	Control	100	98.11	23.87		
LDH (U/L)	Subclinical hypothyroidism	72	241.04	59.71	103.472	**<0.001**
	Overt hypothyroidism	26	249.40	65.84		
	Subclinical hyperthyroidism	81	144.18	27.05		
	Overt hyperthyroidism	19	151.32	25.48		
	Control	100	133.19	22.89		

* One Way ANOVA t test

Table 4: Compare Thyroid profile, CK and LDH activity distribution in Subclinical and Overt hypothyroidism

	Hypothyroidism	Frequency	Mean	Std. Deviation	t value	P value
TSH (mlU/L)	**Subclinical**	74	9.81	2.42	4.269	**<0.001**
	Overt	26	40.41	62.10		
T3 (ng/ml)	**Subclinical**	74	1.03	0.33	9.692	**<0.001**
	Overt	26	0.38	0.17		
T4 (ug/dl)	**Subclinical**	74	8.43	0.94	25.781	**<0.001**
	Overt	26	2.59	1.14		
CK (U/L)	**Subclinical**	74	202.56	43.33	0.374	0.709
	Overt	26	198.51	57.97		
LDH (U/L)	**Subclinical**	74	241.34	58.92	0.581	0.563
	Overt	26	249.40	65.84		

* One Way ANOVA t test

In this table we noted the TSH level and LDH activity were higher in overt hypothyroidism; while T3, T4 and CK 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 ($p>0.05$).

Table 5: Compare Thyroid profile, CK, and LDH activity distribution in Subclinical and Overt hyperthyroidism

	Hyperthyroidism	**N**	**Mean**	**Std. Deviation**	**t value**	**P value**
TSH (mlU/L)	**Subclinical**	81	0.15	0.14	0.078	0.938
	Overt	19	0.14	0.11		
T3 (ng/ml)	**Subclinical**	81	1.54	0.96	4.549	**<0.001**
	Overt	19	2.98	2.07		
T4 (ug/dl)	**Subclinical**	81	6.61	1.35	12.735	**<0.001**
	Overt	19	13.24	3.83		
CK (U/L)	**Subclinical**	81	104.05	22.80	1.044	0.299
	Overt	19	110.21	24.64		
LDH (U/L)	**Subclinical**	81	144.18	27.05	1.045	0.299
	Overt	19	151.32	25.48		

* One Way ANOVA t test

In this table we noted the T3, T4, CK and LDH activity were higher in overt hypothyroidism; while TSH were higher in Subclinical hypothyroidism. The difference between Subclinical and over**t** hypothyroidism in thyroid profile (T3 & T4) was found to be statistically significant ($p<0.05$); but TSH, CK and LDH activity were found to be statistically insignificant differences ($p>0.05$)

Table 6: Correlation of Thyroid profile, CK and LDH activity

Correlations						
Pearson's Correlation Coefficient		**TSH**	**T3**	**T4**	**CK**	**LDH**
TSH	**r**	1.000	-0.201**	-0.269**	0.282**	0.299**
	P value	--	**<0.001**	**<0.001**	**<0.001**	**<0.001**
T3	**r**	-0.201**	1.000	0.317**	-0.238**	-0.227**
	P value	**<0.001**	--	**<0.001**	**<0.001**	**<0.001**
T4	**r**	-0.269**	0.317**	1.000	-0.102	-0.137*
	P value	**<0.001**	**<0.001**	--	0.077	**0.018**
CK	**r**	0.282**	-0.238**	-0.102	1.000	0.813**
	P value	**<0.001**	**<0.001**	0.077	--	**<0.001**
LDH	**r**	0.299**	-0.227**	-0.137*	0.813**	1.000
	P value	**<0.001**	**<0.001**	**0.018**	**<0.001**	--
**. 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)

Above table represent the Pearson Correlation (Bivariate analysis) of thyroid profile, CK and LDH activity and observed a significant association of thyroid profile TSH, T3, T4, CK and LDH activity was significant associated with each other's. Negative sign shows the universally proportional correlation.

Discussion

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.[xix] 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.[xx] 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.[xxi] Literature search shows that the prominence of muscle symptoms correlates fairly closely with the degree and duration of hypothyroidism[xxii] and the serum CK level may be elevated in hypothyroidism: and can be an important differential diagnosis for raised serum CK. Case studies demonstrate that hypothyroidism can manifest with only muscle symptoms or without any other traditional symptoms or indicators of hypothyroidism. **Reena R et al[xxiii]** studied the serum creatine kinase and lactate dehydrogenase to assess muscular involvement in hypothyroidism and

concluded that the serum CK and LDH activity is found to be elevated with low T4 levels, where as normal serum CK and LDH activity with normal T4 levels. . **McGrowder DA et al**[xxiv] conducted retrospective study of the serum creatine kinase, and the lactate dehydrogenase activities in thyroid disorders cases and concluded that significant raise in CK and LDH activities specifies that these could be used as the parameters for screening the hypothyroid cases but not the hyperthyroid cases. **Shanti R et al**[xxv] has made a case control study of the creatine kinase and lactate dehydrogenase activity in hypothyroidism cases and concluded that there was significant raise in CK, and LDH activities in hypothyroid cases. These simple markers could be used for the diagnosing Musculo-skeletal involvement in the hypothyroid patients. the TSH level and LDH activity were higher in overt hypothyroidism; while T3, T4 and CK 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 ($p>0.05$). **Reena R et al**[xxvi] 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. **Soufir JC et** [xxvii]has found 90% and 97% elevation in CK activity in these individuals.

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.[xxviii] 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.[xxix]

Studies have shown that LDH activity was increased and decreased in the hypo- and hyperthyroid states, respectively.[xxx] 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[xxxi] and in one study, 37.0% of hypothyroid patients had elevated LDH.[xxxii.]

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