sciendo

ACTA FACULTATIS
MEDICAE NAISSENSIS

DOI: 10.2478/afmnai-2018-0015

UDC: 616.379-008.64-074

Original article

Acid-Base Status of Patients with Diabetic Ketoacidosis and Ketonuria: Bosnia and Herzegovina Experience

Edhem Hasković[1], Azra Bureković[2], Adnan Husić[1], Muhamed Fočak[1], Erna Islamagić[1]

[1]*Faculty of Science, University of Sarajevo, Sarajevo, Bosnia and Herzegovina*
[2]*Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina*

SUMMARY

The aim of this study was to analyze the values of biochemical parameters in patients with diabetic ketoacidosis and ketonuria.

In this prospective comparative study conducted at the Clinical Center of the University of Sarajevo, hundred patients of both genders with diabetes mellitus were enrolled. Newly diagnosed diabetic patients with complications like acute ketoacidosis (n = 50) and ketonuria (n = 50) were included in this study and compared. The values of biochemical parameters in these patients were analyzed.

We found that mean values of pH, base excess, hydrogencarbonate, sodium, glucose, urea and creatinine concentrations in patients with ketoacidosis were significantly different compared to patients with ketonuria. The values of potassium and calcium serum concentrations were not significantly different. Also, values of pH, base excess, as well as concentrations of hydrogencarbonate, sodium, potassium, calcium, glucose, urea and creatinine were not significantly different between male and female patients with diabetic ketoacidosis.

In patients with diabetic ketonuria we found a correlation between admission glucose concentration and acid-base balance.

Key words: **ketoacidosis, diabetes mellitus, ketonuria**

Corresponding author:
Erna Islamagić
Email: erna.islamagic@hotmail.com

INTRODUCTION

Diabetes mellitus is a serious, public health problem in many countries. Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The cytokines affect the metabolism of glucose, either directly or indirectly by activating endocrine signaling pathways (1). The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. There are two major clinical syndromes: one characterized by insulin dependence and early age of onset with weight loss and ketonuria, and the second characterized by relatively later onset, insensitivity to insulin and partial insulin deficiency (2).

Hyperglycemia results in osmotic diuresis that leads to decreasing in volume of plasma and dehydration, which is characteristic for diabetic ketoacidosis (3). Despite normal or high initial concentration of potassium, total body potassium concentration decreases due to increased diuresis. The value of sodium concentration is low because intracellular fluid passes to blood plasma due to hyperglycemia. Low values of hydrogencarbonate concentration are common in high hydrogen concentrations (low pH) and patients in ketoacidosis (pH 7.1 or lower) are treated with hydrogencarbonate therapy (4). Low hydrogencarbonate concentrations may have negative impact on physiological function of the left ventricle via paradoxical acidification of heart cells because CO_2 enters faster in cells than hydrogencarbonate ions (5). Creatinine and urea are significantly increased due to hypovolemia and body dehydration (6). The cell inability to utilize glucose due to insulin lack results in cell starving and organism switches to other metabolic mechanisms to produce energy, like fat catabolism. Degradation of keton bodies takes place in blood, causes a fall of pH value and has a negative effect on the normal function of vital organs; also, high concentrations of glucose have negative impact on pH value (7, 8).

Diabetes mellitus complications are present in both acute and chronic form. Diabetic ketoacidosis is a severe form of metabolic disorder, which results in a fall of pH value under 7.25 or in fall of hydrogencarbonate concentration under 17 mmol/l. A hypoglycemic crisis is the most common acute complication in the diabetic patients. A hypoglycemic crisis usually occurs when the concentration of glucose in blood is under 2.5 mmol/l (9). The severe form of hypoglycemic disorder is a hypoglycemic coma (10). Macroangiopathic complications are atherosclerosis (internal damage of epithelial cells and a process of thickening of blood vessels), myocardial infarction (heart attack), coronary insufficiency, arterial hypertension, macroangiopatic changes in large vessels on the lower extremities (11). Microangiopthic changes occur on the larger blood vessels and manifest as: retinopathy, nephropathy, polyneuropathy, microangiopathic changes in small vessels in foot and diabetic foot (12). The aim of this research was to analyze the values of biochemical parameters in patients with diabetic ketoacidosis and ketonuria.

PATIENTS AND METHODS

This was prospective comparative study conducted in the Clinic for Endocrinology, Diabetes and Metabolic Diseases at the Clinical Center of the University of Sarajevo. One hundred patients of both genders (50 males and females) were enrolled in this study with a diagnosis of diabetes mellitus in the period from May 2011 to May 2015. Newly diagnosed diabetic patients between the age of 18 and 65, with complications like acute ketoacidosis (n = 50) and ketonuria (n = 50) were included in this study. Data regarding gender, age and risk factors were taken from the medical records. The values of biochemical parameters such as pH and base excess value, concentrations of hydrogencarbonates, potassium, sodium, calcium and glucose were obtained on biochemical autoanalyzer Dimension RXL Max (Siemens, USA). Blood pH values were measured in arterial blood with autoanalyzer ABL 800 FLEX blood gas analyzer (Radiometer, Denmark). The procedures were in accordance with the Helsinki Declaration and the ethical standards of the institutional ethical committee. Preparation and storage of data for statistical analysis were made in Microsoft Excel 2010. Statistical analysis was performed in IBM SPSS Statistics 20.0 software package. Descriptive statistic was presented in tables by the percentage, the mean, and the median. About 95% confidence interval and 5% absolute precision were used in this study.

RESULTS

The obtained mean pH and base excess values, as well as concentrations of hydrogencarbonate, potassium,

sodium, calcium, glucose, creatinine and urea are presented in Table 1.

When we compared the two groups of patients, patients with diabetic ketoacidosis and ketonuria complications, we found that the values of pH, base excess, hydrogencarbonate, glucose, urea and creatinine concentrations showed statistical significance, while potassium, sodium and calcium concentrations did not show significat differencies.

Table 1. **Statistical significance of biochemical parameters in patients with diabetic ketoacidosis and ketonuria**

		$\bar{x}$	t-test		ANOVA	
			p	sig	p	sig
pH	KA*	7.1	0.00	p < 0.05	0.00	p < 0.05
	KN**	7.4				
HCO_3^- (mmol/l)	KA	8.2	0.00	p < 0.05	0.00	p < 0.05
	KN	24.5				
Base excess	KA	- 20.4	0.00	p < 0.05	0.00	p < 0.05
	KN	- 1.5				
Na^+ (mmol/l)	KA	136.2	0.20	p < 0.05	0.69	p < 0.05
	KN	136.7				
K^+ (mmol/l)	KA	4.2	0.46	p < 0.05	0.51	p < 0.05
	KN	4.1				
Ca^{2+} (mmol/l)	KA	2.2	0.22	p < 0.05	0.44	p < 0.05
	KN	2.3				
GLU (mmol/l)	KA	31.7	0.01	p < 0.05	0.02	p < 0.05
	KN	25.7				
Urea (mmol/l)	KA	12.2	0.00	p < 0.05	0.00	p < 0.05
	KN	7.4				
Creatinine (μmol/l)	KA	154.4	0.01	p < 0.05	0.02	p < 0.05
	KN	101.6				

KA* - ketoacidosis
KN** - ketonuria

Mean values and statistical significance of pH and base excess, concentrations of hydrogencarbonate, potassium, sodium, calcium, glucose, urea and creatinine in male patients with diabetic ketoacidosis and ketonuria are presented in Table 2.

Values of pH, base excess, concentrations of glucose, urea and creatinine showed statistically significant difference in male patients with ketoacidosis compared to male patients with ketonuria. Values of potassium, sodium and calcium concentrations did not show statistical significance between compared groups of patients.

In Table 3, statistical analysis and mean values of pH values, base excess, as well as concentrations of hydrogencarbonate, potassium, sodium, calcium, glucose, creatinine and urea estimated in female patients are presented.

The values of pH, hydrogencarbonate concentration and base excess showed statistical differences in patients with ketoacidosis compared to patients with ketonuria, while the values of potassium, sodium, calcium, urea and creatinine concentrations did not show statistical difference.

Table 2. **Statistical evaluation of biochemical parameters in male patients with diabetic ketoacidosis and ketonuria**

♂		$\bar{x}$	t-test		ANOVA	
			p	sig	p	sig
pH	KA*	7.1	0.00	p < 0.05	0.00	p < 0.05
	KN**	7.3				
HCO_3- (mmol/l)	KA	8.5	0.00	p < 0.05	0.00	p < 0.05
	KN	24.2				
Base excess	KA	- 20.7	0.00	p < 0.05	0.00	p < 0.05
	KN	- 1.3				
Na^+ (mmol/l)	KA	135.5	0.14	p < 0.05	0.27	p < 0.05
	KN	137				
K^+ (mmol/l)	KA	4.1	0.49	p < 0.05	0.59	p < 0.05
	KN	4.1				
Ca^{2+} (mmol/l)	KA	2.3	0.38	p < 0.05	0.57	p < 0.05
	KN	2.2				
GLU (mmol/l)	KA	31.5	0.02	p < 0.05	0.04	p < 0.05
	KN	25.3				
Urea (mmol/l)	KA	10.6	0.00	p < 0.05	0.01	p < 0.05
	KN	6.4				
Creatinine (μmol/l)	KA	141	0.00	p < 0.05	0.01	p < 0.05
	KN	87.8				

KA*-ketoacidosis
KN**-ketonuria

The correlation between the values of glucose concentration during patients admission and acid-base balance in patients with diabetic ketonuria are presented in Table 4.

A positive correlation was obtained between the concentrations of glucose and base excess, while a low negative correlation was conducted between the values of glucose and hydrogencarbonate concentrations, and between pH and glucose concentration values.

DISCUSSION

One hundred patients were enrolled in this study, among those 47 patients were male and 53 patients were female. We analyzed the biochemical parameters (pH, base excess, hydrogencarbonate, sodium, potassium, calcium, urea, creatinine and glucose concentration level in the blood). The obtained pH value in the group of patients with diabetic ketoacidosis was 7.11 ± 0.17, and in patients with diabetic ketonuria the mean pH value of blood was 7.37 ± 0.13. In a study performed by Wei et al., the mean pH value was 7.10 ± 0.12 in patients with diabetic ketoacidosis and in patients with diabetic ketonuria the mean pH value was 7.41 ± 0.12, which is similar to results in our study (13). In several recent studies, it was found that the mean pH value ranges from 7.00 to 7.20 in patients with diabetic ketoacidosis (8, 13, 14). The mean value of hydrogencarbonate concentration was 8.16 ± 5.64 mmol/l in patients with ketoacidosis, while in patients with ketonuria the mean value of hydrogencarbonate was 24.47 ± 2.23 mmol/l. In a study conducted by Wei el al., the mean value of hydrogencarbonate concentration in patients with diabetic ketoacidosis was 9.55 ± 2.34 mmol/l, and in patients with diabetic ketonuria was 19.83 ± 3.30 mmol/l (13). Gosmanov et al. have done research where the mean hydrogencarbonate concentration was 9.40 ± 1.4 mmol/l (8). The mean values of hydrogencarbonate concentrations obtained in these studies

and in our study, regarding patients with diabetic ketoacidosis and diabetic ketonuria, differ by in ± 1.50 mmol/l. Reduced glucose utilization of an increased fat catabolism leads to ketone body production in the blood, which results in a fall of blood pH and decreased hydrogencarbonate concentration in blood (8, 13).

Table 3. **Statistical evaluation of biochemical parameters in female patients with diabetic ketoacidosis and ketonuria**

♀		$\bar{x}$	t-test		ANOVA	
			p	sig	p	sig
pH	KA*	7.1	0.00	p < 0.05	0.00	p < 0.05
	KN**	7.4				
HCO_3- (mmol/l)	KA	8.0	0.00	p < 0.05	0.00	p < 0.05
	KN	24.9				
Base excess	KA	- 20.2	0.00	p < 0.05	0.00	p < 0.05
	KN	- 1.7				
Na^+ (mmol/l)	KA	136.5	0.47	p < 0.05	0.93	p < 0.05
	KN	136.2				
K^+ (mmol/l)	KA	4.2	0.42	p < 0.05	0.83	p < 0.05
	KN	4.3				
Ca^{2+} (mmol/l)	KA	2.2	0.08	p < 0.05	0.15	p < 0.05
	KN	2.3				
GLU (mmol/l)	KA	31.7	0.11	p < 0.05	0.22	p < 0.05
	KN	26.2				
Urea (mmol/l)	KA	12.9	0.06	p < 0.05	0.13	p < 0.05
	KN	9.0				
Creatinine (μmol/l)	KA	160.4	0.17	p < 0.05	0.35	p < 0.05
	KN	123.2				

KA*-ketoacidosis
KN**-ketonuria

Table 4. The correlation between glucose and acid-base status in patients with ketonuria

		pH	HCO_3^- (mmol/l)	Base excess
Mean values		7.37	24.47	- 1.49
Mean value of blood glucose (mmol/l)		25.69		
Pearson's coefficient of variation	R	- 0.007	- 0.210	0.150
	sig.	p < 0.05	p < 0.05	p > 0.05

In our study, the mean values of sodium and potassium serum concentrations in patients with diabetic ketoacidosis were 136.18 ± 8.97 mmol/l and 4.16 ± 1.11 mmol/l, respectively. In the study conducted by Chiasson et al., the average values of sodium and potassium concentrations in patients with diabetic ketoacidosis were 134.00 ± 1 mmol/l and 4.50 ± 0.13 mmol/l, respectively (15). The analyzed mean values of sodium and potassium in a study obtained by Gosmanov et al. were 134.00 ± 1 mmol/l and 4.50 ± 0.13 mmol/l, respectively. The results obtained in our study and other studies were similar and differ by ± 2.5 mmol/l. Hyponatremia and hyperkalemia are characteristics of patients with diabetic ketoacidosis caused by body dehydration when water withdraws to the blood (8). The body has to recover potassium because severe acidosis leads to a high value of potassium concentration despite a total body potassium deficit in order to prevent heart arrhythmia (8, 15).

The average value of urea concentration in our study varies by ± 1.5mmol/l from the obtained results in a study conducted by Chiasson et al., while the results in a study conducted by the Karavanke et al. were signifycantly different from our results (15). Our results regarding the mean value of creatinine concentrations in patients with diabetic ketoacidosis were significantly different than the results obtained by Chiasson et al. (154.36 mmol/l vs. 97.2 ± 8.8 mmol/l). The value of creatine increases due to body dehydration, and these values may indicate acute ketoacidosis. Creatinine and urea increase due to hypoosmolarity caused by increased diuresis which suggests that the patients in our study had ketoacidosis (15).

The obtained blood glucose concentration in our study was 31.66 ± 14.89 mmol/l. In the studies conducted by Liu el al. and Wei et al., the mean glucose values in patients with diabetic ketoacidosis were 28.87 ± 9.1 mmol/l and 20.84 ± 6.73 mmol/l, respectively (13), which are similar to our results. Hyperglycemia occurs as a result of insufficient secretion of insulin, essential hormone for glucose uptake into cells, which indicates that there is a pathological state of the pancreas.

After preformed t-test and ANOVA, we found that the mean values of pH, base excess, hydrogencarbonate, sodium, glucose, urea and creatinine concentrations in patients with ketoacidosis were significantly different compared to patients with ketonuria. The values of potassium and calcium serum concentrations were not significantly different.

CONCLUSION

The values of pH, base excess, as well as the concentrations of hydrogencarbonate, sodium, potassium, calcium, glucose, urea and creatinine were not significantly different in male and female patients with diabetic ketoacidosis (statistically significant difference was obtained by t-test and ANOVA).

In patients with diabetic ketonuria we found a correlation between admission glucose concentration and acid-base balance, which leads to a conclusion that increased glucose levels result in the increase of excess base.

References

1. Narayan KMV, Gregg EW, Fagot-Campagna A, et al. Diabetes-a common, growing, serious, costly, and potentially preventable public health problem. Diabetes Res Clin Pract 2000; 50 (2): 77–84. https://doi.org/10.1016/S0168-8227(00)00183-2

2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33(1): 62–9. https://doi.org/10.2337/dc10-S062

3. Nathan DM, Buse JB, Davidson MB, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabeties Care 2009;32:193-203

4. Barma PB, Ranabir S, Prasad L, Singh TP. Clinical and biochemical profile of lean type 2 diabetes mellitus. Indian J Endocrinol Metabol 2011; 15(1): 40–3.

5. Mandel EI, Curhan GC, Hu FB, Taylor EN. Plasma hydrogencarbonate and risk of type 2 diabetes mellitus. Can Med Assoc J 2012; 184(13): 719–25. https://doi.org/10.1503/cmaj.120438

6. Dabla PK. Renal function in diabetic nephropathy. World J Diabetes 2010; 1(2): 48–56. https://doi.org/10.4239/wjd.v1.i2.48

7. Edge JA, Roy Y, Bergomi A, et al. Conscious level in children with diabetic ketoacidosis is related to severity of acidosis and not to blood glucose concentration. Pediatric Diabetes 2006; 7:11-5. https://doi.org/10.1111/j.1399-543X.2006.00143.x

8. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2014; 7:255-64. https://doi.org/10.2147/DMSO.S50516

9. Neu A, Hofer SE, Karges B, et al. Ketoacidosis at Diabetes Onset Is Still Frequent in Children and Adolescents-A multicenter analysis of 14,664 patients from 106 institutions. Diabetes Care 2009; 32(9): 1647-8. https://doi.org/10.2337/dc09-0553

10. Thomsen JL, Kristensen IB, Ottosen PD. The histological demonstration of lipids in the proximal renal tubules of patients with diabetic coma. Forensic Science 2006; 2(4): 249–52. https://doi.org/10.1385/FSMP:2:4:249

11. Lichtenauer UD, Seissler J, Scherbaum WA. Diabetic complications. Micro and macroangiopathic end-organ damage. Internist 2003; 44(7): 840-846, 848-52. https://doi.org/10.1007/s00108-003-0996-3

12. Valensi P, Parièsa J, Attalia JR. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications-the french multicentre study. Metabolism 2003; 52(7): 815–20. https://doi.org/10.1016/S0026-0495(03)00095-7

13. Wei LC, Huang CY. Diabetic ketoacidosis as the initial presentation of hyperthyroidism. Am J Emerg Med 2015; 11(4): 147-60.

14. Chua HR, Schneider A, Bellomo R. Hydrogencarbonate in diabetic ketoacidosis-a systematic review. Ann Intensive Care 2011; 1(1): 23. https://doi.org/10.1186/2110-5820-1-23

15. Chiasson JL, Aris-Jilwan N, Belanger R, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Can Med Assoc J 2003; 168: 859-66.

Acido-bazni status bolesnika sa dijabetičnom ketoacidozom i ketonurijom: bosanskohercegovačko iskustvo

Edhem Hasković[1], Azra Bureković[2], Adnan Husić[1], Muhamed Fočak[1], Erna Islamagić[1]

[1]Prirodno-matematički fakultet, Univerzitet u Sarajevu, Sarajevo, Bosna i Hercegovina
[2]Klinika za endokrinologiju, dijabetes i metaboličke bolesti, Klinički centar Univerziteta u Sarajevu, Sarajevo, Bosna i Hercegovina

SAŽETAK

Cilj ove studije bio je da analiziramo vrednosti biohemijskih parametara kod bolesnika sa ketoacidozom i ketonurijom.

U ovoj prospektivnoj komparativnoj studiji koja je provedena u Kliničkom centru Univerziteta u Sarajevu, uključeno je sto bolesnika oba pola sa dijabetesom melitusom. Uključeni su novodijagnosticirani bolesnici koji imaju dijabetes melitus sa komplikacijama poput ketoacidoze i ketonurije. Analizirane su vrednosti biohemijskih parametara kod ovih bolesnika.

Utvrdili smo da su srednje vrednosti pH, baznog ekscesa, koncentracije hidrogenkarbonata, natrijuma, glukoze, uree i kreatinina kod bolesnika sa ketoacidozom signifikantno različite u odnosu na bolesnike sa ketonurijom. Za vrednosti koncentracija serumskog kalijuma i kalcijuma nije pokazana signifikantna različitost. Takođe, vrednosti pH, baznog ekscesa kao i koncentracije hidrogenkarbonata, natrijuma, kalijuma, kalcijuma, glukoze, uree i kreatinina nisu bile značajno različite kod muških i ženskih bolesnika sa ketoacidozom.

Kod bolesnika sa dijabetičnom ketonurijom utvrdili smo pozitivnu korelaciju između početne vrednosti glukoze i acido-baznog statusa. Povećane vrednosti glukoze vode povećanju baznog ekscesa.

Ključne reči: **ketoacidoza, dijabetes melitus, ketonurija**