Research Article

Assessment of Creatine Kinase and Lactate Dehydrogenase in Type 2 Diabetes Mellitus: A Comparative Case-Control Analysis

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ABSTRACT

Background: Diabetes constitutes a worldwide epidemic, with type 2 diabetes representing the predominant form and elevating the risk of various cardiovascular complications. Furthermore, patients with Type 2 Diabetes Mellitus (T2DM) exhibit dysregulated glucose and lipid metabolism in their skeletal muscles.

Aim and Objectives: This study aimed to evaluate blood levels of Creatine Kinase (CK) and Lactate Dehydrogenase (LDH) in patients with Type 2 Diabetes Mellitus (T2DM) to healthy controls, to assess their potential as indicators of metabolic stress and glycaemic control.

Materials and Methods: Case-control research was conducted involving 200 participants: 100 individuals with Type 2 Diabetes Mellitus (T2DM) and 100 healthy controls. The levels of CK, LDH, and glycemic markers (HbA1c and Fasting plasma glucose) were assessed.

Results: CK and LDH values were substantially higher in T2DM patients than in controls ($p < 0.001$). HbA1c and fasting plasma glucose showed favourable correlations with LDH ($r = 0.55$; $p = <0.001$ and $r = 0.54$; $p = <0.001$ respectively). The glycaemic parameters and CK did not significantly correlate.

Conclusion: The findings imply that these enzymes could be useful indicators of metabolic stress in the treatment of diabetes. Further research is needed to determine their clinical value in tracking illness development.

Keywords: Creatine kinase, Lactate dehydrogenase, Type 2 Diabetes mellitus.

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a pervasive and heterogeneous metabolic disorder, characterized by chronic hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. It constitutes a significant global health burden, with a rapidly escalating prevalence, particularly in low- and middle-income countries [1]. The pathophysiological complexity of T2DM extends beyond glycemic control, as it is intricately associated with multisystem complications involving the cardiovascular, renal, neurological, and musculoskeletal systems [2, 3]. The global diabetes prevalence is anticipated to climb from 171 million in 2000 to 366 million by 2030, with India leading at 79.4 million [4]. Prolonged hyperglycemia and oxidative stress in the diabetic environment set off and spread a chain reaction of molecular and cellular dysfunctions that leads to subclinical organ damage. While significant research has been dedicated towards glucose monitoring and macrovascular risk prediction, there is still a pressing need for auxiliary biomarkers that can offer insights into early tissue injury and metabolic distress [5].

Creatine kinase (CK) and lactate dehydrogenase (LDH) are two ubiquitous intracellular enzymes that play key roles in cellular energy homeostasis and metabolic flux. Creatine Kinase (CK) is a pivotal phosphotransferase enzyme that governs the maintenance of cellular energy homeostasis,

particularly in tissues characterized by high metabolic flux, such as skeletal muscle, myocardium, and the central nervous system. It acts as an intracellular energy store that may quickly regenerate ATP during times of heightened energy demand by catalysing the reversible conversion of creatine and adenosine triphosphate (ATP) into phosphocreatine and adenosine diphosphate (ADP). CK exists in three tissue-specific isoforms: CK-MM (predominant in skeletal muscle), CK-MB (primarily in cardiac muscle), and CK-BB (abundant in brain and smooth muscle). Under physiological conditions, circulating CK levels are modest; however, structural damage to myocytes—due to ischaemia, inflammation, or metabolic injury—promotes its release into the bloodstream.

[6]. Elevated serum CK levels typically signify cellular membrane disruption or muscle degeneration, and have been implicated in diabetic myopathy and subclinical muscle damage associated with insulin resistance [7].

In T2DM, persistent hyperglycemia, impaired insulin signaling, and mitochondrial dysfunction synergistically contribute to muscular fatigue, atrophy, and subclinical myopathy, conditions that are commonly indicated by high CK activity [8]. In diabetic individuals, creatine kinase dimensions increase due to an increase in the isoenzyme, and the source of this expansion is skeletal muscle degradation induced by a loss in vitality. CK-MB and CK-BB are isoenzymes that have similarities. Skeletal muscle injury, specifically the CK-MM isoenzyme is the primary source of increased CK levels in diabetics [9].

Lactate dehydrogenase (LDH) is a cytosolic oxidoreductase enzyme involved in anaerobic glycolysis. It catalyzes the interconversion of pyruvate and lactate, playing a pivotal role in cellular energy metabolism, especially under hypoxic or metabolic stress conditions. LDH is ubiquitously distributed and exists in five isoenzymatic forms (LDH-1 to LDH-5), each with distinct tissue distributions [10]. LDH was utilised to diagnose various conditions, including myocardial infarction, vascular injury, tissue injury, advanced sarcoma, and other mesenchymal tumours [11]. LDH has been identified as a biomarker for disease prognosis, including tumours, metabolic-associated fatty liver disease, and malaria [12-13]. It can also predict lung pathology and the possibility of diabetes [14, 15].

Despite their clinical utility in other pathologies, the diagnostic and prognostic value of CK and LDH in T2DM remains underexplored. Existing literature offers contradictory findings—some investigations report elevated levels of these enzymes in diabetic patients, while others find no significant deviations when compared to normoglycemic individuals. This study seeks to investigate the serum levels of creatine kinase and lactate dehydrogenase in individuals with T2DM and to compare these with age- and sex-matched healthy controls. The study endeavours to elucidate whether these enzymes may serve as surrogate biomarkers for subclinical tissue injury in diabetic patients, thereby offering insight into the metabolic perturbations underpinning the disease process. Understanding the association between CK and LDH levels and T2DM could give clinicians with a non-invasive method of measuring cellular stress and potential damage, allowing for early detection and management of problems.

2. MATERIALS & METHODS

2.1. Study Design and Setting

A comparative case-control study was conducted in the Department of Biochemistry, in collaboration with the Department of General Medicine, Government Medical College, Chennai, Tamil Nadu. The study was conducted over a six-month period receiving ethical approval from the Institutional Ethics Committee. All participants provided written informed permission in accordance with the Declaration of Helsinki.

2.2. Study Population

The study included a total of 200 subjects, divided into two groups: 100 patients diagnosed with Type 2 Diabetes Mellitus (T2DM) as cases, and 100 age- and sex-matched apparently healthy individuals as controls.

2.1.1 Inclusion and Exclusion Criteria

Participants in the T2DM group were adults aged 35-70 years with a confirmed diagnosis of T2DM

according to the American Diabetes Association (ADA) criteria, including fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL on an oral glucose tolerance test, or HbA1c ≥6.5%. With 100 male and 100 female participants, matched for age, the study used an equal gender distribution to reduce gender-related confounding and improve the generalisability of findings between the T2DM and control groups. Pregnant and lactating women were excluded in order to prevent confounding metabolic effects. Individuals with Type 1 Diabetes Mellitus, gestational diabetes, chronic renal or liver illness, malignancies, recent infections, and known muscular diseases were excluded from both groups because they could affect CK and LDH levels separately. The control group consisted of non-diabetic adults with fasting plasma glucose <100 mg/dL and HbA1c <5.7%, with no history of diabetes or other chronic conditions impacting CK and LDH levels.

2.1.2 Sample Size Calculation

A sample size of 200 (100 cases and 100 controls) was chosen to ensure adequate power to detect a significant difference in CK and LDH levels between T2DM patients and controls. Based on a moderate effect size from previous studies, this sample size provided 80% power at a 5% significance level.

2.2. Data Collection and Biochemical Analysis

2.2.1 Blood Sample Collection and Analysis

Venous blood samples were taken from each participant following a minimum of eight hours of fasting during the night. Blood samples were centrifuged for 10 minutes at 3000 rpm to separate the serum, which was then kept at -20°C until analysis. Fasting plasma glucose was determined using the COBAS C 311 autoanalyzer through the hexokinase method. Similarly, HbA1c levels, which provide insight into long-term glycemic control, were analyzed using ion exchange High Performance Liquid Chromatography (HPLC), on the D10 analyzer. CK measured using semi autoanalyzer and LDH was measured according to IFCC in COBAS C 311 autoanalyzer. LDH activity was tested using the lactate-to-pyruvate reaction, whereas CK activity was evaluated using an enzymatic technique that involved creatine phosphate-to-creatine conversion.

2.2.2 Clinical and Anthropometric Data

A systematic questionnaire was used to gather clinical and demographic information, such as age, gender, and the length of time they have had the disease. Anthropometric parameters such as waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR) were recorded using standard WHO guidelines. Blood pressure and resting heart rate were also measured. Among the diabetic gorup, clinical records revealed that 31% had co-morbid conditions, including hypertension (18%), dyslipidemia (9%) and cardiovascular diseases (4%). Among T2DM patients, 86% were on oral hypoglycemic agents (OHAs) such as metformin and sulfonylureas, while the remaining 14% were treatment-naïve or on lifestyle modification alone. None of the patients were receiving insulin therapy, corticosteroids, or statins at the time of enrollment.

2.2.3 Statistical Analysis

SPSS software was used to analyse the statistical data (version 22). For continuous variables, descriptive statistics such as means and standard deviations were computed. The research parameters were compared between the controls and the patients using an unpaired t-test. To examine the relationships between CK, LDH, and clinical indicators (e.g., FPG, HbA1c), correlation analysis was conducted using either the Pearson or Spearman correlation coefficients, depending on the data distribution. A P-value of less than 0.05 was deemed statistically significant.

2.2.4 Quality Control

Strict quality control procedures were followed when performing any laboratory analysis. The intra-assay and inter-assay coefficients of variation were kept below 5%, and the analyser was calibrated every day. To lessen observer bias, lab staff who were evaluating samples were blinded to the participants group designations.

This methodological approach offers a solid basis for evaluating CK and LDH's potential as biomarkers in type 2 diabetes, allowing comparisons between groups with and without

diabetes to investigate their clinical significance in the disease.

3. RESULTS

The study included 200 participants, with 100 individuals in each group (T2DM and control). Table 1 shows baseline characteristics, including age, BMI, fasting plasma glucose (FPG), and HbA1c. T2DM patients had significantly higher BMI, FPG, and HbA1c levels than controls ($p < 0.05$). Additionally, waist circumference and waist-to-hip ratio were found to be significantly elevated in T2DM subjects, indicating central obesity.

Table 1: Baseline Characteristics of Study Participants

Variable	T2DM Group (n=100)	Control Group (n=100)	p-value*
Age (years)	51.50 ± 4.91	50.82 ± 4.44	0.3
BMI (kg/m²)	28.5 ± 4.2	24.1 ± 3.5	<0.001
FPG (mg/dL)	209.14 ± 56.19	95.62 ± 10.06	<0.001
HbA1c (%)	8.744 ± 1.971	5.049 ± 0.303	<0.001
BMI – Body mass index; BMI: Body Mass Index, HBA1c: Glycated haemoglobin *p<0.05 is considered statistically significant			

Table 2 displays the serum CK and LDH levels in both groups. T2DM patients had significantly higher levels of CK and LDH than controls ($p < 0.001$).

Table 2: CK and LDH Levels in T2DM and Control Groups

Variable	T2DM Group (n=100)	Control Group (n=100)	p-value*
CK(U/L)	96.46 ± 24.87	61.76 ± 14.43	<0.001
LDH(U/L)	304.96 ± 74.79	261.82 ± 53.32	<0.001
CK: Creatine Kinase, LDH: Lactate Dehydrogenase *p<0.05 is considered statistically significant			

As shown in Table 3, a positive correlation was observed between LDH and fasting plasma glucose as well as between LDH and HbA1c and this was found to be statistically significant. Figure 1 and 2 presents a scatter plot showing the correlation between LDH with glycemic parameters in T2DM group. However, CK levels did not show a significant correlation with FPG or HbA1c and no significant correlations were observed between these parameters in the control group. Figure 3 and 4 presents a scatter plot showing the correlation between CK and glycemic parameters in the T2DM group.

Table 3: Correlation Analysis Between CK, LDH, and Clinical Parameters in T2DM Patients and in Control groups

Cases		
Parameter	**CK**	**LDH**
FPG	r = -0.08; p = 0.41	r = 0.54; p= <0.001*
HbA1c	r = -0.07; p = 0.49	r = 0.55; p= <0.001*
Controls		
FPG	r = -0.03, p = 0.79	r = -0.13, p= 0.19
HbA1c	r = 0.05, p = 0.58	r = -0.06, p = 0.57
*p<0.05 is considered statistically significant		

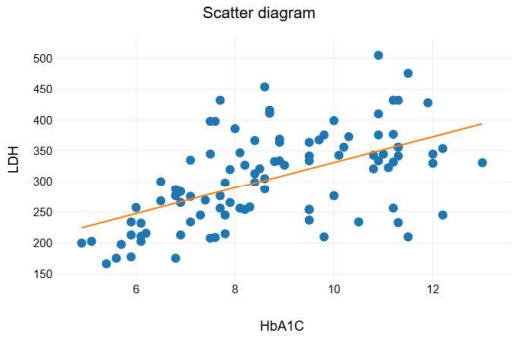

Figure 1: Scatter plot diagram showing correlation between LDH and HbA1c in T2DM

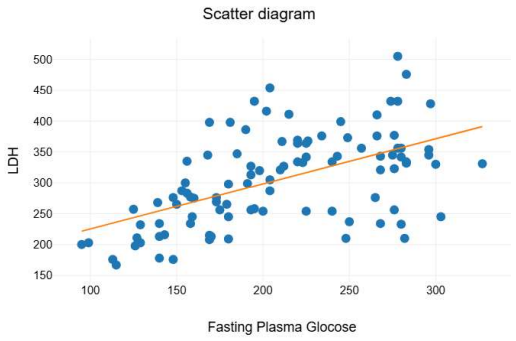

Figure 2: Scatter plot diagram showing correlation between LDH and fasting plasma glucose in T2DM

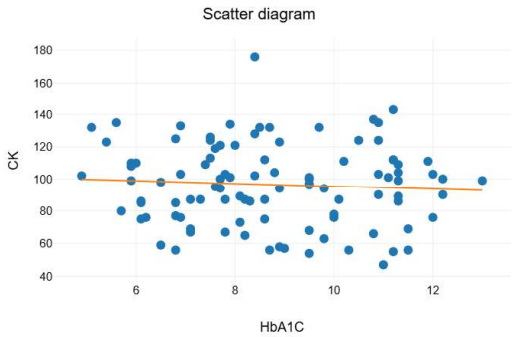

Figure 3: Scatter plot diagram showing correlation between CK and HbA1c in T2DM

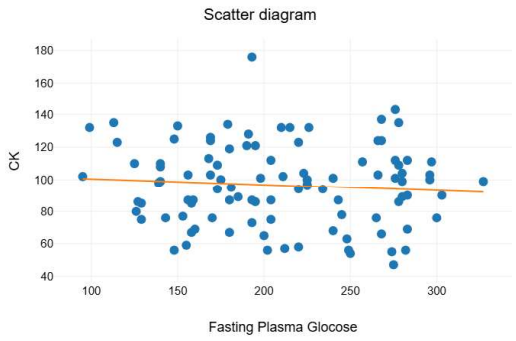

Figure 4: Scatter plot diagram showing correlation between CK and fasting plasma glucose in T2DM

4. DISCUSSION

Millions of individuals with diabetes continue to face substantial challenges due to well-documented traditional diabetic consequences. But as life expectancy has improved due to improvements in diabetes care, there is now evidence that a distinct group of complications from diabetes mellitus exists. As the mortality rate from vascular disease declines, diabetes mellitus is now the leading cause of death in many nations [16]. The present study sought to explore and compare anthropometric, glycemic, and biochemical enzyme profiles-specifically Creatine Kinase (CK) and Lactate Dehydrogenase (LDH)-between individuals with Type 2 Diabetes Mellitus (T2DM) and normoglycemic controls. The findings reveal a significant metabolic and biochemical disparity between the groups, offering insights into the systemic consequences of chronic hyperglycemia and insulin resistance.

Although the mean age did not significantly differ between T2DM participants and controls ($p = 0.3$), a marked increase in body mass index (BMI) was evident in the diabetic group (28.5 ± 4.2 kg/m²) compared to controls (24.1 ± 3.5 kg/m², $p < 0.001$). This aligns with the well-established role of obesity as a pathogenic driver of insulin resistance and β-cell dysfunction in T2DM, as highlighted by Kahn *et al.,* [17]. Adiposity-induced alterations in adipokine signaling and systemic inflammation are key contributors to metabolic dysregulation in diabetic populations. Furthermore, the significantly elevated fasting plasma glucose (209.14 ± 56.19 mg/dL) and HbA1c (8.74 ± 1.97%) in T2DM subjects compared to controls (FPG: 95.62 ± 10.06 mg/dL; HbA1c: 5.05 ± 0.30%) reflect poor glycemic control and persistent hyperglycemia ($p < 0.001$). Findings of Stratton *et al.,* [18] are supported by the substantial correlation between the development of microvascular and macrovascular problems and chronic glycaemic load.

Of particular interest in this study were the enzymatic markers CK and LDH, both of which were significantly elevated in the T2DM cohort. Serum CK levels were markedly higher in diabetic individuals (96.46 ± 24.87 U/L) compared to controls (61.76 ± 14.43 U/L, $p < 0.001$), suggesting subclinical skeletal muscle stress or altered muscle metabolism, potentially influenced by insulin resistance. LDH, a marker of cellular turnover and anaerobic glycolysis, was also significantly elevated in T2DM participants (304.96 ± 74.79 U/L vs. 261.82 ± 53.32 U/L; $p < 0.001$), indicating possible ongoing tissue stress or hypoxia-related metabolic shifts.

Multifactorial biochemical stress may be the cause of the diabetic group's markedly elevated CK and LDH levels. In those with type 2 diabetes, elevated CK levels may be a sign of subclinical myopathy, low-grade muscular inflammation, or underlying sarcopenia [19]. Meanwhile increased LDH activity may be attributed to chronic cellular hypoxia, mitochondrial dysfunction, and oxidative stress, which are hallmarks of the diabetic milieu [20]. Correlation analysis in the diabetic group revealed a statistically significant moderate positive correlation between LDH and both FPG ($r = 0.54$, $p < 0.001$) and HbA1c ($r = 0.55$, $p < 0.001$), suggesting that LDH may serve as a biochemical indicator of hyperglycemia-induced cellular stress. The study's findings were consistent with other research that found a considerable variance in LDH activity and a significant correlation between LDH activity and diabetes [21, 22] and also the relationship is explained by the direct measure of diabetes (glucose) and the indirect consequence of diabetes (LDH) [23-26]. In contrast, CK demonstrated weak and non-significant inverse

correlations with FPG (r = -0.08) and HbA1c (r = -0.07) and was not consistent with the study conducted in an Asian population [27]. Several studies showed a positive correlation between concentration of glucose and serum Creatine kinase activity was observed in Type I and Type II diabetic patients but not in the control groups [28]. These trends were not observed in the control group, emphasizing the metabolic specificity of these associations to the diabetic milieu.

It is crucial to integrate systematic lifestyle changes, such as consistent aerobic and resistance training, a balanced diet, weight optimisation, and stress-reduction methods, into clinical care. Furthermore, especially in sedentary or neuropathic patients, adjunctive therapies such as neuromuscular electrical stimulation (NMES) and transcutaneous electrical nerve stimulation (TENS) have demonstrated promise in boosting glycaemic control, lowering oxidative damage, and improving muscle metabolism [29-31]. Such therapeutic strategies should be incorporated into future research to assess their impact on the dynamics of CK and LDH in diabetic populations.

Elevated CK and LDH levels in T2DM indicate a shift towards anaerobic metabolism and mitochondrial inefficiency, supporting the hypothesis that T2DM is linked to impaired cellular energy production [32]. In light of these observations, CK and LDH may serve as potential biomarkers indicative of underlying metabolic stress in T2DM patients. However, definitive causal inferences remain limited due to the cross-sectional design of the study and absence of longitudinal or interventional clinical data. Nonetheless, the persistent elevation of these enzymes-especially among individuals with suboptimal glycemic control and associated comorbidities-underscores the need for vigilant biochemical monitoring in routine clinical practice.

5. CONCLUSION

This comparative case-control study underscores the profound biochemical and metabolic alterations associated with Type 2 Diabetes Mellitus (T2DM), highlighting significant elevations in serum creatine kinase (CK) and lactate dehydrogenase (LDH) among diabetic individuals in contrast to healthy controls. While traditional glycemic markers such as fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) effectively reflect chronic hyperglycemia, the concurrent rise in CK and LDH may signal broader systemic perturbations, including subclinical muscle injury, metabolic stress, and cellular turnover.

The significantly elevated LDH levels, coupled with their moderate positive correlations with both FPG and HbA1c, imply that LDH may serve as a supplementary biomarker indicative of ongoing glycemic insult and tissue stress in T2DM. Although CK levels were also increased, their weak inverse correlation with glycemic indices implies a more complex, perhaps muscle mass–related, interaction that merits further exploration. These findings align with growing evidence suggesting that T2DM is not solely a disorder of glucose metabolism but also a condition involving multisystem dysfunction.

These findings emphasise the importance of comprehensive metabolic monitoring in diabetes patients, which includes both traditional and new biochemical indicators. Further longitudinal and mechanistic studies are recommended to delineate the diagnostic and prognostic significance of CK and LDH in the context of diabetes-related complications and therapeutic outcomes.

6. LIMITATIONS OF THIS STUDY

Despite its valuable insights, the present study is not without limitations. First, its cross-sectional nature makes it impossible to demonstrate causal links between glycaemic state and enzyme changes. Second, the study did not take into consideration confounding factors such as physical activity levels, muscle mass indices, diabetes duration, medication history, or the presence of subclinical problems, all of which could affect CK and LDH levels. Furthermore, isoenzyme differentiation was not done, which could have improved specificity about the tissue origin of enzyme increases. Finally, because this is a single-center study with a small sample size,

the generalisability of the results may be limited, necessitating bigger multicenter trials.

CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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