



## EVALUATION OF ABNORMAL SERUM CREATINE KINASE AND LACTATE DEHYDROGENASE ACTIVITY IN PATIENTS WITH HYPOTHYROIDISM

### Biochemistry

**Dr. Savita Kc Rathore**

Associate Professor, Department Of Biochemistry, Amaltas Institute Of Medical Sciences, Dewas, Madhya Pradesh.

**Dr. Khushbu Suryaprakash Soni\***

Assistant Professor, Department Of Biochemistry, Amaltas Institute Of Medical Sciences, Dewas, Madhya Pradesh \*Corresponding Author

### ABSTRACT

**Background:** Hypothyroidism, one of the most common endocrine disorders, resulting from insufficient production or decreased action of thyroid hormone. 30-80% of hypothyroid patients presents with muscular symptoms.

**Aims and Objectives:** The aims of the present study were to determine the activities of serum Creatine kinase (CK) and lactate dehydrogenase (LDH) in hypothyroidism patients, and to evaluate the relationship between CK, LDH and TSH levels.

**Material and Methods:** The present work was conducted in the Department of Clinical Biochemistry at Sri Aurobindo Institute of Medical Sciences, Indore. Serum CK and LDH were measured in 55 patients with known history of hypothyroidism and the results were compared with that of 30 healthy adults who taken as control group.

**Results:** A positive correlation found between CK, LDH levels with TSH levels. The results showed the CK and LDH levels significantly ( $p < 0.0001$ ) higher in patients with hypothyroidism in comparison to control group.

**Conclusion:** The significant increase in serum CK and LDH activities shows that muscle involvement occurs in hypothyroid patients and the role of CK as an alternative diagnostic tool in patients of thyroid disorder can be evaluated.

### KEYWORDS

Hypothyroidism, Thyroid Hormone, Creatine Kinase (CK), Lactate Dehydrogenase (LDH)

### Introduction

Hypothyroidism is known to be one among the most common endocrine disorders resulting from insufficient production or impaired action of thyroid hormone. Thyroid hormones facilitate normal growth and function of nearly all the tissues with prominent effect on oxygen consumption. Thyroid hormone plays an important role in cell differentiation and helps to maintain metabolic homeostasis in the body; its alteration can affect the metabolism and can alter the activity of serum enzymes. Thyroid stimulating hormone (TSH) is a very sensitive and specific parameter to assess thyroid function and has importance in early detection or exclusion of thyroid disorder<sup>(1-2)</sup>. Muscle dysfunction symptoms, involving pain and cramps, proximal weakness, and slow reflexes, are seen commonly in hypothyroidism<sup>(3)</sup>. Myopathy may be the only clinical manifestation of hypothyroidism in some cases with increase in serum Creatine kinase (ck) activity and increase in lactate dehydrogenase and aldolase levels<sup>(4)</sup>. Skeletal muscle may be the major source of increased plasma CK activity in hypothyroidism. Total CK activity is considered to be a sensitive and fruitful biochemical marker for diagnosis of neuromuscular diseases<sup>(5)</sup>. An increase in the level of above mentioned enzymes indicates an index of cellular necrosis and tissue damage.

Serum Creatine kinase (CK) was first used as a diagnostic tool in progressive muscular dystrophy in 1959 by Ebashi et al<sup>(6)</sup>. It has since become an important clinical marker to assess muscle damage.

Lactate dehydrogenase (LDH) catalyzes the inter conversion of pyruvate and lactate along with inter conversion of NADH and NAD<sup>+</sup>.

It has been noted that various conditions can increase the LDH levels including hypothyroidism which is a highly prevalent disorder<sup>(7)</sup>.

The present study was carried out to determine the serum CK and LDH activities in patients with overt as well as subclinical hypothyroidism and to explore the relationship between thyroid hormone (T3 & T4) and TSH involvement of skeletal muscle in the thyroid disorder.

**Material and methods** The current prospective cohort study was conducted in the Department of Clinical Biochemistry at Sri Aurobindo Institute of Medical Sciences, PG Institute Indore. An informed consent was obtained from each participant of the study population. It consisted of 81 subjects, aged between 20-50 years. Following biochemical tests were performed in 51 subjects: thyroid

function tests (T3, T4 & TSH), serum CK and LDH. Out of this 29 having subclinical and 22 having overt hypothyroidism. The results were compared with that of 30 healthy euthyroid adults, taken as control and all the above biochemical tests were measured in control group also. Exclusion criteria, which can alter the results of study like neuromuscular or any recent cardiovascular or cerebrovascular event, were taken to rule out other diseases. Patients were also screened for any drug history, especially which can affect CK, LDH levels and recent history of intramuscular injections or strenuous exercise were ruled out.

The serum was used for the estimation of total T3, T4, TSH, total Creatine kinase and lactate dehydrogenase activities. Serum T3, T4 and TSH was estimated on auto analyzer Roche/Hitachi COBAS e411 (Elecys) by the electrochemiluminescence (ECLIA). Serum total CK and LDH activities were estimated by NAC and ENZOPAK activated (commercial kit) method respectively.

### Statistical analysis

The results are expressed as Mean±SD. Significance was assessed at 5 % level. Student t test (two tailed, independent) and analysis of variance (ANOVA) was used to find the significance of measured parameters. Pearson correlation was used to assess any relation between the various parameters in study groups.

### Results

The data of hypothyroid and control groups were compared with respect to measured biochemical parameters as serum T3, T4 (levels of thyroid hormone), TSH (thyroid stimulating hormone), total CK and LDH levels are shown in Table 1. Depending on the value of T3, T4 and TSH the hypothyroid group were further divided into overt and subclinical hypothyroidism as shown in Table 2.

**TABLE: 1 Comparison of all biochemical parameters between Hypothyroidism and Control group**

S. NO.	PARAMETER	HYPOTHYROIDISM (Mean±SD)	CONTROL (Mean±SD)	P values
1.	CPK U/L	218.10±269.74	46.13±16.95	<0.0001
2.	LDH IU/L	276.51±154.56	74.16±19.56	<0.0001
3.	T3 ng/ML	0.93±0.42	1.67±0.27	<0.0001
4.	T4 µg/ML	5.03±2.08	9.69±1.05	<0.0001
5.	TSH µIU/ML	35.81±31.69	3.59±0.98	<0.0001

**TABLE:2 Comparison of all biochemical parameters between all three Study Groups**

S. NO.	PARAM ETERS	OVERT HYPOTHYR OIDISM (Mean±SD)	SUBCLINICAL HYPOTHYROID ISM (Mean±SD)	CONTR OL (Mean± SD)	P values
1.	CPK $\mu$ IU/ML	490.51±337.28	178.71±63.05	46.13±1 6.95	<0.0001
2.	LDH $\mu$ IU/ML	363.24±184.06	210.39±83.65	74.16±1 9.56	<0.0001
3.	T3 ng/ML	0.60±0.34	1.18±0.28	1.67±0.2 7	<0.0001
4.	T4 $\mu$ g/ML	2.96±1.11	6.61±0.93	9.69±1.0 5	<0.0001
5.	TSH $\mu$ IU/ML	60.11±33.10	17.37±12.47	3.59±0.9 8	<0.0001

**Table 3 Correlation between thyroid profile and measured enzymes activities in hypothyroidism**

	R	P
T3/CK	-0.650	<0.0001
T4/CK	-0.643	<0.0001
TSH/CK	0.814	<0.0001
T3/LDH	-0.538	<0.0001
T4/LDH	-0.492	0.0002
TSH/LDH	0.522	<0.0001

In the present study TSH levels were found more than ten folds higher in hypothyroid subjects as compared to controls (Table 1). It was nearly threefold higher in overt hypothyroidism than subclinical hypothyroidism (Table 2). The total CK activity was seen highly significant in overt hypothyroid on comparison with subclinical hypothyroid ( $p < 0.001$ ) and controls (Table 2). Significant difference in CK and LDH activity between subclinical hypothyroid and control groups was observed. A significant increase in serum CK and LDH levels were seen in overt hypothyroid as compared to subclinical hypothyroid and control groups ( $p < 0.001$ ) (Table 2). In overt hypothyroid, there were decrease in circulating levels of thyroid hormones (T3 & T4) resulting in significant increase in TSH secretion. So, the levels of thyroid hormones were significantly reduced in all categorized (hypothyroid, overt and subclinical) class as compared to control group.

A significant relation between T3 and T4 ( $p < 0.001$ ) in overt hypothyroid was found, indicating the fall in T3 level is directly dependent on T4 level of thyroid hormones (Table 1,2). A significant negative correlation was observed between T3 and T4 with total CK activity ( $p < 0.001$ ) in hypothyroid cases indicating that decrease in T3, T4 levels and increase in total CK levels may cause muscle damage (Table 3). Highly significant negative correlation between T3, T4 with serum LDH activity was also reported. (Table 3).

Increased TSH level and increase in serum CK activity was observed in hypothyroid subjects. However, the rise in CK activity was many folds higher in overt cases as compared to subclinical cases (table 1). Decrease in T4 levels causes increased secretion of TSH in overt cases. A positive correlation was found between TSH and CK activity with  $p$  value  $< 0.001$  in hypothyroid cases (Table 3). TSH levels were also shown a significant positive correlation with the levels of LDH in hypothyroid.

### Discussion

Hypothyroid patients have decreased myocardial contractility, cardiac output and peripheral oxygen consumption with higher peripheral vascular resistance. Serum CK was first used as a diagnostic aid in progressive muscular dystrophy.<sup>(6)</sup> It has since then become important clinical marker for muscle damage. Musculoskeletal disorders often accompany thyroid dysfunction.

Musculoskeletal disorders as seen in hypothyroidism, also observed in thyrotoxicosis and level of CK is altered in both these conditions.<sup>(7)</sup> In recent years, studies have been conducted to establish a relationship of CK levels in thyroid disorders.<sup>(8)</sup> Hekimsoy et al in a study conducted in 2005, found that skeletal muscle is affected by hypothyroidism more profoundly in cases of overt hypothyroidism and less so when subclinical hypothyroidism is present.<sup>(9,10)</sup>

Histological picture shows the muscle fibers enlargement, focal myofibrillar degeneration, and increase in glycogen accumulation and mitochondrial aggregations and type II fiber atrophy<sup>(11)</sup>. Sluggish muscle contraction and relaxation, known as hypothyroid myopathy results from a shift in the distribution of muscle fiber types from fast twitch fibers to slow-twitch fibers. A decrease in muscle mitochondrial oxidative capacity and beta adrenergic receptors, along with induction of an insulin-resistant state, is responsible for all these changes. A study by Sinclair and colleagues suggests that a decrease in muscle carnitine level in patients with thyroid disease may contribute to thyroid myopathy<sup>(12)</sup>. Serum enzyme activity of muscle enzymes correlated with the degree of hypothyroidism which is in accordance with other studies<sup>(13-17)</sup>.

The present study shown the elevated total CK activity in hypothyroid that was three times higher in overt hypothyroid as compared to subclinical hypothyroid and tenfold higher than control group approximately, that was agreed to Hekimsoy et al<sup>(9)</sup> and Tejomani et al<sup>(18)</sup> studies who have noted increased prevalence of skeletal muscle dysfunction in overt hypothyroid as compared to subclinical hypothyroid. The rise in total CK activity may result from rise in concentration of the enzyme in circulation resulting from leakage of the enzyme from muscle cells as declared by Klein I et al 1980.

The present study confirmed that serum CK activity is frequently increased in patients with overt hypothyroidism. These findings were in accordance with those of other studies, which reported a 43% to 97% elevation of serum CK activity in hypothyroid patients<sup>(14,19)</sup>. However this is in contrast to findings as Hartl et al, who found an elevation of CK activity in only 2 of 69 patients<sup>(20)</sup>.

In above study, an inverse relation was found between thyroid hormone (T3 & T4) and total CK activity in hypothyroid. It was agreed to Archana P (2007) et al reported in their study, there was increase in CK levels with decreased T3 levels in subjects with hypothyroidism. They found serum CK activity showed an inverse relation with thyroid hormones<sup>(21)</sup>.

Thus, it follows that the assay of CK activity in serum may prove to be important in screening of thyroid disorder in the present study; the study was done to evaluate the role of CK as a supportive biochemical parameter for diagnosing thyroid disorders. The levels of CK are found to be significantly higher in patients of hypothyroidism as compared to normal subjects which may be due to skeletal muscle involvement in thyroid disorders.

In present study LDH activity was five times higher in overt hypothyroid and two times higher in subclinical hypothyroid on comparison with control group. The negative correlation was shown with thyroid hormone (T<sub>3</sub> & T<sub>4</sub>) while a positive correlation with TSH. It was similar to Fleisher GA et al., who reported that 37% of hypothyroid patients had elevated LDH levels<sup>(22)</sup>. In another study elevation of LDH activity was found in 33% of patients with overt hypothyroidism and in 74% of patients with subclinical hypothyroidism<sup>(24)</sup>. In contrast, Navneet et al., reported the correlation with the degree of hypothyroidism; but with no significant relation were found with thyroid hormones. Therefore significant elevation of serum LDH activity indicates no direct relation of LDH with thyroid hormones in both clinical and subclinical stages of hypothyroidism<sup>(2)</sup>.

### Conclusion

The present study concluded significant elevation in serum CK and LDH activities in hypothyroid which indicates usefulness of these parameters for screening hypothyroid patients. Hypothyroidism is a common cause of endocrine myopathy and should be considered in patients with unexplained persistent elevation of serum muscle enzymes, which are higher in patients with overt hypothyroidism and lower in subclinical hypothyroidism. However, further studies are required in large population to provide better understanding of effect of changes in thyroid hormone levels on musculoskeletal dysfunction and abnormality.

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