Assessment of Brain Natriuretic Peptide (BNP) and Lactate Dehydrogenase (LDH) levels in type 2 Diabetic Patients with Cardiovascular Disease

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Abstract

The metabolic condition type 2 diabetes mellitus (T2DM) causes organ malfunction and damage due to insulin secretion or resistance abnormalities. The clinical assessment of monitoring short-term blood glucose variability could benefit from the addition of a less interference-prone biomarker for nutritional status and blood cell health. In type 2 diabetic individuals with cardiovascular disease (CVD), this study looks at the significance of serum B-type natriuretic peptide (BNP) and lactate dehydrogenase (LDH) and how it relates to other variables. This study included 100 T2DM patients with cardiovascular disease (57 males and 43 females) with 70 healthy controls (39 males and 31 females) aged 45 to >74 years with a diabetes duration of 12 to 26 years. the present study shows that in T2DM patients with CVD, there was an increase in Brain Naturiertic Peptide and a high increase in LDH levels. The statistical significance of these differences is very significant (P>0.001). Comparing the patient group to the control group, there is a highly significant increase in BNP and LDH. BNP and LDH were greater in people with type 2 diabetes who also had cardiovascular disease (CVD) and elevated LDH level was associated with elevated BNP. BNP and LDH are useful biomarkers that support diagnosis, and risk assessment, as well as the diagnosis and management of cardiovascular disease in diabetic individuals by facilitating the assessment of heart function and risk factors for cardiovascular disease.

Introduction

Diabetes type 2 (hyperglycemia) is a persistent metabolic condition marked by high levels of glucose in the blood, caused by the body's insufficient synthesis or use of insulin.Moreover, diabetes gives rise to numerous persistent issues that significantly impair an individual's overall health and welfare.Diabetes carries a significant risk of getting cardiovascular disease (CVD), Heart failure, stroke, and coronary artery disease are the primary factors leading to mortality and impairment in individuals with diabetes. Multiple studies indicate that those with diabetes have a 2 to 4 times higher likelihood of developing cardiovascular disease (CVD). Several factors, including systemic inflammation, hypertension, dyslipidemia, and insulin resistance, contribute to the formation and worsening of atherosclerosis. Diabetes increases the likelihood of heart issues by worsening endothelial dysfunction, oxidative stress, and inadequate platelet function[1]. T2DM is distinguished by the presence of inflammation throughout the body, impaired functioning of the beta cells in the pancreas, and high levels of glucose in the blood due to inadequate production or utilization of insulin [2]. Diabetes complications can be categorized as either macrovascular (such as cardiovascular disease) or microvascular (such as kidney, retina, and nervous system issues)[3]. These disorders are among the complications of diabetes mellitus and contribute to both illness and death [4]. BNP, also known as B-type or brain natriuretic peptide, was initially identified in the brains of pigs. However, further research demonstrated that BNP functions as a cardiac hormone in humans and serves as a highly effective diagnostic for heart failure. The reason for this is that plasma BNP levels rise in direct correlation to the seriousness of heart failure and can quickly rise or fall in reaction to changes in a patient's physiological condition[5].ProBNP, also known as pro-B-type natriuretic peptide, is released by cardiomyocytes when they are stretched. It is rapidly broken down into two fragments that circulate in the body. One fragment is the active form of the peptide, called C-terminal BNP, which consists of 32 amino acids. The other fragment is the inactive form, called NT-proBNP, which consists of 76 amino acids and is located at the N-terminal.The numbers are 1 and 2. Both pieces are commonly employed to help in the diagnosis of heart failure, forecast outcomes, and monitor the impact of therapy[6].B-type natriuretic peptide (BNP) This hormone, which are produced by the heart, have physiological effects on glucose and lipid metabolism in addition to cardiovascular homeostasis. Lipolysis, browning of white adipocytes, oxygen consumption, glucose uptake in adipose tissue, and modulation of cytokine and adipokine responses are all enhanced by both natriuretic peptides (NPs). The cumulative consequence of these physiological changes is an improvement in insulin

resistance and glucose regulation [7]. BNP is primarily synthesized in response to cardiac stress or pathogenic stimuli[8]. Guidelines support BNP and N-terminal-proBNP (NT-proBNP) tests for the diagnosis, prognosis, and guided therapy of heart failure, as well as for risk stratification in patients with acute coronary syndromes. Lactate dehydrogenase (LDH) is a crucial enzyme in the anaerobic metabolic cycle. There exists an enzyme that is present in both plants and animals. It has a widespread distribution across various organs and plays a vital role. "checkpoint" for DNA metabolism and gluconeogenesis. It is frequently used to identify tissue damage, several forms of malignant malignancies, and myocardial infarction. One useful tool for diagnosing myocardial infarction is the LDH level. According to research by Komolafe et al [9]. The enzyme lactate dehydrogenase (LDH) is responsible for converting the reduced form of nicotinamide adenine dinucleotide (NADH) to its oxidized form. This conversion is crucial for glycolysis in cytoplasmic anaerobic metabolism. LDH converts pyruvate into lactate, leading to the production of ATP, which serves as the primary energy source in humans. The LDHA (also known as LDH-M) and LDHB (also known as LDH-H) subunits can be represented as LDH1 = 4H, LDH2 = 3H1M, LDH3 = 2H2M, LDH4 = 1H3M, and LDH5 = 4M.homomeric and dimeric tetramers make up the five LDH isoforms. Heart LDH1 predominates, whereas skeletal muscle LDH5. LDH can be found in many different tissues, including the kidney, liver, pancreas, brain, skeletal muscle, heart, and lung. The pathogenic conditions of acute tissue or cellular injury are indicated by the elevated LDH. Prior research has shown that increased sLDH is linked to several health issues, such as osteoporosis, cirrhosis of the liver, hypoxia, congestive heart failure (CHF), inflammatory disease, chronic obstructive pulmonary disease (COPD), human immunodeficiency diseases, and cancer. Furthermore, greater sLDH raised the risk of all-cause mortality in US populations with metabolic syndrome and improved the cardiovascular mortality of people in Taiwan who had long-term exposure to arsenic [10]. Furthermore, a possible association between LDH levels and cardiovascular mortality has been studied. An observational study of 12,597 participants revealed a possible correlation between higher LDH levels and arterial stiffness (AS) as well as a 10-year risk of cardiovascular disease (CVD)[11].Most body cells contain the enzyme lactate dehydrogenase (LDH). It is important to note that LDH is primarily found in the cell's cytoplasm and turns extracellular during cell death. It has been suggested that the energy needs of various tissues influence the variation of LDH concentrations. In blood and saliva, there are multiple isoenzymes for LDH with varying activity. Where LDH4 and LDH5 are primarily found in saliva, LDH1 and LDH2 are primarily found in blood. In people with diabetes,

insulin is released in response to glucose concentrations, regulating sugar metabolism through the process of glycolysis and subsequently via the mitochondrial oxidation of pyruvate, Glycolysis is thought to trigger the release of insulin[12].

Methods

The investigation was conducted at consultation clinics in Iraq's Baquba Teaching Hospital from January to March 2024. The study comprised a total of 170 participants, The study included a cohort of 100 individuals diagnosed with both type 2 diabetes and cardiovascular disease, comprising 57 males and 43 females. Additionally, there were 70 healthy controls, consisting of 39 males and 31 females, who were either medical professionals or family members. The participants' ages ranged from 45 to 74 years old. A 5 ml single-use syringe was utilized to obtain a 5 ml blood sample by a vein puncture. During the period from nine to noon, the blood sample was divided into two equal parts. The vacationer gel tube was utilized for the administration of the initial blood sample. Centrifugation was utilized to gather serum after it had coagulated at a temperature of 25 Celsius for 5 minutes. The serum was subsequently employed to assess random blood glucose levels. After adding the 2.5 ml second component, the blood sample is transferred to a tube that contains an anticoagulant called ethylene diamine tetraacetic acid/EDTA, it was utilized to measure RBS, HbA1c, and the Lipid profile was measured using An automated spectrophotometer (Roche cobas E411), whereas BNP and LDH were measured using sandwich ELISA.

Statistical analysis.

The data for this study was evaluated, coded, and analyzed using the "Statistical Package of Social Science (SPSS) version 26.0".Use mathematical presentation methods like mean and standard error, tabular data presentation using a complicated frequency distribution table, and t-test for independent samples to display data. Statistical significance was applied by a p-value less than 0.001.

Results

The study's findings revealed differences in the levels of RBS and HbA1c between diabetic patients with CVD and the controls. Table (1) shows that P-values for these differences are ≤0.0001, indicating a high level of statistical significance. Table (1) shows the value of Total Cholesterol in the control

group was (178.51 ±32.70) while in the patient's group was (214.82 ±22.54). These variations were statistically significant (HS) (P≤0.001). The value of Triglycerides in the control group was (149.47 ±25.81) while in the patient's group was (198.89 ±15.76). These differences were statistically significant (HS) (P≤0.001). Also, LDL in the control group was (101.50 ±33.06) while in the patients group was (126.74 ±29.10). These differences were statistically significant (HS) (P≤0.0001). While HDL in the control was (45.79 ±5.87) while in the patients group was (48.21 ±6.13), Statistics showed that these differences were (HS) (P≤0.0001). And VLDL value in the control group was (30.01 ±5.34) while in the patients' group was (39.87 ±3.16). These differences were statistically highly significant (P≤0.001) as shown in table (1)below.

Table (1): Comparison between patients and controls in some examined biochemical parameters

Parameters	Patients	Control	t-test	p-value
RBS (76-126 mg/dl)			17.64	≤0.0001 (H.S)
Mean±SD	226.66 ±67.02	97.75 ±14.46		
HbA1C (4-5.7 %)			17.04	≤0.0001 (H.S)
Mean±SD	9.17 ±1.76	5.75 ±0.57		
Cholesterol (<200 mg/dl) Mean±SD			7.49	≤0.0001 (H.S)
	214.82 ±22.54	178.51±32.70		
Triglycerides (<150 mg/dl) Mean±SD			13.27	< 0.0001 (H.S)
	198.89 ±15.76	149.47 ±25.81		
HDL (>40 mg/dl) Mean±SD			2.42	≤0.0001 (H.S)
	48.21 ±6.13	45.79 ±5.87		
LDL (<133 mg/dl) Mean±SD			4.8	
	126.74 ±29.10	101.50±33.06		

				≤0.0001(H.S)
VLDL (25-35 mg/dl)			12.86	≤0.0001 (H.S)
Mean±SD	39.87 ±3.16	30.01 ±5.34		

Results of Table (2) show a comparison of the serum levels of LDH and BNP between the group of diabetic type 2 patients with CVD and the control group. The mean serum BNP level was significantly higher in patients compared to the controls, with values of (1024.15±181.19) and (406.92±113.81) respectively, and t-test =5.08 with p-values ≤0.0001(H.S). The average serum of BNP was significantly higher in patients compared to control (healthy), (125.82±46.78)(42.00±5.62) respectively and t-test=16.81 with p--value ≤0.0001(H.S)

Table(2): Comparison of BNP and LDH between diabetic type 2 patients with CVD and healthy control.

Characteristics	Patinets group(100)	Control group(70)	T-test	P-value
LDH (258-689 pg/ml)				
Mean±SD	(1024.15±181.19)	(406.92±113.81)	5.08	≤0.0001(H.S)
BNP (30-50 pg/ml)			16.81	≤0.0001(H.S)
Mean±SD	(125.82±46.78)	(42.00±5.62)		

***T-test for independent samles to evaluate the differences between two different samles (patients &controls),the greater value of t-test greater the probability that differences between thevmeans will be statistically significant.**

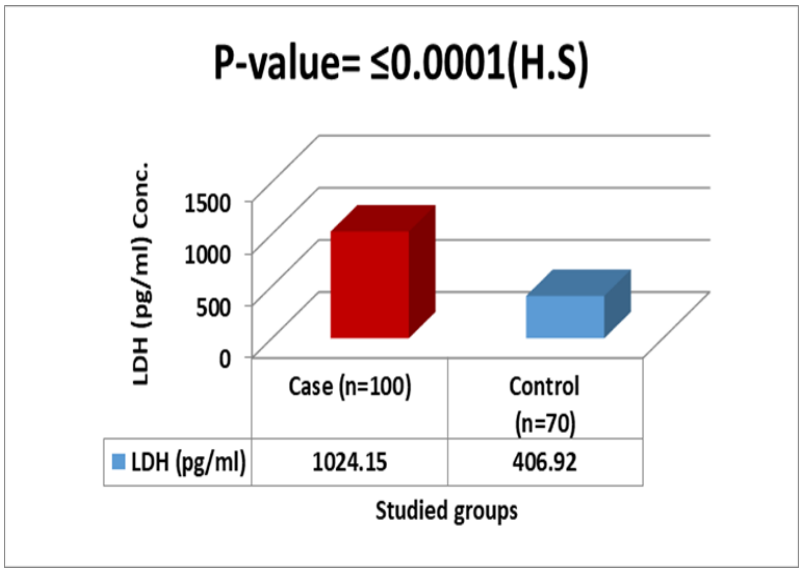

Figure 1 displays the comprasion of LDH between diabetic type 2patients with Cardiovascular diseas and healthy control .

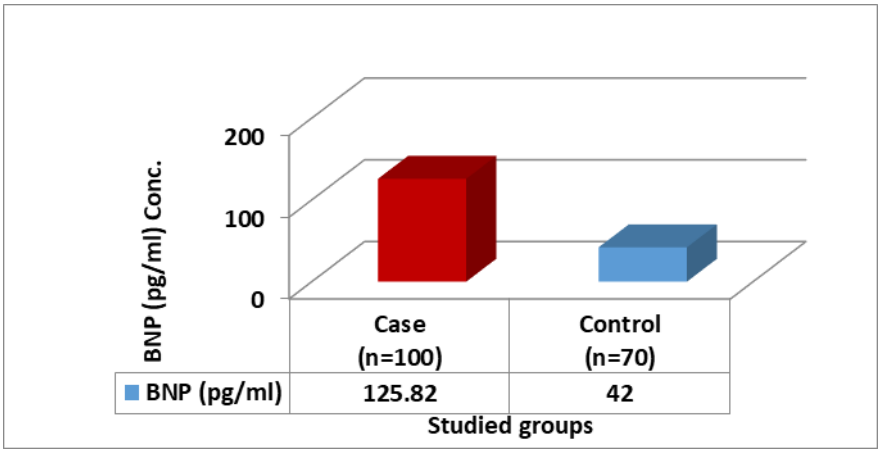

Figure 2 displays the comprasion of BNP between diabetic type 2 patients with cardiovascular disease and healthy control.

The current investigation discovered a considerable positive correlation between BNP levels and FBS, as demonstrated by Pearson's link Coefficient (r=.616) and p-value ≤0.001. BNP levels have a moderate positive connection with HbA1c, triglycerides, and VLDL (r=.564, .596, .597) with p-values ≤0.001, respectively. BNP levels have a weak positive connection with cholesterol, LDL, and HDL (r= .363, .077, .229) p-values. 240, ≤0.001, .352, .005), respectively. This implies that there is a very modest positive association

between the levels of BNP and other parameters in patients and control, as arranged in Table (3)

Table (3) shows the correlation between BNP and the examined parameters in patients and controls.

Test	BNP		Status
	R	P	
Cholesterol (mg/dl)	.363	≤0.0001	Weak positive correlations
FBS (mg/dl)	.616	≤0.0001	Strong positive correlations
LDH(pg/ml)	.735	≤0.0001	
Triglyceride (mg/dl)	.564	≤0.0001	Moderate positive association
HbA1c (%)	.596	≤0.0001	
VLDL(mg/dl)	.597	≤0.0001	
HDL(mg/dl)	.077	.352	Weak Positive correlation
LDL(mg/dl)	.229	.005	

The current investigation found a significant positive association between

LDH levels and RBS, HbA1C, triglycerides, and VLDL (r=-.687, .662 , .688, .687) with p-values ≤0.0001. LDH levels have a weak positive connection with Cholesterol, HDL, and LDL (r= .414, .108, .278), with p-values ≤0.0001, respectively. As shown in Table (4).

Table (4): Correlation of the LDH levels with measured parameters of diabetic type 2 with CVD patients and control.

Test	LDH		Status
	R	P	
Cholesterol (mg/dl)	.414	≤0.0001	Weak positive association
RBS (mg/dl)	.687	≤0.0001	Strong positive association
HbA1c (%)	.662	≤0.0001	
Triglyceride (mg/dl)	.688	≤0.0001	
HDL(mg/dl)	.108	.187	Weak positive association
LDL(mg/dl)	.278	≤0.0001	
VLDL(mg/dl)	.687	≤0.0001	Strong positive association
BNP(pg/ml)	.735	≤0.0001	

Discussion

According to the present study serum RBS& HbA1c high levels among type 2 patients with CVD and it is known DM is defined by high plasma glucose levels (hyperglycemia)[13] this aligns with the results in Table (2) which mean glucose levels in patients and participants had significantly increased. As we age our beta cells lose their ability to compensate for increased insulin resistance, leading to decreased function. It affects insulin sensitivity and the progression of glucose intolerance in the elderly. [14], also agree with the study [15]. In our study mean of HbA1c patients and control groups was significantly different and this agrees with [16]and [17].BNP is positively correlated with diabetic 2 patients associated with adiponectin, a particular adipokine produced by adipocytes that has anti-inflammatory and anti-atherosclerosis properties. Adiponectin is involved in the chronic low-grade inflammation associated with Metabolic Syndrome (MetS)[8]**.** Cardiomyocytes secrete BNP in reaction to biomechanical strain, excessive volume, damage to the heart muscle, lack of blood supply, cell death, restoration of blood flow, metabolic disturbances, or toxic harm**.**BNP plays a crucial influence in early HF diagnosis, according to studies. Though referred to as "brain natriuretic peptide," BNP production begins in the ventricular myocardium, making it a sign of hemodynamic stress. Research indicates that DM2 is a significant risk factor for developing diabetes complications, including HF. BNP is a utilized marker. BNP measures HF severity biologically. High laboratory sensitivity and specificity make BNP a useful biomarker for early diagnosis and treatment optimization, monitoring the effectiveness of therapy.Our research indicates that patients with CVD and type 2 diabetes had greater BNP levels and upper LDH levels, confirming a negative correlation Metabolic problems affect the development and progression of HF in this concomitant disease [18]. NT-proBNP levels exhibit a correlation with lipid markers in a group of individuals who are quite advanced in age. We focused our study on individuals who are in an advanced stage of old age, as they frequently exhibit elevated or exceptionally elevated levels of NT-proBNP, even in the absence of a formal diagnosis of heart failure. Increased NT-proBNP levels were correlated with decreased TC, LDLc, and non-HDLc, even after accounting for potential confounding variables [19]. The key finding from this study is that diabetic patients with certain conduction anomalies in their electrocardiograms are more likely to have elevated NT-proBNP levels and this agrees [20]. There is a strong association between the serum LDH level and the incidence of CVDs and cardiovascular events[9]. Globally, the measurements of sLDH have been applied in clinical settings as markers of numerous organ diseases,

inflammatory illness, muscular exhaustion, and tissue damage. Cancer and other chronic diseases may be significantly influenced by the persistent inflammatory process. Metabolic syndrome (MetS) is seen as a long-term inflammatory condition. Recent research has shown a connection between obesity and type 2 diabetes, IR, and chronic inflammation, particularly inflammation of the skeletal muscles.[10]We discovered that the trend for higher LDH to raise the risk of cardiovascular mortality was constant throughout the different substrata[11]. It has been shown that serum LDH can signal a wide range of illnesses or conditions. The study's findings suggest that unstable hyperglycemia fluctuation and uncontrollably high blood LDH levels may also be indicators of these conditions. Here, we showed a relationship between serum DM type2(RBS&HbA1c) and LDH levels and a diabetic hematological marker, specifically aberrant increased LDH[21].

Conclusion

Those in the healthy control group had lower levels of BNP and LDH compared to those with the disorder (T2DM &CVD). This is because chronic metabolic syndrome (high glucose) damages blood vessels, which in turn increases pressure on the heart (and potentially damages cardiomyocytes) and this will increase levels of these biomarkers.

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