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Original Research Article

Comparison of urinary and plasma ketone using urinary nitroprusside strip in patients with diabetic ketoacidosis

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ABSTRACT

Background: Diabetic ketoacidosis is one of the most important and serious acute complications of diabetes and one of the medical emergencies that has been the most common cause of death in patients with diabetes. Prompt diagnosis and therapeutic intervention play an important role in reducing complications and mortality. The aim of this study was to compare urinary and plasma ketones using urinary nitroprusside strip in patients with diabetic ketoacidosis.
Methods: In this cross-sectional study, 38 diabetic ketoacidosis patients were included in this study during the years 2017 and 2018 in the emergency department of Imam Khomeini hospital in Ardabil city. To test for plasma ketones, 2 cc of venous blood samples were taken and transferred to the laboratory for plasma isolation. The resulting plasma was examined with a urine dipstick and the discoloration was recorded. This was repeated at 0, 6 and 12 o'clock for serum ketones. All patients received their treatment according to the treatment protocol of diabetic ketoacidosis and urine ketone, PH and bicarbonate and BE patients were measured routinely.
Results: Serum ketones were positive in all patients and 34 patients had positive urinary ketones. In this study, serum ketone levels were significantly correlated with blood acidity at baseline and with bicarbonate and basal arterial gas deficit at all three stages. However, urinary ketones had a significant correlation with blood acidity at baseline and at 12 hours, with bicarbonate at baseline and with arterial gas deficiency at 12 hours.
Conclusions: The results showed that examination of plasma ketones with dipstick can be a useful, rapid and accurate clinical trial for the diagnosis of diabetic ketoacidosis in patients with diabetes.

Keywords: Diabetic ketoacidosis, Urinary nitroprusside, Ketones body

INTRODUCTION

Diabetes mellitus is a complex metabolic disease characterized by hyperglycemia as well as disturbances in the metabolism of carbohydrates, proteins and fats. Potentially fatal complications of uncontrolled diabetes mellitus have occupied an important part of medical emergencies, and the most important of them are diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. The global prevalence of diabetes mellitus has increased dramatically over the past two decades and has reached 285 million cases in 2010, from about 30 million cases in 1985.[1] If the situation continues like this, according to the prediction of the International Diabetes Federation, more than 438 million people will be diagnosed with diabetes by 2030. Although the prevalence of type 1 and type 2

diabetes mellitus is increasing all over the world, but the rate of increase in the prevalence of type 2 diabetes mellitus is much higher.[2] Diabetes has many acute and chronic complications. Diabetic ketoacidosis (DKA) is one of the emergencies caused by the acute complications of hyperglycemia, which occurs in both types of diabetes and mainly in type one.[3] Diabetic ketoacidosis is a life-threatening condition in which a severe decrease in body insulin causes hyperglycemia, severe lipolysis uncontrolled oxidation of fatty acids and production of ketone bodies (beta hydroxybutyrate, acetoacetate and acetone).[4] Although many years have passed since medical science recognized the pathophysiology of diabetic ketoacidosis, but the way to diagnose and treat it is still challenging. Part of this challenge is related to the different individual responses of human physiology to the treatment process, and another part is related to speeding up diagnosis and the cost-effectiveness and availability of diagnostic tools. Currently, the mainly diagnostic methods for diagnosis diabetic ketoacidosis are blood sugar above 250, metabolic acidosis and ketosis.[5-7] Diabetic ketoacidosis is one of the most important and serious complications of diabetes and one of the medical emergencies, which is mainly seen in type 1 diabetes. This complication may occur as the first manifestation of diabetes in a newly diagnosed person or in a patient who has been suffering from diabetes for a long time. According to statistics, diabetic ketoacidosis is the most common cause of hospitalization and death in patients with diabetes.[8] Measurement of ketones in serum or urine is basically done using nitroprusside kits, which is based on the color change from light purple to deep purple in the presence of acetoacetate and in lesser amounts of acetone.[6] But most importantly, it is very difficult and time-consuming to prepare a urine sample in ketoacidosis patients due to the lack of volume and severe dehydration.[9-10] This is a double challenge in emergency rooms with many patients, because the rapid diagnosis and treatment of ketoacidosis is as important and valuable as the rejection of ketoacidosis. Rapid assignment of hyperglycemic patients and possibly rejecting the diagnosis of ketoacidosis for early discharge and as a result reducing the bed occupancy rate in overcrowded emergency rooms is very valuable. This study aimed to compare urine and plasma ketones using urinary nitroprusside strips in patients with diabetic ketoacidosis.

METHODS

This cross-sectional study was conducted on all 38 patients diagnosed with diabetic ketoacidosis (plasma sugar >250, blood pH >7.3, urine ketone >+2 and bicarbonate <15) during the years 2017 and 2018 in the emergency department of Imam Khomeini hospital in Ardabil city. All patients were measured simultaneously for serum and urine ketones. After obtaining consent, to check plasma ketones, first, 2 cc of venous blood samples were taken from all participants, and to separate the plasma, it was transferred to the laboratory and centrifuged at 4000 revolutions per minute for 3 minutes. The obtained plasma was examined with a urinary dipstick strip and the created color change was registered based on deep violet +4 equivalent to 80 mg/dl, pale violet +3 equivalent to 40 mg/dl, deep purple +2 equivalent 15 mg/dl and pale purple +1 equal to 5 mg/dl. For a more accurate evaluation, in the case of four plus positive results, the serum sample was re-examined in a ratio of one to two to one, and in the case of a similar result, the concentration was doubled, and in the case of no color change, the same amount was considered. Patients with negative serum ketones were tested twelve hours later for serum and urinary ketones. This was repeated at 0, 6 and 12 hours for serum ketones. All patients received their treatment according to the diabetic ketoacidosis treatment protocol, and urine ketone, pH, bicarbonate, and BE measurements were monitored routinely. And the above findings were recorded in the designed questionnaire including the demographic information of the patients. Serum ketone levels were measured three times at baseline, 6 and 12 hours, and its correlation with blood pH was investigated.

Inclusion and exclusion criteria

Patients with pH less than 7.3, bicarbonate less than 15 and sugar above 250 and urinary ketone >2+ were entered in the study and patients treated with captopril and penicillamine were excluded from the study due to the possibility of false positive results.

Statistical analysis

The collected results were analyzed in the form of descriptive statistics using a Venn diagram table and analytical statistics using the Spearman correlation test to evaluate the correlation between variables. SPSS version 25 was used for analysis and a significance level of 0.05 was selected for all tests.

RESULTS

The average age of patients was 39.32±18.63 years (a range of 14-74 years). Most of patients were in the 30-40 age group (N=10, 26.3%). Of the studied patients, 19 (50%) were male and most of them have education degree (Table 1). The serum ketone level had a significant inverse correlation with blood pH at arrival time (r=-0.588, p=0.001). That is, at zero hour, with the increase of serum ketones, the pH of the blood decreases and the blood goes towards acidification (Table 2). The serum level of ketone and bicarbonate in patients had an inverse and significant correlation at all three measurement times, that is, at zero hour, blood bicarbonate decreases with the increase of serum ketone, and at 6 and 12 hours, with the decrease of serum ketone, the bicarbonate increases. Serum ketones had a significant inverse correlation with arterial gas deficiency in all three times of measurement, that is, at zero hour, with the increase of serum ketone, the Arterial gas deficiency decreases, and at 6 and 12 hours, with the decrease of serum ketone, the Arterial gas deficiency increases (Table 3).

Table 1: Demographic data of patients in the study.

Variables		N	%
Age groups (years)	<20	7	18.4
	20-30	7	18.4
	30-40	10	26.3
	40-50	2	5.3
	50-60	4	10.3
	>60	8	21.1
Jender	Male	19	50
	Female	19	50
Education	Illitrate	9	23.7
	Non-illitrate	29	76.3

Urine ketone was also measured in patients using a nitroprusside strip and evaluated based on the clinical diagnosis of ketoacidosis. Urinary ketones were reported positive in 34 patients and negative at 4 patients. Urinary ketones had a significant correlation with blood pH measured upon arrival (r=-0.475, p=0.003).

There was also a significant inverse correlation between urinary ketone and blood pH in patients measured after 12 hours (r=-0.57, p= 0.001). That is, at 0 o'clock, with the increase of urinary ketone, the blood pH decreases, and after 12 hours, with the decrease of urinary ketone, the blood pH increases. Urinary ketone with blood bicarbonate at the time of admission had a significant inverse correlation (r =-0.398, p=0.013). That is, at zero hour, with the increase of urinary ketone, serum bicarbonate decreases. Also, urinary ketones had a significant inverse correlation with arterial gas deficit in patients at 12 hours (r=-0.433, p=0.007). That is, after 12 hours, with the decrease of urinary ketone, the arterial gas deficit increases. After 12 hours, there was a significant correlation between serum ketone and urine ketone. The sensitivity and positive predictive value of measuring serum ketone at zero time were 97% and 89.1%, respectively.

Table 2: Correlation of serum ketone with the studied variables at 0, 6 and 12 hours.

Variables	Measurement time	Variable		R value	P value
		Serum ketone (Median)	Blood pH (Median)		
pH	0	2	7.08	-0.588	0.001
	6	1	7.25	-0.227	0.17
	12	0	7.35	-0.27	0.101
Bicarbonate serum	0	2	10.15	-0.476	0.003
	6	1	12.40	-0.44	0.005
	12	0	17.10	-0.346	0.033
Arterial gas deficiency	0	2	-22.6	-0.577	0.001
	6	1	-14	-0.518	0.001
	12	0	-8.8	-0.408	0.011

Table 3: Correlation of urinary ketone with the studied variables at 0, 6 and 12 hours.

Variables	Measurement time	Variables		R value	P value
		Urinary ketones (Median)	Blood pH (Median)		
pH	0	2	7.08	-0.475	0.003
	6	2	7.25	-0.173	0.298
	12	1	7.35	-0.57	0.001
Bicarbonate serum	0	2	10.15	-0.398	0.013
	6	2	12.40	-0.054	0.746
	12	1	17.10	-0.255	0.123
Arterial gas deficiency	0	2	-22.6	-0.223	0.178
	6	2	-14	-0.16	0.338
	12	1	-8.8	-0.433	0.007

DISCUSSION

The average age of the patients was 39.32±18.63 years. 50% of all patients were male. Serum ketone was positive in all 37 patients but of all patients, 34 had positive urinary ketones. Plasma samples had a sensitivity of 97% and a positive predictive value of 89.1%. A false negative result was found in the serum ketone during the study. In our study, the results were based on the interpretation of the calorimetric reaction. Urine results were used as the standard, as this is the most common test to diagnosis ketone production. The results of this study showed that checking plasma ketone with dipstick, can be a useful and quick clinical test for diagnosing diabetic ketoacidosis in patients with diabetes, although urine sampling is still necessary. In line with the present study, in the study of Tabolt et al which was conducted with the aim of investigating the relationship between the measurement of

urinary ketones and blood ketones on 529 patients with high blood sugar who went to the emergency room, it showed that in patients with hyperglycemia in the emergency department, there is a good correlation between urine ketone and blood ketone, so, both tests can be used to detect ketones, but the blood ketone test is more accurate to confirm ketoacidosis regardless of the type of ketone measurement method, is consistent with the results of the present study.[9] In this study, the serum ketone level had a significant correlation with blood pH at the time of admission and with bicarbonate and arterial gas deficit in all three times of measurement. But urinary ketone had a significant correlation with blood pH measured on arrival and after 12 hours, with bicarbonate on arrival and with arterial gas deficit after 12 hours. The reason for the lack of correlation in some hours can be due to the different speed of correction of ketoacidosis during the treatment process in different people, as well as the conversion of beta-hydroxybutyrate to acetoacetate during treatment and recovery at different times in patients with different underlying diseases. In the study of Kinsella et al on 72 insulin-treated diabetic patients who had referred to the emergency department with hyperglycemia, it was shown that 17% of the patients had an increase in blood ketone levels, and 5 of them were hospitalized with a diagnosis of DKA. That in the present study, all patients had positive ketones in the serum, and the reason for this difference can be due to the difference in the selection of patients in the two studies. Because if the insulin level does not increase during the period of infection and disease, hyperglycemia may lead to diabetic ketoacidosis.[11] Abdur et al in their study showed that the relative frequencies of DKA, using urinary ketone and blood ketone criteria, were 15.6% (19 out of 122) and 13.9% (17 out of 122), respectively. Correlation analysis shows that electrolytes, blood gas, and acid-base status have highly significant correlation with blood ketone levels (Na+, $r=-0.303$, $p<0.001$; K+, $r=0.449$, $p<0.001$; Mg2+, $r=-0.174$, $p<0.05$; TCO2, $r=-0.573$, $p<0.001$; venous blood pH, $r=-0.659$, $p<0.001$, and osmolality $r=-0.273$, $p<0.002$). No such correlation was found with plasma glucose except that for serum sodium ($r=-0.301$, $p<0.001$). The results of this study was in line with our study results.[12] Hirobata et al in another study showed that Serum ketone body levels were negatively correlated with the levels of blood HCO3 - and pH which was in line with our study results because in this study we found that this correlation was negative and significant.[13]

Limitations

The limitations of this study include the small size of the examined sample, the absence of a control group, and the lack of access to the serum beta-hydroxybutyrate test as the gold standard for diagnosing diabetic ketoacidosis to compare the dipstick test, and the impossibility of calculating chlorine for Accurate measurement of the anion gap indicated.

CONCLUSION

The results of this study showed that plasma ketone examination with dipstick can be a useful, quick and accurate clinical test for diagnosing diabetic ketoacidosis in patients with diabetes, although urine sampling is still necessary. To confirm the results of this study as much as possible, it is suggested to conduct similar research with a higher sample size, in the form of case-control studies, and using serum beta-hydroxybutyrate test to compare the results. Future prospective studies are needed to confirm the use of serum ketone instead of urinary ketone.

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