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*Original Article*

# Correlation of blood glucose level and blood pH value with cardiac enzyme, amylase and other markers in patients with diabetic ketoacidosis

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**Abstract:** Purpose: To investigate the correlation of blood glucose level and blood pH value with the cardiac enzyme, amylase (AMY) and other markers in patients with diabetic ketoacidosis (DKA). Methods: A total of 96 patients with diabetes mellitus were enrolled. According to whether these diabetic patients were accompanied with ketoacidosis, they were divided into 49 patients with DKA (observation group) and 47 patients only with diabetes mellitus (control group). Changes in blood glucose levels, blood pH values, cardiac zymetology indexes (creatine phosphokinase (CPK), aspartate aminotransferase (AST), creatine kinase-MB (CPK-MB) and lactate dehydrogenase (LDH) and AMY in the blood were detected and the correlation analysis was conducted. Results: The levels of CPK, AST, CPK-MB, LDH and AMY in the observation group were significantly higher than those in the control group. The fasting blood glucose (FBG) or 2 h postprandial blood glucose (2hPBG) levels in the observation group were significantly higher than those in the control group ($P < 0.05$). Pearson product-moment correlation coefficient (PPMCC) showed that the blood glucose level was positively correlated with CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$), while the blood pH value was negatively correlated with CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$). Conclusion: The persistently high blood glucose levels and reduced blood pH values in patients with DKA can lead to abnormal increases in cardiac enzymes and amylases. We paid close attention to the changes in blood glucose levels and blood pH values in patients with DKA and took effective measures to relieve patients' illness.

**Keywords:** Diabetes mellitus type 2, ketoacidosis, cardiac enzymogram, AMY

## Introduction

Diabetes mellitus is seriously threatening human health. It is estimated that the global population of diabetic patients will reach 500 million by 2030 [1]. Diabetes complications, such as diabetic ketoacidosis (DKA), are difficult to be cured and potentially fatal [2]. DKA is mainly clinically manifested as dehydration and hyperglycemia metabolic acidosis [3]. DKA patients may have different degrees of myocardial injuries, and the cardiac enzymogram is an important indicator of myocardial damages, including creatine phosphokinase (CPK), aspartate aminotransferase (AST), creatine kinase-MB (CPK-MB) and lactate dehydrogenase (LDH) [4, 5]. High amylase (AMY) levels is an important indicator of pancreatitis in DKA patients, and the incidence rate of it combined with hyperamylasemia reaches 40%-75% [6]. In this study, blood glucose levels, blood pH values, cardiac enzymes and amylases were measured, and correlation analysis was carried out to provide a basis for the diagnosis and treatment in the early stage of DKA.

## Materials and methods

Totally, 96 patients with diabetes mellitus type 2 (T2DM) who were admitted to our hospital from January 2016 to December 2016 were selected. According to whether these diabetic patients were accompanied with ketoacidosis, they were divided into 47 patients only with T2DM (the control group) and 49 patients with T2DM and DKA (the observation group). Inclusion criteria: 1) All patients met the diagnostic criteria for T2DM: fasting blood glucose (FBG) levels ≥ 7.8 mmol/L or 2 h postprandial blood glucose (2hPBG) levels ≥ 11.1 mmol/L; 2)

**Table 1.** Baseline data of patients in two groups

| Item | Observation group (n = 49) | Control group (n = 47) | $t/\chi^2$ | *p* |
|---|---|---|---|---|
| Age (years old) | 35~80 | 35~78 | | |
| Gender (male/female) | 29/20 | 27/20 | 0.001 | 0.973 |
| Average age (years old) | 57.36 ± 8.45 | 56.95 ± 8.13 | 0.242 | 0.809 |
| Educational level | | | | |
| Junior high school or below | 16 (32.65) | 15 (31.91) | 0.222 | 0.895 |
| Senior high school or technical secondary school | 19 (38.78) | 19 (40.42) | | |
| Junior college or above | 14 (28.57) | 11 (23.40) | | |
| Smoking (n, %) | 19 (38.78) | 18 (38.29) | 0.026 | 0.872 |
| Alcohol drinking (n, %) | 21 (42.85) | 19 (40.42) | 0.318 | 0.573 |

**Table 2.** Comparisons of cardiac enzyme and AMY indicators between the two groups

| Group | Case | CPK (IU/L) | AST (IU/L) | CPK-MB (U/L) | LDH (U/L) | AMY (U/L) |
|---|---|---|---|---|---|---|
| Observation group | 49 | 98.95 ± 15.13 | 73.97 ± 21.47 | 17.76 ± 3.38 | 165.79 ± 23.78 | 94.64 ± 9.62 |
| Control group | 47 | 43.69 ± 9.06 | 18.93 ± 9.36 | 4.43 ± 1.27 | 129.73 ± 20.16 | 85.31 ± 9.15 |
| *t* | | 21.597 | 16.161 | 25.370 | 7.998 | 4.865 |
| *p* | | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

DKA diagnostic criteria: urine ketone tested to be positive, blood ketone > 0.3 mmol/L and pH value by blood gas analysis < 7.35, suggesting the metabolic acidosis; 3) Patients signed the informed consent. Exclusion criteria: 1) Patients with chronic hepatitis A, hepatitis B, coronary heart disease or malignant tumors; 2) Patients took analgesics, diuretics, statins, aspirin tablets or other non-steroidal drugs recently. This study was reviewed and approved by the Ethics Committee of our hospital. There were no significant differences in general data between the two groups ($P > 0.05$) (**Table 1**).

FBG and 2hPBG were detected on the day of the admission of patients by the blood glucose monitor (Guilin Zhonghui Technology Development Co., Ltd). Forearm arterial blood was collected and then placed in heparin anticoagulant tubes. Within 30 minutes, a PL2200 Ruifeng blood gas analyzer (Nanjing Perlong Medical Equipment Co., Ltd) was used to analyze blood pH. An Abbott's blood glucose and ketone analyzer (Abbott, U.S.) was used to detect blood ketones. An Olympus AU5400 automatic biochemistry analyzer (Beckman Coulter, Inc., U.S.) was used to detect the cardiac enzymogram, including CPK, AST, CPK-MB and LDH levels. If there were abnormalities, we would have a review every day until these abnormalities returned to the normal state. Heart-related tests were performed for all patients, including 12-lead electrocardiogram (ECG), cardiac color Doppler ultrasonography and left ventricular function detection, and the 24-hour ambulatory ECG monitoring should be conducted if arrhythmia occurred.

The levels of CPK, AST, CPK-MB, LDH and AMY were measured by an automatic biochemical analyzer. FBG, 2hPBG and blood pH values were measured by blood sampling. Then the PH index value was determined as follows: PH < 7.35 represented acidosis while PH > 7.45 represented alkalosis.

Data were processed using Statistical Product and Service Solutions (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA) software. The measurement data were expressed as mean ± standard deviation ($\overline{x} \pm s$) and detected by t test; count data were represented as ratio and detected by $X^2$ test. The correlation was analyzed by Pearson correlation coefficient. $P < 0.05$ represented that the difference was statistically significant.

## Results

Cardiac enzymes and AMY indicators of patients in both groups were compared and the results showed that the levels of CPK, AST, CPK-MB, LDH and AMY in the observation group were significantly higher than those in the control group ($P < 0.05$, **Table 2**).

**Table 3.** Comparisons of blood glucose levels (mmol/L) and blood pH values between the two groups

| Group | Case (n) | FBG (mmol/L) | 2hPBG (mmol/L) | pH |
|---|---|---|---|---|
| Observation group | 49 | 9.98 ± 3.15 | 13.48 ± 3.35 | 7.28 ± 0.19 |
| Control group | 47 | 7.83 ± 3.04 | 11.45 ± 3.23 | 7.39 ± 0.17 |
| *t* | | 3.401 | 3.020 | 2.985 |
| *p* | | 0.001 | 0.003 | 0.004 |

After the comparisons of blood glucose levels and blood pH values between the two groups, it could be found that the levels of FBG and 2hPBG in the observation group were significantly higher than those in the control group ($P < 0.05$), while the blood pH value in the observation group was significantly lower than that in the control group ($P < 0.05$, **Table 3**).

The correlation of blood glucose levels with cardiac enzyme and amylase indicators was analyzed by Pearson correlation coefficients. The results showed that blood glucose levels were positively correlated with the levels of CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$, **Figure 1**; **Table 4**).

The correlation of blood pH values with CPK, AST, CPK-MB, LDH and AMY was analyzed by Pearson correlation coefficients. Blood glucose levels were negatively correlated with the levels of CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$, **Table 5**; **Figure 2**).

## Discussion

DKA is one of the common complications of diabetes, and it is a clinical syndrome represented as the imbalance between water-electrolytes and acid-base equilibrium caused by a serious lack of insulin, mainly characterized by dehydration and hyperglycemia metabolic acidosis [7]. DKA occurs when acute diabetes of patients become severe. At that time, the blood glucose is significantly increased, insulin lacks activity, the blood ketone body is elevated and the ketone excretion is increased. When it occurs, the body is in the state of hypoxia and dehydration with relatively low immune resistance, so patients often fall into high blood potassium or low blood sodium state. With the progression of the disease, patients will suffer mental disorders, coma and other symptoms and even die [8]. DKA has many inducing factors, including alcohol, improper diet, acute pancreatitis, myocardial infarction, drugs and other factors [9]. The mechanism of DKA is that when the acute diabetes occurs, the glucose metabolism becomes seriously disordered, thus making oxaloacetates deficient and keeping the acetyl-CoA outside the tricarboxylic acid cycle so as to be condensed into a ketone body. Decreased effective insulins in the body lead to decreased protein synthesis and increased blood ketone amino acid, thus further increasing blood ketones. Increased insulin antagonist hormones in the body enable a large number of free fatty acids to enter the blood circulation, thus causing the unlimited oxidation and decomposition of fatty acids in the liver and generating a large number of ketones. The formation of β-hydroxybutyric acid, acetoacetic acid and acetone leads to the metabolic acidosis finally [10, 11].

Cardiac enzymes are collectively referred as a variety of enzymes in the myocardium and include CPK, AST, CPK-MB and LDH. CPK is mainly distributed in the skeletal muscle and myocardium of the human body and is the main phosphorylase that can form energy. It can provide energy sources for muscle contraction and transportation system [12]. AST is a relatively important transaminase mainly distributed in the cardiomyocytes and liver. When the tissue is damaged, the serum AST concentration increases, so it is often used as an indicator of disease diagnosis and prognosis [13]. CPK-MB is a dimer of two subunits of creatine phosphokinase (CK), which is mainly distributed in the myocardium and its serum concentration increases when the myocardium gets injured [14]. When DKA occurs, the hypertonic state of hyperglycemia can lead to ischemia, hypoxia and myocardial injury. The results of this study showed that the levels of CPK, AST, CPK-MB and LDH in the observation group were significantly higher than those in the control group ($P < 0.05$) as the occurrence of DKA put the body into the dehydrated state, thus leading to hypoxia and ischemia of myocardial tissues. Meanwhile, the high osmotic pressure of the hyperglycemia will increase the permeability of the cell membrane and cell metabolism

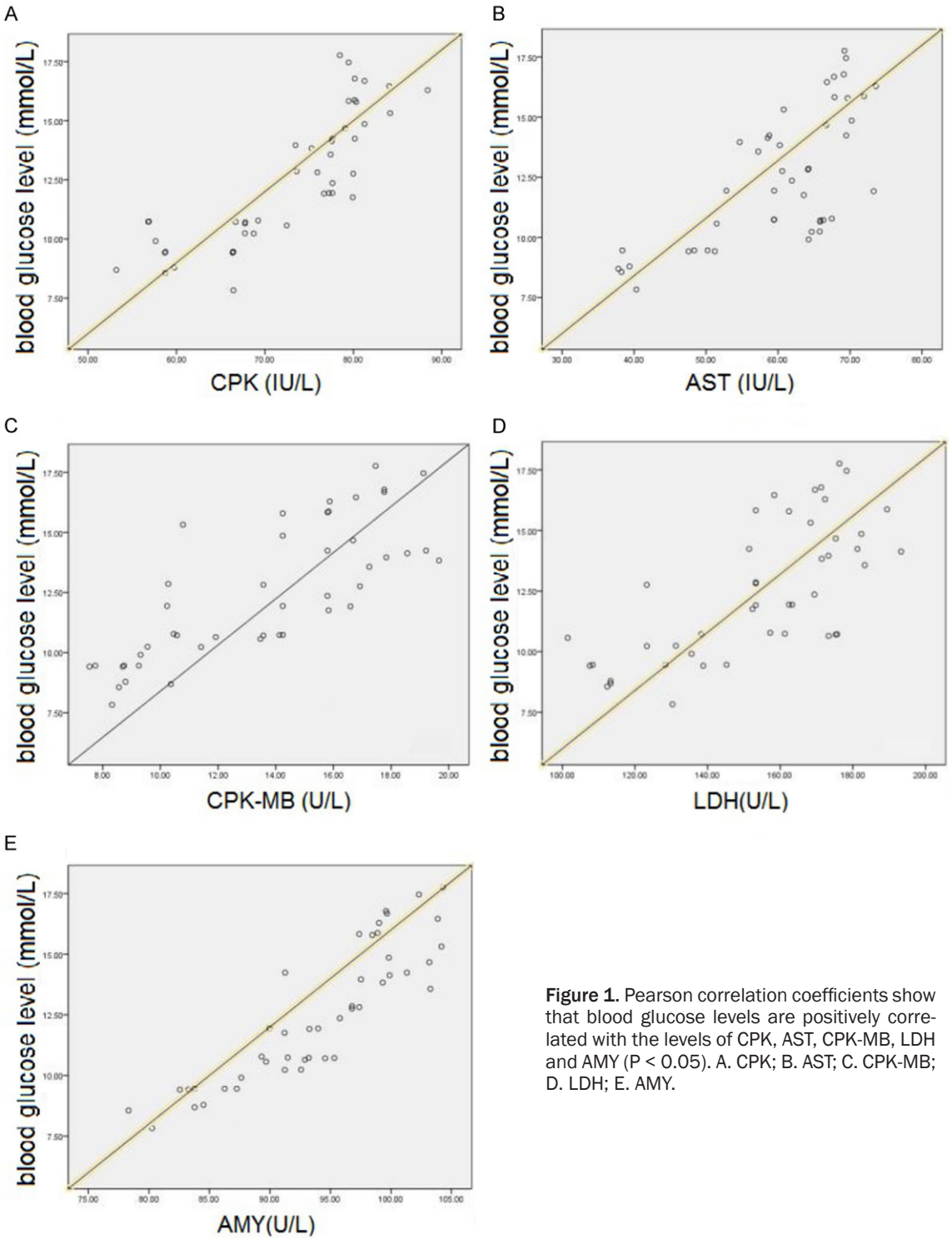


**Figure 1.** Pearson correlation coefficients show that blood glucose levels are positively correlated with the levels of CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$). A. CPK; B. AST; C. CPK-MB; D. LDH; E. AMY.

becomes disordered, resulting in mitochondrial necrosis and cell apoptosis so as to increase the release of intracellular cardiac enzymes, thus making the abnormal increase in cardiac enzymes.

AMY mainly derives from the salivary glands and pancreas [15]. Normally, AMY will be cleared by the mononuclear-macrophage system and excreted by the kidneys [16]. The results of this study showed that the level of

**Table 4.** Correlation analysis of blood glucose levels with cardiac enzyme and amylase indicators

| Item | r | *p* |
|---|---|---|
| CPK | 0.418 | 0.023 |
| AST | 0.401 | 0.027 |
| CPK-MB | 0.418 | 0.013 |
| LDH | 0.394 | 0.025 |
| AMY | 0.317 | 0.017 |

**Table 5.** Correlation analysis of blood pH values with cardiac enzyme and amylase indicators

| Item | r | *p* |
|---|---|---|
| CPK | -0.516 | 0.014 |
| AST | -0.501 | 0.023 |
| CPK-MB | -0.508 | 0.005 |
| LDH | -0.415 | 0.017 |
| AMY | -0.301 | 0.016 |

AMY in the observation group was significantly higher than that in the control group ($P < 0.05$). As the occurrence of DKA leads to the disorder in the body's normal metabolism and increased fat mobilization, lecithin and free fatty acids were increased. As such, the pancreas continuously decomposes AMY, resulting in the increased pancreatic acinar leakage of AMY. Meanwhile, high blood glucose leads to microvascular atherosclerosis even triggering microcirculation disorder. Besides, necrotic pancreatitis may be emergence, and further lead to the increasing of AMY levels [17].

The pH value, also known as the hydrogen ion concentration index, is a measure of the degree of acid ion activity in the solution [18]. Human blood pH normal value is ranged from 7.35 to 7.45, so the process of maintaining the blood pH in this range is called acid-base balance. The blood PH < 7.35 represents the acidosis. The results of this study showed that the blood pH in the observation group was significantly lower than that in the control group ($P < 0.05$) as the concentrations of cortisol, catecholamines, growth hormone and glucagon and other negative regulatory hormones in diabetic patients were increased, thus leading to DKA. Acetoacetic acid and β-hydroxybutyric acid are acidic metabolites, which will consume the reserved bases of the body, but with the progress of the disease, the blood PH value is declining, thus leading to the occurrence of decompensated DKA.

The results of this study shows that blood glucose levels are positively correlated with CPK, AST, CPK-MB, LDH, AMY levels ($P < 0.05$), because CPK, AST, CPK-MB and LDH reflect the degree of myocardial injuries. High blood glucose levels of patients with DKA lead to neurological capillary disease and damaged vagal and sympathetic nerves, which leads to the increased pain threshold, malignant arrhythmia and sudden death. At the same time, continuously elevated blood glucose levels lead to the formation of sugar products, affect the hemodynamic and cell signaling pathways and result in thickened basement membranes, endothelial injuries, and the formations of microvascular tumors and microthrombosis, thus leading to microcirculation disorders and tissue hypoxia [19]. The anaerobic glycolysis in myocardial tissues will be increased in the state of hypoxia and ischemia, resulting in the accumulation of a large number of acidic metabolites in cells caused by cell acidosis, and as the blood glucose leads to intracellular calcium overload, potassium channel density is decreased, thus resulting in myocardial injuries, so blood glucose levels are positively correlated with the levels of CPK, AST, CPK-MB and LDH. In the high-glucose and high-stress state, the hypoxia and abnormal metabolism of arachidonic acid caused by the abnormalities of the red blood cell oxygen-carrying system cause the pancreatic function to be disturbed and lead to pancreatic injuries, thus increasing AMY levels.

The results of the study showed that blood pH values were negatively correlated with the levels of CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$) as when DAK occurrs, the continuous decrease in pH values results in acidosis and acid base imbalance followed by severer acidosis, thus resulting in hypercalcemia and severe systemic dehydration caused by high osmotic pressure. This obstructs the exclusion of pancreatic fluid, causing pancreatitis, so that the release of AMY was increased. Hyperkalemia affects the balance of internal and external potentials and cardiac conduction, resulting in

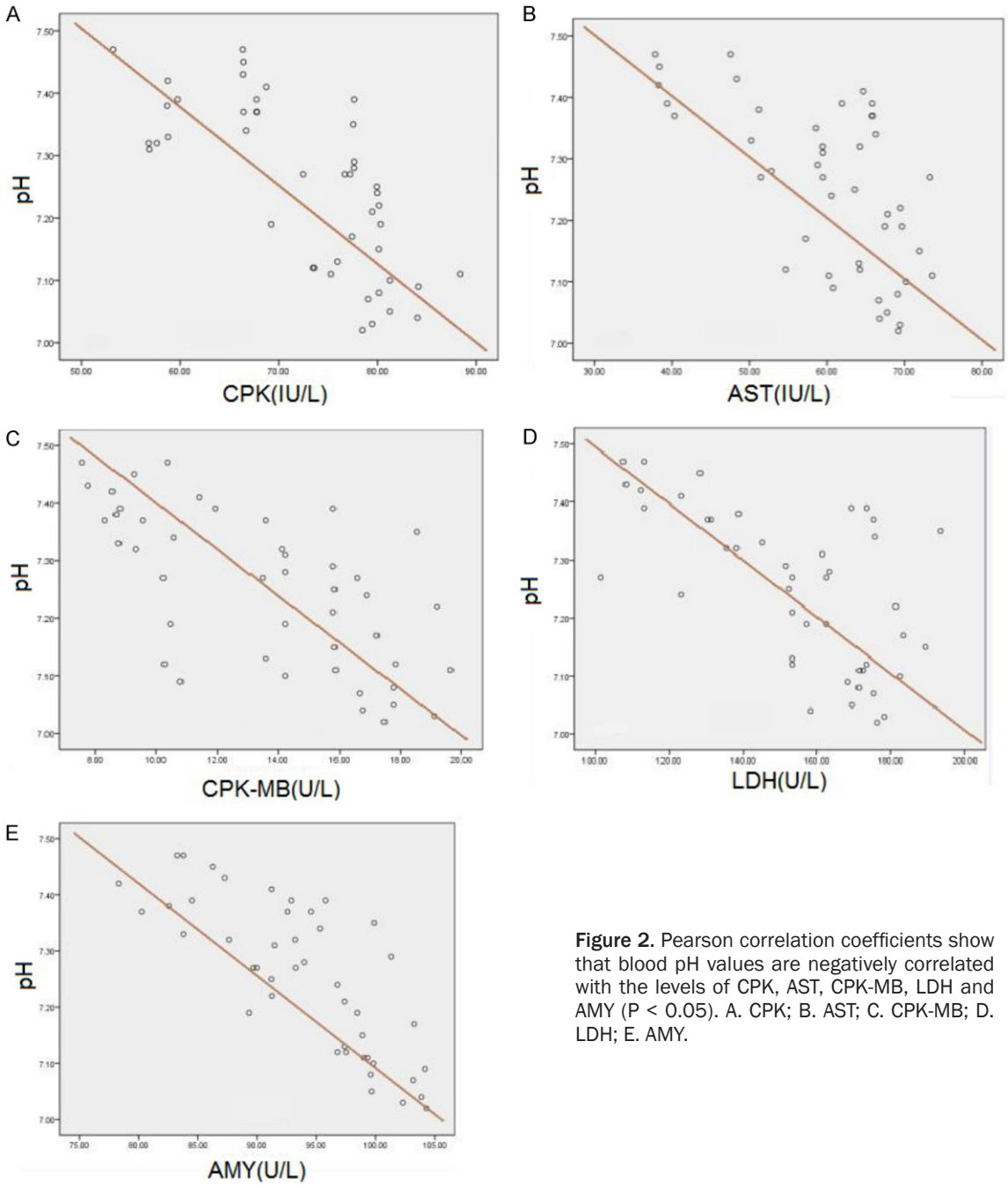


**Figure 2.** Pearson correlation coefficients show that blood pH values are negatively correlated with the levels of CPK, AST, CPK-MB, LDH and AMY ($P < 0.05$). A. CPK; B. AST; C. CPK-MB; D. LDH; E. AMY.

elevated CPK, AST, CPK-MB and LDH, so the levels of CPK, AST, CPK-MB and LDH are continuously increased with decreased blood pH values. They are negatively correlated.

In summary, there is a certain correlation of the blood glucose levels and blood pH values of patients with DKA with the levels of cardiac enzymes and amylases, which provides a reference for the levels of myocardial and pancreatic damages of patients when DKA occurs in the early stage.

## Disclosure of conflict of interest

None.

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## References


[1] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R and Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the american diabetes association (ADA) and the european association for the study of diabetes (EASD). Diabetologia 2012; 55: 1577-96.

[2] Erondu N, Desai M, Ways K and Meininger G. Response to comment on erondu et al. Diabetic ketoacidosis and related events in the canagliflozin Type 2 diabetes clinical program. Diabetes Care 2016; 39: e19.

[3] Maahs DM, Hermann JM, Holman N, Foster NC, Kapellen TM, Allgrove J, Schatz DA, Hofer SE, Campbell F and Steiglederschweiger C. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, wales, the U.S., austria, and germany. Diabetes Care 2015; 38: 1876-82.

[4] Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, Hoogeveen RC, Sharrett AR, Ballantyne CM, Coresh J. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. Circulation 2014; 130: 1374-82.

[5] Wang W, Li J, Ma G, Li N, Wang P, Xiao Q, Li B, Liu Y, Gao X and Li W. [Effect of rhubarb as the main composition of sequential treatment in patients with acute paraquat poisoning: a prospective clinical research]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2015; 27: 254-258.

[6] Abliz A, Deng W, Sun R, Guo W, Zhao L and Wang W. Wortmannin, PI3K/Akt signaling pathway inhibitor, attenuates thyroid injury associated with severe acute pancreatitis in rats. Int J Clin Exp Pathol 2015; 8: 13821-33.

[7] Storgaard H, Bagger JI, Knop FK, Vilsbøll T and Rungby J. Diabetic ketoacidosis in a patient with type 2 diabetes after initiation of sodium-glucose cotransporter 2 inhibitor treatment. Basic Clin Pharmacol Toxicol 2016; 118: 168-70.

[8] Jefferies C, Cutfield SW, Derraik JGB, Bhagvandas J, Albert BB, Hofman PL, Gunn AJ and Cutfield WS. 15-year incidence of diabetic ketoacidosis at onset of type 1 diabetes in children from a regional setting (auckland, new zealand). Sci Rep 2015; 5: 10358.

[9] Karges B, Rosenbauer J, Holterhus PM, Beyer P, Seithe H, Vogel C, Böckmann A, Peters D, Müther S and Neu A. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. Eur J Endocrinol 2015; 173: 341-50.

[10] Misra S and Oliver N. Pathophysiology of diabetic ketoacidosis: a response to Rosival. Diabetic Med 2015; 32: 1527-1528.

[11] Nyenwe EA and Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis and management. Metabolism 2016; 65: 507-521.

[12] Fatemeh DT, Mohadese G, Mona M and Farahnaz A. The role of plasma creatine phosphokinase (CPK) level in prediction of response to methotrexate for ectopic pregnancy. J Family Reprod Health 2016; 10: 59-63.

[13] Maximos M, Bril F, Portillo SP, Lomonaco R, Orsak B, Biernacki D, Suman A, Weber M and Cusi K. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. Hepatology 2015; 61: 153-60.

[14] Henrik E, Einar H, David E, Eggert JS, Erik NJ, Jean-Luc DR, Sigrun H, Pavel H, Sasha K and Marcus C. Sample size in clinical cardioprotection trials using myocardial salvage index, infarct size, or biochemical markers as endpoint. J Am Heart Assoc 2016; 5: e002708.

[15] Sasaki T, Kato D, Sakamoto R, Shinya S, Shiwaku H, Yamashita K, Nakashima R and Yamashita Y. Safety and feasibility of oral rehydration solution prior to endoscopic retrograde cholangiopancreatography. Surgical Science 2015; 6: 91-99.

[16] Li HC, Fan XJ, Chen YF, Tu JM, Pan LY, Chen T, Yin PH, Peng W and Feng DX. Early prediction of intestinal mucosal barrier function impairment by elevated serum procalcitonin in rats with severe acute pancreatitis. Pancreatology 2016; 16: 211-217.

[17] Li H, Liu J, Wang W, Zhang Z, Li D, Lin K, Chen Z and Lin W. Matrix metalloproteinase 9 and vasodilator-stimulated phosphoprotein related to acute kidney injury in severe acute pancreatitis rats. Dig Dis Sci 2015; 60: 3647-3655.

[18] Eastwood GM, Suzuki S, Lluch C, Schneider AG and Bellomo R. A pilot assessment of alpha-stat vs pH-stat arterial blood gas analysis after cardiac arrest. J Crit Care 2015; 30: 138-144.

[19] Sada K, Nishikawa T, Kukidome D, Yoshinaga T, Kajihara N, Sonoda K, Senokuchi T, Motoshima H, Matsumura T and Araki E. Hyperglycemia induces cellular hypoxia through production of mitochondrial ROS followed by suppression of aquaporin-1. PLoS One 2016; 11: e0158619.