

# Serum creatine kinase and lactate dehydrogenase activities in patients with thyroid disorders

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## Abstract

**Background and Objectives:** There is the recognition of a pattern of elevations of serum enzymes in hyperthyroid and hypothyroid patients. The aims of this study were to determine the activities of serum creatine kinase (CK) and lactate dehydrogenase (LDH) in thyroid disorders, and to evaluate the relationship between CK, LDH and FT<sub>4</sub>, and TSH levels.

**Materials and Methods:** In this retrospective study, thyroid function tests, serum CK and LDH activities were obtained from the medical records of newly diagnosed hyperthyroid and hypothyroid patients attending the Endocrinology Clinic at the University Hospital of the West Indies from 2005- 2009.

**Results:** Elevation of CK activity was found in 5 patients (28%, 5/18) with overt hypothyroidism and in 12 patients (24.0%, 12/50) with subclinical hypothyroidism. The mean CK activity in subclinical hypothyroid patients was  $179.80 \pm 125.68$  U/L compared with  $389.901 \pm 381.20$  U/L in overt hypothyroid patients. The elevation of LDH activity was found in 6 patients (33.3%, 6/18) with overt hypothyroidism and in 37 patients (74.0%, 37/50) with subclinical hypothyroidism. In the hypothyroid patients, a positive correlation was found between CK activity and TSH ( $r = 0.292$ ,  $P = 0.015$ ), and a negative correlation between CK activity and FT<sub>4</sub> ( $r = - 0.325$ ,  $P = 0.007$ ); and between FT<sub>4</sub> and TSH ( $r = - 0.371$ ,  $P = 0.002$ ).

**Conclusion:** The significant elevation in serum CK and LDH activities indicates that these can be used as parameters for screening hypothyroid patients but not hyperthyroid patients.

**Key words:** Hyperthyroidism, hypothyroidism, lactate dehydrogenase, serum creatine kinase

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## Introduction

Overt abnormalities in thyroid function are common endocrine disorders affecting 5-10% of individuals over a lifespan.<sup>[1]</sup> Clinical symptoms and signs are often nonspecific, and the diagnosis and monitoring of therapy depends crucially on measurements of thyroid hormones (triiodothyronine, T<sub>3</sub> and thyroxine, T<sub>4</sub>), and thyroid stimulating hormone (TSH) in blood.<sup>[2]</sup> Minor abnormalities in thyroid function with subclinical hypothyroidism or hyperthyroidism are even more common.<sup>[3,4]</sup> Both subclinical hypothyroidism and hyperthyroidism are associated with an increase in risk of disease,<sup>[3,4]</sup> as well as abnormalities

in biochemical and physiologic measures that are often abnormal in patients with overt thyroid disease.<sup>[5]</sup>

Both subclinical hyperthyroidism and hypothyroidism are increasingly being recognized as having significant health implications with subclinical hypothyroidism more common than subclinical hyperthyroidism.<sup>[6]</sup> Subclinical hypothyroidism is defined by the finding of elevated serum TSH concentrations associated with normal free thyroid hormone levels (FT<sub>4</sub> and FT<sub>3</sub>).<sup>[7]</sup> The prevalence of this

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condition is higher in women than men and increases with age, reaching a peak of 21% in women and 16% in men over 74 years of age.<sup>[8,9]</sup>

The serum creatine kinase (CK) activity in healthy individuals depends on age, race, lean body mass and physical activity.<sup>[10]</sup> It has since become an important clinical marker for muscle damage. Musculoskeletal disorders often accompany thyroid dysfunction. The association of myopathy with both myxedema and thyrotoxicosis is well known.<sup>[11]</sup> Concentrations of CK in serum are often increased in patients with primary hypothyroidism,<sup>[12,13]</sup> but evidence for any change in thyrotoxicosis is conflicting. Some authors<sup>[14]</sup> reported normal and others subnormal<sup>[15]</sup> CK activity. Furthermore only a few studies have investigated serum lactate dehydrogenase (LDH) activity in patients with thyroid dysfunction.<sup>[16,17]</sup>

In recent years studies have been conducted to establish a relationship of CK activity in thyroid diseases.<sup>[18]</sup> However, no correlation has been consistently described between CK activity and circulating concentrations of either T<sub>3</sub>, T<sub>4</sub>, or TSH.<sup>[19-21]</sup> The aims of this study were to determine serum activities of CK and LDH in overt and subclinical hypothyroidism, and also in overt and subclinical hyperthyroidism; to evaluate the relationship between FT<sub>4</sub> and TSH levels and the degree of skeletal muscle involvement in these thyroid disorders, as determined by serum CK activity in these thyroid dysfunctions.

## Materials and Methods

This is a retrospective study where information was extracted from the medical records of newly diagnosed hypothyroidism or hyperthyroidism patients attending the Endocrinology Clinic at the University Hospital of the West Indies from 2005-2009.

Exclusion criteria were previous use of L-thyroxine or antithyroid medication and thyroidectomy. Also, patients with risk factors for having high CK activity were excluded: recent fall, intoxication, intramuscular injection, seizure, stroke, surgery, excessive physical exercise, and certain medications (antiarrhythmics,  $\beta$ -blockers, lithium, fibrates, phenothiazines, steroids and statins). We included 18 patients (14 females, 4 males) with overt hypothyroidism; 50 patients (34 females, 16 male) with subclinical hypothyroidism; 31 patients (26 females, 5 males) with overt hyperthyroidism; 61 patients (46 females, 15 male) with subclinical hyperthyroidism, and 99 controls (healthy persons who did their annual routine tests; 64 females and 25 males) in the study. Serum levels of TSH and FT<sub>4</sub> were measured by radioimmunoassay on AXSYM System (Abbott Laboratories, Abbott Park, USA); serum CK and LDH activities were determined using an automated analyzer

(c8000, Abbott Architect, Abbot Park, Illinois, USA) in all subjects.

The patients in the study were classified into one of the following four groups based on their thyroid function tests. These were (1) overt thyrotoxicosis defined as a TSH level of less than 0.40 mU/L (normal, 0.4 – 4.0 mU/L) with an elevated FT<sub>4</sub> concentration (normal, 0.8 – 1.9 ng/dL); (2) subclinical hyperthyroidism defined as a TSH level of less than 0.40 mU/L with a normal FT<sub>4</sub> concentration; (3) subclinical hypothyroidism defined as a TSH level of more than 4.0 mU/L and less than 20 mU/L with a normal FT<sub>4</sub> concentration; and (4) overt hypothyroidism was defined as a TSH level of 20 mU/L or more or a TSH level of more than 4.0 mU/L with an FT<sub>4</sub> concentration below normal.<sup>[22]</sup>

Chi-square was used to examine non-metric variables. A *P*-value < 0.05 (two-tailed) was used to establish statistical significance. Statistical analyses were carried out using linear regression analysis.

## Results

Patient groups (overt hypothyroidism and subclinical hypothyroidism; overt hyperthyroidism and subclinical hyperthyroidism) and control groups were similar in regard to age (60.67  $\pm$  17.96 and 59.16  $\pm$  21.16; 58.38  $\pm$  18.33 and 58.65  $\pm$  17.91 years) and 52.75  $\pm$  16.44 years, respectively; and gender (16/4 and 34/16; 26/5 and 46/15) and 64/25, female/male, respectively.

Elevation of CK activity was found in 5 patients (28%, 5/18) with overt hypothyroidism and in 12 patients (24.0%, 12/50) with subclinical hypothyroidism. The mean CK activity in subclinical hypothyroid patients was 179.80  $\pm$  125.68 U/L compared with 389.901  $\pm$  381.20 U/L in overt hypothyroid patients [Table 1]; while values for patients with overt and subclinical hyperthyroidism was 88.37  $\pm$  69.22 U/L and 105.98  $\pm$  57.00 U/L respectively [Table 2].

Elevation of LDH activity was found in 6 patients (33.3%, 6/18) with overt hypothyroidism and in 37 patients (74.0%, 37/50) with subclinical hypothyroidism. The mean LDH activity in subclinical hypothyroid patients was 340.38  $\pm$  153.38 compared with 421.00  $\pm$  203.91 U/L in overt hypothyroid patients [Table 1]; while values for patients with overt and subclinical hyperthyroidism were 233.80  $\pm$  77.37 U/L and 227.81  $\pm$  54.99 U/L respectively [Table 2].

In the hypothyroid patients, a positive correlation was found between CK activity and TSH levels ( $r = 0.292$ ,  $p = 0.015$ ), and a negative correlation between CK activity and FT<sub>4</sub> concentration ( $r = -0.325$ ,  $P = 0.007$ ); and between FT<sub>4</sub> concentration and TSH levels ( $r = -0.371$ ,  $P = 0.002$ ). No significant correlations were found between

FT<sub>4</sub> concentration and LDH activity ( $P = 0.836$ ), between TSH levels and LDH activity ( $P = 0.714$ ), between CK and LDH activities ( $P = 0.133$ ).

There was statistically significant difference in CK and LDH activities in patients with overt hypothyroidism and the control, and subclinical hypothyroidism and the control [Table 1]. Although a statistically significant elevation of FT<sub>4</sub> concentration was found in patients with overt hyperthyroidism when compared with the subclinical hyperthyroidism patients ( $P = 0.0001$ ); no statistical difference was found for TSH, CK, and LDH [Table 2].

In the hyperthyroid patients compared with the control group, CK activity was found not to be statistically significant in the subclinical and the control ( $P = 0.326$ ), and the overt and the control group ( $P = 0.147$ ). However, significant statistical differences in levels were found in FT<sub>4</sub>, TSH and

LDH activity between the subclinical and the control; and the overt hyperthyroidism and the control group [Tables 2]. However, no statistical correlation was found between FT<sub>4</sub> and TSH ( $P = 0.128$ ), CK and FT<sub>4</sub> ( $P = 0.120$ ) and LDH and FT<sub>4</sub> ( $P = 0.545$ ) in hyperthyroid patients; a positive correlation existed between CK and LDH activities ( $r = 0.341$ ,  $P = 0.021$ ). A significant statistical difference was found among the means of CK activity for the hyperthyroid and hypothyroid patients, and control group [Table 3].

### Discussion

The findings of this study confirm that elevated serum CK activity is frequently increased in hypothyroidism and decreased in hyperthyroidism. This study also indicates that CK activity correlates with the degrees of hypothyroidism and hyperthyroidism, as evident by the magnitude of

**Table 1: Comparison of FT<sub>4</sub>, TSH, CK, and LDH levels between controls, overt and subclinical hypothyroid patients**

Variables	Subclinical hypothyroidism (n = 59)	Overt hypothyroidism (n = 10)	P value
FT <sub>4</sub>	1.04 ± 0.29	0.38 ± 0.15	0.0001
TSH	16.08 ± 40.98	70.52 ± 99.22	0.004
CK	179.80 ± 125.68	389.90 ± 381.20	0.001
LDH	340.38 ± 153.38	421.00 ± 203.91	0.106
Subclinical hypothyroidism (n = 59)		Control group (n = 100)	
FT <sub>4</sub>	1.04 ± 0.29	1.22 ± 0.21	<0.0001
TSH	16.08 ± 40.98	1.64 ± 0.59	0.003
CK	179.80 ± 125.68	102.19 ± 46.41	<0.0001
LDH	340.38 ± 153.38	202.85 ± 36.06	<0.0001
Overt hypothyroidism (n = 10)		Control group (n = 100)	
FT <sub>4</sub>	0.38 ± 0.15	1.22 ± 0.21	<0.0001
TSH	70.52 ± 99.22	1.64 ± 0.59	0.012
CK	389.90 ± 381.20	102.19 ± 46.41	0.007
LDH	421.00 ± 203.91	202.85 ± 36.06	0.0003

FT<sub>4</sub> = Free thyroid; TSH = Thyroid stimulating hormone; and LDH = lactate dehydrogenase; CK = Creatine kinase

**Table 2: Comparison of FT<sub>4</sub>, TSH, CK, and LDH levels between controls, overt and subclinical hyperthyroid patients**

Variables	Subclinical hyperthyroidism (n = 62)	Overt hyperthyroidism (n = 31)	P value
FT <sub>4</sub>	1.37 ± 0.46	4.02 ± 1.94	0.0001
TSH	0.34 ± 1.28	0.05 ± 0.08	0.086
CK	105.98 ± 57.00	88.37 ± 69.22	0.238
LDH	227.81 ± 54.99	233.80 ± 77.37	0.794
Subclinical hyperthyroidism (n = 62)		Control group (n = 100)	
FT <sub>4</sub>	1.37 ± 0.46	1.22 ± 0.21	0.007
TSH	0.34 ± 1.28	1.64 ± 0.59	<0.0001
CK	105.98 ± 57.00	102.19 ± 46.41	0.326
LDH	227.81 ± 54.99	202.85 ± 36.06	0.001
Overt hyperthyroidism (n = 31)		Control group (n = 100)	
FT <sub>4</sub>	4.02 ± 1.94	1.22 ± 0.21	<0.0001
TSH	0.05 ± 0.08	1.64 ± 0.59	<0.0001
CK	88.37 ± 69.22	102.19 ± 46.41	0.147
LDH	233.80 ± 77.37	202.85 ± 36.06	0.012

FT<sub>4</sub> = Free thyroid; TSH = Thyroid stimulating hormone; and LDH = lactate dehydrogenase; CK = Creatine kinase

**Table 3: Descriptive statistics of hyperthyroidism (subclinical and overt) and hypothyroidism (subclinical and overt) patients and control**

Variables	Subclinical hyperthyroidism	Overt hyperthyroidism	Subclinical hypothyroidism	Overt hypothyroidism	Control group Mean (SD)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
FT <sub>4</sub> <sup>1</sup>	1.37 (0.46)	4.02 (1.94)	1.04 (0.29)	0.38 (0.15)	1.22 (0.21)
TSH <sup>2</sup>	0.34 (1.28)	0.005 (0.08)	16.08 (40.98)	70.52 (99.22)	1.64 (0.59)
CK <sup>3</sup>	105.98 (57.00)	88.37 (69.22)	179.80 (125.68)	389.90 (381.20)	102.19 (46.41)
LDH <sup>4</sup>	227.81 (55.00)	233.80 (77.37)	340.38 (153.38)	421.00 (203.91)	202.85 (36.06)

<sup>1</sup>F-statistic = 109.60,  $P < 0.0001$ ; <sup>2</sup>F-statistic = 18.06,  $P < 0.0001$ ; <sup>3</sup>F-statistic = 22.13,  $P < 0.0001$ ; <sup>4</sup>F-statistic = 18.69,  $P < 0.0001$

the TSH. Elevated serum CK activity was observed in hypothyroid patients, and was higher in patients with overt hypothyroidism, and less so in subclinical hypothyroid patients. These findings are in accordance with those of other studies, which report a 43% to 97% elevation of serum CK activity in hypothyroidism: Beyer *et al*, 43%<sup>[22]</sup> Giampietro *et al*, 90%<sup>[19]</sup> and Soufir *et al*,<sup>[23]</sup> 97%. This is in contrast to the findings of Hartl *et al*, who found an elevation of CK activity in only 2 of 69 patients (3%), one with overt and one with subclinical hypothyroidism.<sup>[24]</sup> The finding of decreased CK activity in patients with hyperthyroidism compared with controls is in accordance with other studies.<sup>[14,25]</sup>

In a few of the severely hypothyroid patients with TSH exceeding 40 mU/mL, the increase in serum CK activity was pronounced with CK values over 500 U/L. Unexpectedly, normal CK values was observed in older patients, despite marked overt hypothyroidism could presumably be related to inter-individual variations,<sup>[26]</sup> for example due to reduced muscle mass and lack of physical activity. Nonspecific muscle stiffness related to myalgia may be associated with serum muscle enzyme elevations. Skeletal muscle is affected more profoundly in patients with overt hypothyroidism, less so when subclinical hypothyroidism is present.<sup>[27]</sup> However, clinical muscular symptoms are not usually the chief complaint at presentation. More than 40% of patients with hypothyroidism also had neuromuscular complaints at the time of diagnosis.<sup>[28]</sup>

Some patients with primary hypothyroidism may have a marked myopathy,<sup>[29]</sup> with associated histological changes in muscle cells.<sup>[11]</sup> It is widely suggested that this increase results from leakage of the enzyme from muscle cells,<sup>[30]</sup> perhaps related to the subnormal body temperature accompanying primary hypothyroidism.<sup>[31]</sup> The increase may also reflect a decrease in enzyme clearance.<sup>[32]</sup>

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.<sup>[19,20]</sup> The hypo-metabolic state of hypothyroidism can cause a reduction in glycolysis and oxidative phosphorylations and thus reducing adenosine triphosphate (ATP) concentrations beyond a critical

limit. The alteration in sarcolemmal membranes can cause increased cell permeability and the leakage of CK from cells.<sup>[33,34]</sup> Another possibility is reduced turnover of CK because of hypothyroidism, allowing serum activities to rise generating a marked release of CK through the altered sarcolemmal membranes.<sup>[31]</sup>

Our finding of lower CK activity in hyperthyroidism, is in accordance with other reports<sup>[14,25]</sup> and suggests that in the hypermetabolic state there may be increased enzyme degradation which may have contributed to these low CK activity. 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.<sup>[25]</sup>

A key finding in the study is significant inverse correlation in hypothyroid patients between serum CK and TSH ( $P < 0.001$ ), regardless of whether FT<sub>4</sub> concentrations were normal ( $P < 0.01$ ) or decreased ( $P < 0.01$ ). The elevated CK activity in subclinical hypothyroid patients might be explained by the fact that just as the pituitary gland releases TSH in response to suboptimal levels of thyroid hormones, the muscles probably respond by releasing CK into the circulation.<sup>[22]</sup> Further, the results of this study are in accordance with others<sup>[22,35,36]</sup> as we found that the severity of hypothyroidism to correlate with the elevation of serum CK activities: however, still others have not found such a relationship<sup>[23,24,28]</sup> or have found a reciprocal relationship.<sup>[37]</sup> These conflicting results may depend more on the degree of clinical manifestations of hypothyroidism, rather than on the amount of elevation of serum markers.

Hypothyroid patients have increased activity of creatine kinase that is mostly due to increased CK-MM as CK isoenzyme analysis in six cases of primary hypothyroidism showed only the MM isoenzyme to be present in four patients, and MM with a trace of MB in the other two.<sup>[38]</sup> These findings also confirm previous studies that indicated skeletal muscle to be the major source of the increased plasma CK activity.<sup>[39,40]</sup>

Studies have shown that LDH activity was increased and decreased in the hypo- and hyperthyroid states,

respectively.<sup>[16,17]</sup> The study found increase in LDH activity in patients with hypothyroidism which correlates with the degree of hypothyroidism. LDH activity have been reported to be increased in primary hypothyroidism<sup>[41,42]</sup> and in one study, 37% of hypothyroid patients had elevated LDH.<sup>[39]</sup> In another study of six untreated primary hypothyroid patients, LDH activities from 473 to 1885 U/L<sup>[38]</sup> was reported; and in a latter study 27 of 45 hypothyroid patients had elevated total LDH levels.<sup>[43]</sup> Further isoenzyme analysis showed a normal pattern of LDH isozyme in 12 patients, while in the remaining ten, three showed increased LDH<sub>1</sub> levels, one showed an increased lactate dehydrogenase isozyme 3 level (LDH<sub>3</sub>), and six showed elevated lactate dehydrogenase isozyme 5 (LDH<sub>5</sub>) levels.<sup>[43]</sup> Studies of LDH isozymes in myxedema heart disease have shown that LDH isozyme 1 (LDH<sub>1</sub>) may be elevated in this disorder and gradually fade with thyroid replacement therapy.<sup>[44]</sup> The elevations of LDH levels could reflect increased release and/or decreased clearance from the liver.<sup>[45]</sup> In addition, lactate dehydrogenase values were inversely related to both the thyroxine and triiodothyronine concentrations. The finding of the latter study differ 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.<sup>[46]</sup>

## Conclusion

The study found an inverse relation in the serum levels of FT<sub>4</sub> concentration and serum CK activity in thyroid diseases; and between FT<sub>4</sub> concentration and LDH activity in hypothyroidism. In hypothyroid patients with decrease in serum FT<sub>4</sub> concentration, there is a significant increase in CK and LDH activities, which indicates that these can be used as parameters for screening hypothyroid patients and to lesser extent hyperthyroid patients.

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