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Creatine kinase & lactate dehydrogenase activity in patients with hypothyroidism

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Abstract

Thyroid hormone exerts its action in all tissues and modulates several metabolic activity. Alteration in thyroid levels has a profound effect on skeletal muscle The aim of this study is to study the association of thyroid levels and the activities of serum creatine kinase (CK) and lactate dehydrogenase (LDH) in hypothyroidism and to correlate the relationship between CK, LDH and Thyroid Stimulating Hormone (TSH) levels.

Materials and Method: In this case control study, thyroid function tests, serum creatinine, CK and LDH activities were measured in 50 cases in the age group of 20-55years of overt hypothyroidism and the results obtained were compared with 50 healthy euthyroid controls. Patients with impaired renal function, ischemic heart disease, rheumatoid arthritis, Duchenne's muscular dystrophy, polymyositis and other neuromuscular disorders, patients with drug history like statins, non-steroidal anti-inflammatory drugs, steroids, oral contraceptives, recent history of intramuscular injections or strenuous physical activity were ruled out.

Results: The mean serum levels of CK activity in hypothyroid patients was 224.94.2±76.7 IU L compared with 107±30 U L in euthyroid controls. The mean serum concentration of LDH was 346±33.8 IU L with overt hypothyroidism and 176.18±33.64 in controls. In the hypothyroid patients, a moderate positive correlation was found between CK activity and TSH ($r = +0.517$, $p = 0.001$), and a weak positive correlation between TSH activity and LDH ($r = +0.331$, $p = 0.018$).

Conclusion: There was a significant elevation in serum CK and LDH activities in hypothyroid individuals. These simple serum markers can be used for diagnosing musculoskeletal involvement in hypothyroid patients.

Keywords: Hypothyroidism, Creatine Kinase, Lactate Dehydrogenase, Myopathy.

Background

Thyroid dysfunction is one of the leading causes of endocrine disorders affecting nearly 13 million people in the US[(1)] and approximately 42 million in India.[(2)] Among the various types of thyroid disorders, hypothyroidism is more common. The prevalence of hypothyroidism is 4.6% in US[(1)] when compared to the prevalence of 4- 10% in India.[(3)] The Clinical signs and symptoms are often vague and non-specific and diagnosis is based on serum measurement of thyroid stimulating hormone (TSH), Free T4 and Free T3 levels.

Normal level of thyroid hormone are essential for proper growth, development, cellular differentiation and function of almost all the tissues and helps to uphold metabolic homeostasis in the body. Any variations in the levels of thyroid hormone has profound impact on metabolic processes, such as reduced protein turnover, derangement in carbohydrate metabolism and others. The systemic effects are also caused due to myxoedematous infiltration of glycosaminoglycans in the tissue of various organs including skeletal muscle, kidney and others thereby leading to organ dysfunction.[(4)]

The symptoms of hypothyroidism ranges from mild fatigue, cold intolerance, weight gain, to severe forms such as cardiomyopathy, myxoedamatous coma.[(5)] Neuromuscular and musculoskeletal manifestations are frequrntly observed in these cases at any stage of the disease process.[(6)] In some instances, patients present solely with myopathy with concommittant elevation in serum creatine kinase activity and lactate dehydrogenase levels.

Serum Creatine Kinase (CK) is a marker of muscular damage and the skeletal muscle is the chief source of increased plasma CK activity. The serum levels of this enzyme is influenced by age, sex, race, lean body mass and physical activity. Serum CK levels are found to be elevated in 57-90% of hypothyroid cases.[(7)] Evidences from studies suggest that skeletal muscle is affected more intensely in cases of overt hypothyroidism and to a lesser extent in subclinical hypothyroidism.[(8)] A majority of patients with hypothyroidism have been shown to have an elevated serum CK.

Furthermore several studies have observed alterations in serum lactate dehydrogenase (LDH)) activity in patients with thyroid dysfunction.[(9)] Hence the present study aims to evaluate the activity of Creatine Kinase and LDH in cases of overt hypothyroidism and to correlate the enzyme activity with thyroid stimulating hormone (TSH) levels.

Materials and Method

This case-control study was conducted in the Department of Biochemistry at Government Stanley Medical College, Chennai. The study was approved by institutional ethical committee.

The study group comprised of 50 cases of overt hypothyroidism in the age group of 20-55years who attended the Outpatient Department of Endocrinology. 50 normal healthy euthyroid subjects who attended the hospital for routine health check-up were included as

control group for the study. A detailed history including drug history using standardized proforma was taken from each patient.

Inclusion criteria: Subjects with clinical suspicion of hypothyroidism and further confirmed by serum levels of FT4, FT3 and TSH were included. The normal reference ranges for the serum levels of various thyroid hormones were considered as below.

FT4 - 0.8 – 2.7 ng/dl
FT3 – 1.8- 3 nmol/L
TSH - 0.4 -4.2 µIU/ml

Overt hypothyroidism was diagnosed at a serum TSH level of ≥20µIU/ml or TSH level of more than 4.2 µIU/ml with low FT_3 and FT_4 levels.[10] Subjects who fulfilled the above criteria were included in the study after obtaining informed consent from each participant.

Patients with impaired renal function, ischemic heart disease and cerebrovascular disease, rheumatoid arthritis, Duchenne's muscular dystrophy, polymyositis and other neuromuscular disorders that cause transient increase in CK were excluded from the study. Patients were further screened for drug intake like statins, non-steroidal anti-inflammatory drugs, steroids, oral contraceptives that can affect serum CK activity. Recent history of intramuscular injections or strenuous physical activity was also ruled out.

Under strict aseptic precautions about 4ml of fasting blood samples were collected from antecubital vein in red topped vacutainer tube without applying tourniquet. After the blood clotted, it was centrifuged at 1500 RPM for 10 minutes and immediately the serum was separated. The serum was used for the estimation of blood glucose, serum urea, serum creatinine, total creatine kinase, lactate dehydrogenase and thyroid function tests (FT_3, FT_4 & TSH). Serum FT_3, FT_4 & TSH were performed in Roche e411using electrochemiluminescence (ECLIA) method. Blood glucose was estimated by glucose-oxidase peroxidase method. Serum urea by Urease method, serum creatinine by modified Jaffe's method using ERBA kit. Serum total CK and LDH activity were measured using ERBA kit by IFCC method in fully automated clinical chemistry analyser (Beckman AU480).

Data Analysis: The data obtained was compiled and analysed using SPSS software version 16.0. All the results are expressed as Mean ± SD. To find the statistical significance among the various parameters, Student's t-test was used. Statistical significance was considered when p value was less than 0.05. Pearson's correlation coefficient was used to evaluate the relation among various parameters.

Results

The data of results from 50 overt hypothyroid cases were compared with the values obtained from 50 apparently healthy euthyroid controls with respect to thyroid function test, total CK, LDH activity, Blood glucose, Serum Urea and Serum creatinine. The age group of the study population was between 20 years to 60 years. Table 1 shows age wise distribution of overt hypothyroid cases and euthyroid controls. It is evident that hypothyroidism is more common in the age group between 31-40. Table 2 shows the 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.

The mean & SD of various biochemical parameters and thyroid parameters among hypothyroid cases and controls are compared in Table 3. It is observed from the table that Serum creatinine, Serum Ft4, FT3 and TSH, Serum CK and LDH showed statistically significant elevation among the overt hypothyroid subjects when compared to healthy euthyroid controls. The mean values of the above parameters between study groups was found to be statistically significant with a p value < 0.05. This is also represented graphically in terms of mean as bar diagrams in Fig. 3 & 4.

Table 3 shows the correlation of serum TSH with various biochemical parameters. It is evident that there is a positive weak correlation (r=0.414) between TSH and Serum creatinine levels in hypothyroid and in euthyroid controls (r=0.432) indicating that decrease in thyroid function results in renal dysfunction. On comparing TSH vs CK activity, it is found that there is a moderate positive correlation (r=0.517) in overt hypothyroid subjects while there was a strong correlation (r=0.968) among euthyrod individuals. Similarly correlation of TSH with LDH activity showed a weak positive correlation (r=0.331) in hypothyroid cases, whereas there was a strong correlation (r=0.8 in euthyroid controls. This is also represented graphically in Fig. 5 & 6.

Table 1: Age distribution of hypothyroids and controls

Age Distribution	Cases (n= 50)		Controls (n= 50)	
	N	%	N	%
20-30	14	28%	16	32%
31-40	23	46%	21	42%
41-50	09	18%	7	14%
51-60	04	8%	6	12%
Mean ± SD	35.4±9.2		36.2±9.8	
P value	0.67			

Table 2: Gender Distribution among Overt hypothyroid cases and controls

Gender	Cases (n= 50)		Controls (n= 50)	
	N	%	N	%
Males	14	28%	19	38%
Females	36	72%	31	62%

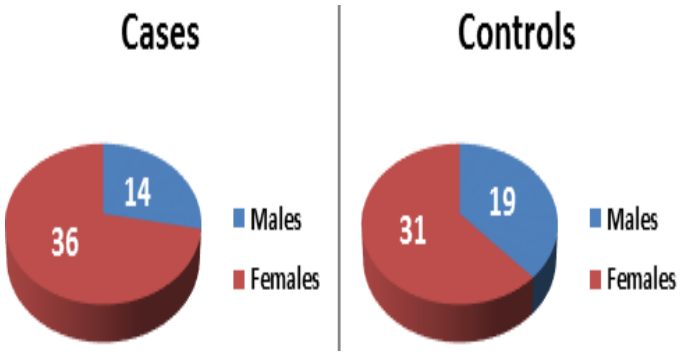

Fig. 1: Gender distribution between the study groups

Table 3: Comparison of Biochemical Parameters between Overt Hypothyroid Cases and Euthyroid Control Subjects

Parameter	Cases Mean ±SD	Controls Mean ±SD	Significance P<0.05
Serum Creatinine (mg/dl)	1.42±0.5	0.9±0.36	0.0001**
Serum FT4 (ng/dl)	0.9±0.5	1.8±0.6	<0.0001**
Serum FT3 (nmol/L)	2.2±0.7	2.6±0.1	<0.001**
Serum TSH (µIU/ml)	16.4±3.7	2.7±1.6	<0.0001**
Serum Creatine Kinase(IU/L)	224.94.2±76.7	107±30	<0.0001**
Serum LDH(IU/L)	346±33.8	176.18±33.64	<0.0001**

** - highly significant

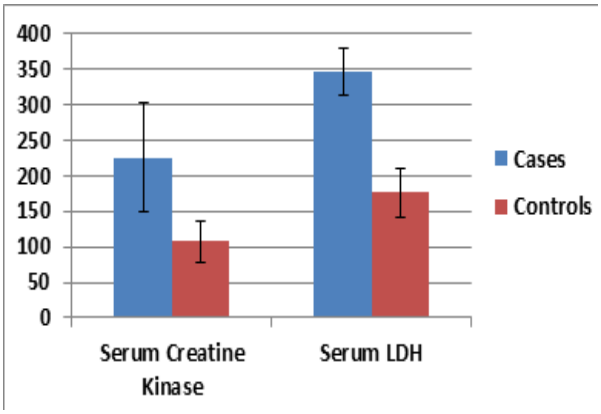

Fig. 2: Comparison of mean & SD of CK and LDH levels among study population

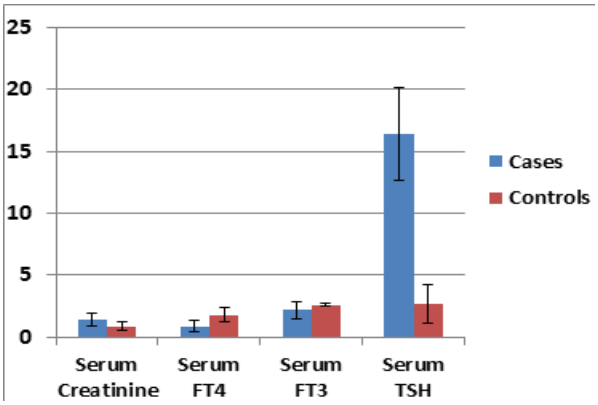

Fig. 3: Comparison of mean & SD of thyroid profile and serum creatinine levels among study population

Table 4: Correlation of TSH with other biochemical parameters in Overt Hypothyroid cases and Euthyroid controls

Parameter	Overt hypothyroid		Controls Mean ±SD	
	r value	p value	r value	p value
TSH with Serum Creatinine	+0.414	0.002**	+0.432	<0.001**
TSH with Serum CK	+0.517	0.001**	+0.968	<0.0001**
TSH with Serum LDH	+0.331	0.018*	+0.842	<0.0001**

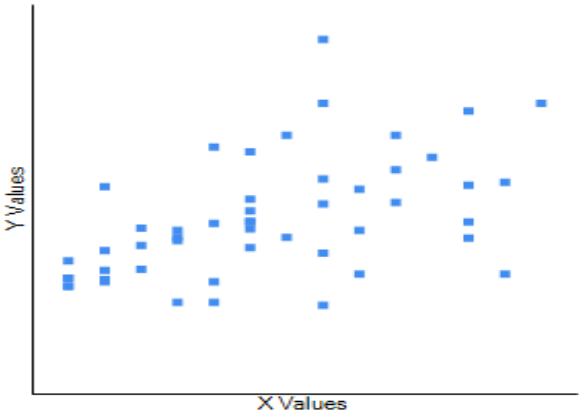

Fig. 5: Correlation between TSH and CK in Overt Hypothyroid

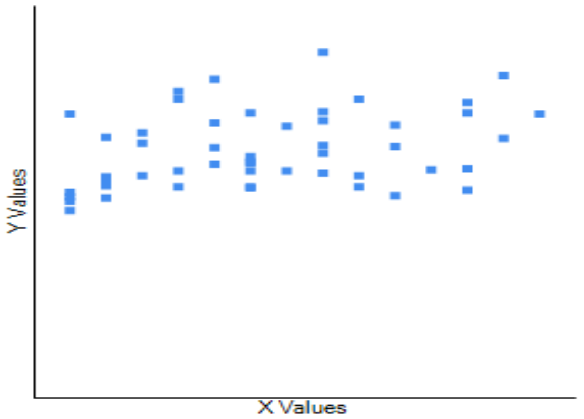

Fig. 6: Correlation between TSH and LDH in Overt Hypothyroid

Discussion

In this study, the serum CK activity was found to be significantly elevated in overt hypothyroid individuals (224.94.2±76.7) compared to euthyroid individuals (107±30.1). This finding is in agreement with that of Beyer et al[10] who has reported a 43- 97% increase in CK activity in overt hypothyroids. Similarly Giampietro O et al[11] and Soufir JC et al[12] has found 90% and 97% elevation in CK activity in these individuals. In the present study, there is a moderate positive correlation between CK and TSH (r = 0.517; p = 0.0001) in the overt hypothyroid subjects which shows the impact of TSH on myopathy. This finding is in accordance with the studies by Tejomani M et al[4] and Panag et al.[8]

In a study conducted in 2002 by Scott et al showed that thyroid hormone replacement in an individual with progressive proximal weakness has produced marked reduction in CK levels along with resolution of clinical symptoms.[13] Also Madhu et al[14] in his study showed that patients with hypothyroidism presented only with symptoms of myositis and elevated levels of CK activity which normalized after thyroid replacement and Shaeen et al[15] has found in a patient of Grave's disease who developed myalgia with high level of CK after undergoing total thyroidectomy, These evidences support the hypothesis that skeletal muscle is involved in thyroid disorders.

The probable mechanism could be hypometabolic state of hypothyroidism which causes decrease in glycolysis and oxidative phosphorylation and thus reduced Adenosine Triphosphate (ATP) levels. Also it causes modification in sarcolemmal membrane that increases cell permeability and seepage of CK from the muscle cells. Another reason may be a reduced turnover of CK due to lowered thyroid function.[16,17] Furthermore a decrease in muscle carnitine in either hypothyroidism or hyperthyroidism may lead to thyroid myopathy.[18]

The study also found that serum creatinine was significantly higher in cases (1.42±0.5mg/dl) compared to controls (0.9±0.36 mg/dl) with a p<0.0001). There exists a strong positive correlation between TSH and serum creatinine levels (r= 0.331, p= 0.018) these findings are consistent with other studies.[4,19] who have reported significant alteration in creatinine levels in hypothyroidism. Low thyroid levels causes negative inotropic and chronotropic effect on cardiovascular system which leads to increased vascular resistance due to decreased nitric oxide synthase activity. Increased vascular resistance and low cardiac output in hypothyroidism leads to impaired renal blood flow and thus elevated serum creatinine levels.[20]

In the present study, serum LDH activity is significantly elevated in overt hypothyroid cases (346±33.8) compared to euthyroid controls (176.18±33.64) with a p value of <0.001 and also shows a weak positive correlation with TSH(r= 0.331, p= 0.018). Fleisher GA et al[21] has also found that 37% of hypothyroid patients have raised LDH levels and in another studies by McGrowder DA et al[22] and Strasberg GD,[23] elevation of LDH activity was found in 33% and 74% of patients with overt hypothyroidism respectively. Analysis of LDH isoezymes in myxedema heart disease patients has shown that LDH isoenzyme 1 (LDH 1) was elevated in and its level gradually normalised with thyroid replacement therapy. The elevations of LDH levels could probably be due to increased release and/or reduced clearance from the liver.[20]

Conclusion

It can be concluded from the present study that there is significant involvement of skeletal muscle in hypothyroidism. Elevated levels of CK and LDH enzymes 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. Thus measurement of thyroid function tests along with muscle enzymes can be used for screening and early diagnosis of hypothyroidism.

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