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EVALUATION OF SERUM CREATINE PHOSPHOKINASE AND LACTATE DEHYDROGENASE AS BIOMARKERS OF SKELETAL MUSCLE INVOLVEMENT IN HYPOTHYROIDISM

Biochemistry

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ABSTRACT

Hypothyroidism is a common endocrine disorder characterized by insufficient thyroid hormone production, affecting multiple organ systems including skeletal muscles. Myopathy in hypothyroidism often remains underdiagnosed, necessitating reliable biomarkers for early detection. Present study evaluates serum Creatine Phosphokinase (CPK) and Lactate Dehydrogenase (LDH) as potential biomarkers for skeletal muscle involvement in hypothyroidism. This observational cross-sectional study included 150 patients with hypothyroidism (56 with overt and 94 with subclinical hypothyroidism) attending a tertiary care center. Venous blood samples were collected following standardized protocols. Thyroid function tests (TSH, T_3, T_4) were performed using ELISA, while serum CPK and LDH activities were measured using modified IFCC methods. Patients with conditions affecting muscle enzyme levels were excluded. Statistical analysis included correlation coefficients, regression analysis, and t-tests. Results revealed significantly higher levels of serum CPK and LDH in overt hypothyroidism compared to subclinical hypothyroidism ($p<0.001$ and $p=0.002$, respectively). A larger proportion of patients with overt hypothyroidism exhibited elevated enzyme levels than those with subclinical hypothyroidism. Correlation analysis demonstrated significant positive associations between serum TSH and CPK ($p<0.001$), while significant negative correlations were observed between thyroid hormones and muscle enzymes. Regression analysis confirmed these relationships, with thyroid hormone levels explaining a significant portion of the variation in enzyme concentrations. These findings suggest that serum CPK and LDH can serve as valuable biomarkers for detecting skeletal muscle involvement in hypothyroidism, particularly in overt cases, potentially improving early diagnosis and management of hypothyroid myopathy.

KEYWORDS

Hypothyroidism; Creatine Phosphokinase; Lactate Dehydrogenase; Myopathy; Skeletal Muscle; Biomarkers; Overt Hypothyroidism; Subclinical Hypothyroidism

INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders worldwide, characterized by insufficient production or diminished action of thyroid hormones. This condition affects approximately 4-5% of the global population, with a notably higher prevalence in women and older adults[1]. In India, the prevalence reaches approximately 11%, significantly higher than global averages, making it a substantial public health concern[2].

Thyroid hormones play a critical role in regulating various metabolic processes throughout the body, including skeletal muscle physiology. They influence contractile function, myogenesis, metabolism, and thermogenesis in muscle tissue[3]. The thyroid hormone receptor α (THRA) in skeletal muscle is essential for thyroid hormone-mediated increases in energy expenditure[4]. Consequently, thyroid hormone deficiency can lead to significant alterations in muscle function and integrity.

Myopathy is a recognized complication of hypothyroidism that can significantly impact quality of life[5]. In some cases, it may be the sole clinical manifestation of the disease, presenting as proximal muscle weakness, exercise intolerance, and myalgia. However, hypothyroid myopathy often remains underdiagnosed or misdiagnosed due to its nonspecific symptoms and the absence of routine muscle enzyme evaluation in clinical practice.

Serum Creatine Phosphokinase (CPK) and Lactate Dehydrogenase (LDH) are established markers of muscle damage[6]. CPK, primarily present in skeletal muscle, heart, and brain tissue, catalyzes the transfer of high-energy phosphate groups essential for muscle contraction. LDH, an enzyme involved in anaerobic metabolism, catalyzes the interconversion of pyruvate and lactate. Elevated levels of these enzymes in the bloodstream often indicate muscle damage or disease[7].

Despite the established association between hypothyroidism and muscle involvement, there is limited research comprehensively evaluating both CPK and LDH as biomarkers of skeletal muscle involvement in hypothyroidism, particularly comparing their utility in overt versus subclinical hypothyroidism[8]. This study aims to address this gap by evaluating serum CPK and LDH activities as potential biomarkers for skeletal muscle involvement in patients with different severities of hypothyroidism, thereby contributing to earlier detection and management of hypothyroid myopathy.

MATERIALS AND METHODS

Present observational cross-sectional study was conducted at the Department of Biochemistry in collaboration with the Department of Medicine at Gandhi Medical College and Hamidia Hospitals, Bhopal, over an 18-month period. A total of 150 patients with hypothyroidism attending the Medicine OPD were enrolled in the study. The research protocol was approved by the Institutional Ethics Committee (Ethical clearance certificate no. 32228/MC/IEC/2022), and written informed consent was obtained from all participants.

Inclusion criteria comprised adult patients (>18 years) of either gender with recently detected or poorly controlled hypothyroidism. Exclusion criteria were stringently applied and included patients with known impaired renal function, ischemic heart disease, cerebrovascular disease, hypertension, diabetes mellitus, autoimmune disorders related to musculoskeletal system, active infections, recent trauma, and those on medications known to affect serum creatinine or CPK activity (such as NSAIDs, steroids, oral contraceptives, and lithium)[9]. Patients who had engaged in strenuous exercise or consumed alcohol within 24 hours prior to sampling were also excluded[6].

Participants were categorized into two groups based on their thyroid hormone profiles: Group A (overt hypothyroidism), characterized by decreased thyroid hormone levels (T_4) with elevated TSH; and Group B (subclinical hypothyroidism), defined by normal thyroid hormone levels with elevated TSH (Biondi and Cooper, 2008).

Five milliliters of venous blood were collected using standardized aseptic techniques. Blood samples were allowed to clot and then centrifuged at 3000 rpm for 15 minutes to separate serum. All investigations were performed on the same day of sample collection to minimize pre-analytical variables.

Thyroid function tests (TSH, T_3, and T_4) were performed using Enzyme Linked Immunosorbent Assay (ELISA) with a MicroLab ELISA Reader. Serum CPK and LDH activities were measured using modified International Federation of Clinical Chemistry (IFCC) methods on a fully automatic biochemistry analyzer (BA 400). The reference ranges were: TSH (0.4-5.5 µIU/ml), T_3 (0.8-2.1 ng/ml), T_4 (5-13 µg/dl), CPK (up to 170 U/L), and LDH (120-220 U/L).

Statistical Analysis

Data was analyzed using SPSS version 21.0. Categorical data was expressed as frequency and percentage, while continuous data was presented as mean and standard deviation. Comparison between groups was performed using Student's t-test. Pearson correlation coefficient was used to assess relationships between thyroid hormones and muscle enzymes. Regression analysis was conducted to evaluate the predictive value of thyroid hormone levels for muscle enzyme activities. A p-value <0.05 was considered statistically significant (Bland and Altman, 2000).

RESULTS AND DISCUSSION

Of the total participants, 37.3% (n=56) had overt hypothyroidism, while 62.7% (n=94) had subclinical hypothyroidism (Figure-1). This distribution is consistent with findings by Taylor et al., 2018[10], who reported a higher prevalence of subclinical hypothyroidism in the general population. Similarly, Hollowell et al., 2002[11] also documented higher rates of subclinical hypothyroidism compared to overt hypothyroidism in community-based studies, further supporting present study findings. This distribution can be explained by the fact that subclinical hypothyroidism often represents an early stage of thyroid dysfunction that may progress to overt hypothyroidism over time. Improved diagnostic techniques and increased screening also contribute to earlier detection of subclinical cases[12,13].

Among the 150 patients with hypothyroidism enrolled in this study, a female predominance (64%) was observed, consistent with the known epidemiological pattern of thyroid disorders. The majority of patients were between 31-40 years (33.3%), followed by 41-50 years (28%) (Figure-2). These findings align with previous research in the field. Unnikrishnan et al., 2011[14] reported a higher prevalence of hypothyroidism among females in the Indian population. Similarly, Vanderpump, 2011[15] documented comparable age distribution patterns among hypothyroid patients, with middle-aged individuals being more frequently affected. This demographic pattern can be attributed to the influence of female hormones on thyroid function, with estrogen increasing thyroid-binding globulin production and affecting immune function, predisposing women to autoimmune thyroid disorders[16].

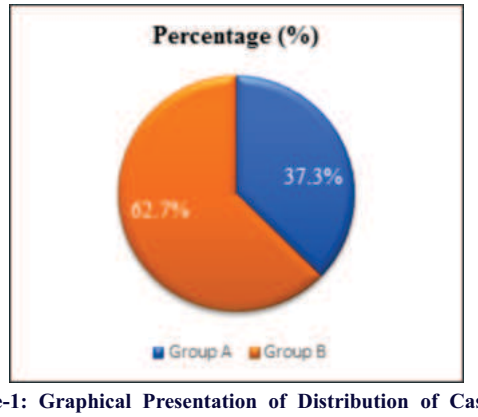

Figure-1: Graphical Presentation of Distribution of Cases in Different Study Groups

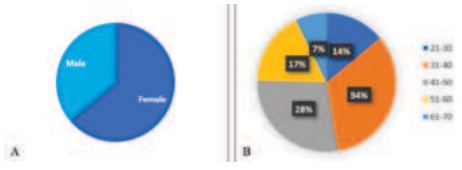

Figure-2: Distribution of Hypothyroid Patients According to A. Gender and B. Different Age Groups

Table-1: Distribution of Serum CPK and LDH Levels Among Different Types of Hypothyroidism

Study Groups	Serum CPK (U/L)		Serum LDH (U/L)	
	High	Mean ± SD	High	Mean ± SD
Group A	36 (64.3%)	218.88 ± 81.86	27 (48.2%)	304.63 ± 171.96
Group B	46 (48.9%)	178.84 ± 58.73	38 (40.4%)	233.94 ± 107.95

Serum CPK activity was significantly elevated in patients with overt hypothyroidism compared to those with subclinical hypothyroidism (p<0.001) (Table-1). Among patients with overt hypothyroidism, 64.3% exhibited elevated CPK levels compared to 48.9% in the subclinical group. These findings are consistent with studies by Shanti et al., 2021[17], who reported significantly higher CPK levels in overt hypothyroid patients compared to controls, Tejomani et al., 2019[18], who observed a tenfold increase in CPK levels in overt hypothyroidism compared to control subjects. However, Koner and Chaudhuri, 2019[9] documented elevated serum CPK as a valuable biochemical marker for screening muscle damage in hypothyroidism. The elevated CPK in hypothyroidism is the direct impact of thyroid hormone deficiency on muscle metabolism, leading to decreased protein synthesis, impaired mitochondrial function, and increased muscle breakdown, resulting in enzyme leakage from damaged muscle cells[3,19].

Serum LDH activity was significantly higher in patients with overt hypothyroidism compared to subclinical hypothyroidism (Table-1). Elevated LDH levels were observed in 48.2% of overt hypothyroid patients versus 40.4% of subclinical hypothyroid patients. These results corroborate findings by McGrowder et al., 2011[20], who documented increased LDH activity in hypothyroid patients. Similarly, Shanti et al., 2021[17], who observed elevated LDH as an indicator of muscle damage in hypothyroidism. However, Iervasi et al., 2003[21] reported contrasting results, finding no significant difference in LDH levels between subclinical hypothyroid patients and euthyroid controls, suggesting that mild thyroid dysfunction might not always lead to significant muscle enzyme alterations. The probable reason for increased LDH is the shift from aerobic to anaerobic metabolism in hypothyroidism, leading to increased lactate production and LDH activity. Additionally, myxedematous infiltration of muscles may cause mechanical disruption of muscle fibers[22].

Correlation Analysis

Pearson correlation analysis revealed a significant positive correlation between serum TSH and CPK (r=0.435, p<0.001), and significant negative correlations between T_4 and CPK (r=-0.363, p<0.001) (Figure-3), T_4 and LDH (r=-0.201, p=0.013), and T_3 and LDH (r=-0.272, p<0.001) (Figure-4). However, no significant correlations were observed between T_3 and CPK (r=0.020, p=0.812), or between TSH and LDH (r=-0.048, p=0.560). Additionally, a significant positive correlation was observed between serum CPK and LDH activities (r=0.253, p=0.002) (Figure-5), indicating that as CPK levels increase, LDH levels also tend to increase. This finding is consistent with McGrowder et al., 2011[20] and Shanti et al., 2021[17], who reported similar interrelations between these biochemical markers in hypothyroid patients.

The probable reason for these correlations is that elevated TSH reflects the severity of thyroid hormone deficiency, which corresponds to greater muscle damage and enzyme leakage. Conversely, adequate thyroid hormone levels are protective for muscle integrity[18,23]. The positive correlation between CPK and LDH suggests that these enzymes are being released concurrently from damaged muscle tissue, further supporting their utility as complementary biomarkers of muscle involvement in hypothyroidism[24].

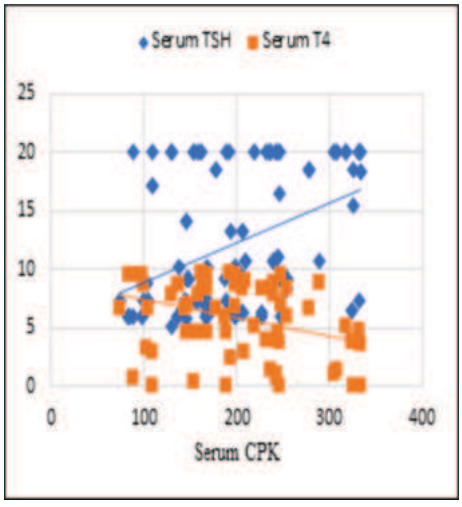

Figure-3: Scatterplot Diagram of Correlation Between Serum CPK With Serum TSH and Serum T_4 in Patients Of Hypothyroidism

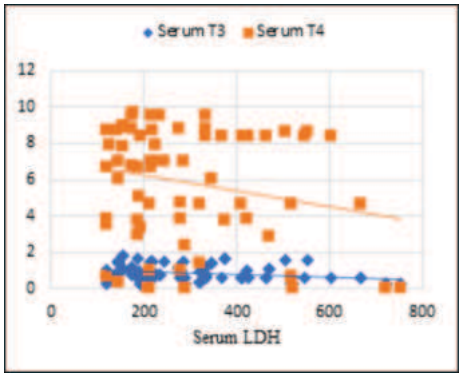

Figure-4: Scatterplot Diagram of Correlation Between Serum LDH With Serum T_3 and Serum T_4 in Patients of Hypothyroidism

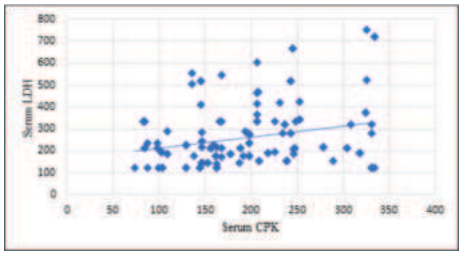

Figure-5: Scatterplot Diagram of Correlation Analysis Between Serum CPK and Serum LDH in Patients of Hypothyroidism

Table-2: Regression Analysis of Thyroid Profile With Serum CPK [*Statistically Significant]

Variables	Serum CPK		Serum LDH	
	t value	Adjusted R^2	t value	Adjusted R^2
Serum TSH	4.005 (p<0.001*)	0.245 (p<0.001*)	-2.853 (p=0.005*)	0.115 (p<0.001*)
Serum T_3	2.715 (p=0.007*)		-2.937 (p=0.004*)	
Serum T_4	-2.578 (p=0.011*)		-2.666 (p=0.009*)	

Regression analysis confirmed that thyroid hormone levels were significant predictors of muscle enzyme activities. TSH, T_3, and T_4 collectively explained 24.5% of the variation in serum CPK (p<0.001) and 11.5% of the variation in serum LDH (p<0.001) (Table-2). These findings support the mechanistic relationship between thyroid function and muscle integrity reported by Bloise et al., 2018[3], who described the molecular pathways by which thyroid hormones regulate skeletal muscle physiology. Similarly, Davies et al., 2020[22] identified the essential role of thyroid hormone receptor α in skeletal muscle for T3-mediated energy expenditure. The direct regulation of muscle gene expression by thyroid hormones through nuclear receptors accounts for this predictive relationship. The moderate R^2 values suggest that while thyroid function is important, other factors also contribute to muscle enzyme variations[25,26].

CONCLUSION

Present study demonstrates that serum CPK and LDH activities are significantly elevated in hypothyroidism, with more pronounced elevations in overt hypothyroidism compared to subclinical hypothyroidism. The significant correlations observed between thyroid hormones and muscle enzymes suggest a direct relationship between thyroid hormone deficiency and skeletal muscle damage. These findings establish serum CPK and LDH as valuable biomarkers for detecting skeletal muscle involvement in hypothyroidism and underscore the importance of routine assessment of muscle enzymes in hypothyroid patients. Early detection of muscle involvement through these biomarkers could facilitate timely intervention and management, potentially improving patient outcomes.

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