DOI: 10.5937/halo27-34535

UDC: 616.379-008.64-06
616-008.9

ORIGINAL ARTICLE

Đorđević M. Diabetic
ketoacidosis. Halo 194. 2021;
27(3):84-90.

DIABETIC KETOACIDOSIS IN A ONE-YEAR ANALYSIS

Milan ĐORĐEVIĆ

Emergency medical Services, Health Centre, Jagodina, Serbia

Rad primljen: 22.10.2021.

Prihvaćen: 15.12.2021.

Correspondence:

Milan Đorđević
Health Center Jagodina, EMS
Karadorđeva 4
35000 Jagodina.
Email: milan_mdj@hotmail.com
Phone: +381641720593,
<https://orcid.org/0000-0002-3905-5506>

Abstract

Introduction/Objective Diabetic ketoacidosis (DKA) is a common and most severe acute complication of diabetes. It is a severe metabolic disorder with a high morbidity rate. This article aims to examine patients hospitalized for DKA during a one-year timeframe, present their findings and determine the precipitating factors for the occurrence of DKA.**Methods** The retrospective study included 63 patients with DKA. The research was performed using descriptive statistics based on demographic data (age and gender) and laboratory findings (blood sugar value, pH value and blood bicarbonate level).**Results** The obtained results show that out of 63 patients, 20 (31.74%) were male and 43 (68.26%) female. The average age of male patients was 56.25 ± 18.25 SD years and the average age of female patients 49.75 ± 14.42 SD years. The total average was 53.71 ± 15.58 SD years. The total number of Type 1 diabetes patients was 29 (46.03%), 12 of which were male and 17 female. The total number of Type 2 diabetes patients was 34 (53.97%), 8 of which were male and 26 female. Blood sugar values on admission were 24.36 ± 7.68 SD mmol/L, pH values 7.14 ± 0.12 SD and bicarbonate values 11.2 ± 3.76 SD mmol/L. Ketone bodies were measured qualitatively in urine samples marked as “+” to “+++” and therefore not included in the statistics. The patients had been diagnosed with diabetes for 15.2 ± 8.3 SD years before hospitalization and their hospitalization lasted 7.89 ± 2.87 SD days. The required time for resolving ketoacidosis was 16.21 ± 12.02 SD hours. The time required to begin the administration of the GIK (glucose, potassium, insulin) regimen as a form of therapy was 4.88 ± 2.33 SD hours. Blood sugar levels when switching to the GIK solution were 10.9 ± 0.32 SD mmol/L. The most common precipitating factor for DKA was infection (48.32%), followed by the absence of insulin in therapy (43.13%), while other causes accounted for 8.55% of the cases.**Conclusion** Treating patients with DKA was based on current therapeutic algorithms. Our one-year study presents their findings and treatment protocols. Since the incidence of diabetes mellitus is on the rise, its complications are also becoming more frequent which is why prevention is much needed.**Keywords:** ketoacidosis, acid-base status, diabetes, parameters, electrolytes.

Introduction

Diabetic ketoacidosis (DKA) is a common and most severe acute complication of diabetes, accompanied by a high rate of morbidity, hyperketonemia, hyperglycemia and metabolic acidosis [1]. DKA is a severe metabolic disorder characterized by extremely unregulated diabetes followed by a lack of insulin (absolute or relative) that requires urgent treatment [2].

The basic pathophysiological mechanisms are insulin deficiency, an excess of counterregulatory hormones (glucagon, adrenaline, cortisol and growth hormone), dehydration and starvation. Glucagon concentration increases as a consequence of insulin deficiency. While under stress, adrenaline is the trigger for glucagon release. Insulin deficiency reduces the utilization of glucose in skeletal muscles, the liver and fat cells. Glucagon promotes glycogenolysis and gluconeogenesis. The activity of cellular lipase, which regulates the hydrolysis of triglycerides to glycerol and free fatty acids that go into the circulation, increases. In insulin deficiency, ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone) are produced from fatty acids by the liver. The balance is disturbed and counterregulatory hormones overcome the effect of

small amounts of insulin. Hyperglycemia leads to glycosuria which causes osmotic diuresis and dehydration. Hypokalaemia occurs because potassium is also used to neutralize ketone bodies. Hypovolemia, dehydration and hemoconcentration occur. The most significant disorder in the development of ketoacidosis is ketogenesis. Ketone bodies are moderately strong organic acids, which disrupt the normal pH of the blood reducing the alkaline reserve. Acetone is partly eliminated through exhaled air, which is why the patient's breath smells of acetone. Chemical buffers (bicarbonate and phosphate) are rapidly depleted and the role of the lungs as a buffer is insufficient for the elimination of acetone by respiration, as is the participation of kidneys in the elimination of H⁺ ions. The resulting metabolic acidosis worsens insulin resistance [3-11].

Ketoacidosis usually develops gradually, over several days, from unregulated diabetes with ketonuria. Clinical symptomatology is as follows:

Stage I - ketonuria, hyperketonemia, breath smells of acetone. Acid-base balance preserved.

Stage II - dehydration and acidosis are present with moderate bicarbonate deficiency and preserved consciousness. Somnolence and sopor may occur.

Stage III - Diabetic coma is the most severe form of DKA. Severe dehydration, acidosis, pH <7.2, standard bicarbonate deficiency, hyperketonemia, ketonuria and loss of consciousness [1-3].

Diagnostic criteria for DKA are as follows: glycaemia >14mmol/l, blood pH <7.3, bicarbonate level <15mmol/L accompanied by ketonuria or ketonemia [1-4,6].

Objective

This article aims to examine patients hospitalized for DKA during a one-year timeframe, present their findings and determine the precipitating factors for the occurrence of DKA. All patients received treatment based on current therapeutic guidelines published by Joint British Diabetes Societies, American Diabetes Association and Serbian National Guidelines for Diabetes Mellitus.

Methods

The retrospective study included 63 patients diagnosed with DKA, who were hospitalized and treated at the Clinic of Endocrinology, Clinical Centre Nis, Serbia during the timeframe of one year. Data was collected from the intensive care unit patient logs.

Therapeutic protocols in our study include the following steps:

Fluid replacement: 1L per hour of 0.9% saline solution should be administered on average in the first 2-4 hours of therapy with an additional 250-500ml (half of the initial amount) per hour during the next 4-8 hours. If sodium levels in the blood increase above 150mmol/L switch to a hypotonic saline solution (0.45% NaCl) or a 5% glucose solution with a corresponding increase in insulin. After 8 to 12 hours of therapy, patients are given fluid by mouth. Intravenous fluid administration is reduced and discontinued [2-8].

Insulin replacement: A bolus of 16-20 units IV should be administered first, followed by a 0.1 unit per kg per hour in a continuous IV drip (6 units per hour). Glycaemia should drop by an average of 3-5mmol/L every hour. When the glycaemia drops to 12-14mmol/l, 2-4 units per hour of insulin should be administered with a 5% glucose solution for as long as the patient is in acidosis [2-8].

Potassium replacement: If potassium levels are above 5.5mmol/L, it should not be replaced. Replacement should begin after the first 1-2L of infused fluid had been administered or when the patient has established diuresis. If potassium levels are below 2.5mmol/L administer 40mmol per hour of potassium, if they are below 3.5mmol/L administer 30mmol per hour, and if they are below 5mmol/L administer 10-20mmol per hour. Blood levels of potassium should be maintained at 4-5mmol/L. If potassium should fall below 3mmol/L, it is recommended to temporarily discontinue the administration of insulin until hypokalemia is corrected [2-7].

Bicarbonates: Administer in the following cases:

- Severe acidosis with a pH less than 7 or HCO_3^- less than 8mmol/L
- Life-threatening hyperkalemia $\text{K}^+ > 6.5\text{mmol/L}$
- Cardiogenic shock and general collapse.

Administer 150mmol/L of NaHCO_3 in a normal saline solution for 6 hours. Repeat the bicarbonate dose until the pH reaches 7.0 - 7.1. It is recommended to add 10-20 ml of potassium for every 100 ml of HCO_3^- [2-8].

The research was performed using descriptive statistics based on demographic data (age and gender) and laboratory findings (blood sugar value, pH value and blood bicarbonate level measured in venous blood by a gas analyser - GEM Premier 3000, Instrumentation Laboratory).

Results

The obtained results show that out of 63 patients, 20 (31.74%) were male and 43 (68.26%) female. The average age of male patients was 56.25 ± 18.25 SD years and the average age of female patients was 49.75 ± 14.42 SD years. The total average age of all patients was 53.71 ± 15.58 SD years. The number of patients with Type 1 Diabetes (T1DM) was 29 (46.03%), 12 of which were male and 17 female. The number of patients with Type 2 Diabetes (T2DM) was 34 (53.97%), 8 of which were male and 26 female. Glycemia, pH and bicarbonate levels on admission, as well as other parameters concerning the treatment of DM, are shown in Table 1. Ketone bodies were measured qualitatively in urine samples marked as "+" to "+++" and were therefore not included in the statistics.

Figure 1 shows the distribution of patients according to sex and age. There is a clear prevalence of female patients with DKA admitted for treatment as opposed to male.

Figure 1. The distribution of patients according to sex and age

Table 1. Obtained results

Characteristics analyzed	N - %
Male	31,744 - %
Female	68,256 - %
The average age of men	56,25 years
The average age of women	49,75 years
The overall average age	53,71 years (21 - 89)
Number of patients with Type 1 diabetes mellitus	29 (46,03%)
Number of patients with Type 2 diabetes mellitus	34 (53,97%)
Glycemia on admission	24,36 mmol/l (15,3 - 42,8)
pH	7,14 (6,89 - 7,3)
Bicarbonates HCO_3^-	11,2 mmol/l (3,5 - 18,2)
Ketonuria	++
Time since diabetes mellitus diagnosis	15,2 years (1 - 32)
Length of hospitalization	7,89 days (4 - 13)
Time for resolving ketoacidosis (pH>7,3; HCO_3^- >15 mmol/l)	16,21 hours (3,9 - 53)
Time before administering GPI (glucose, potassium, insulin) solution	4,88 hours (2,5 - 14)
The glycemic value during the administration of the GPI solution	10,9 mmol/l.
Precipitating factor	infection 48,32 % not taking insulin 43,13 % other causes (cardiovascular) 8,55 %

Figure 2 shows the distribution of patients according to sex and type of diabetes mellitus.

Figure 2. The distribution of patients according to sex and type of diabetes mellitus.

Figure 3 shows the precipitating factors for DKA in percentages.

Figure 3. Precipitating factors for DKA in percentages

Discussion

The results of the study show that the patients vary to a significant degree when it comes to DKA. It also shows that patients with T2DM can also develop ketoacidosis, although historically the largest number of patients with DKA have T1DM. Our results, however, show a slight advantage of T2DM over T1DM. The patients with DKA clinically presented with classical symptoms. Based on the duration of the symptoms, we concluded that the patients had suffered from unrecognized diabetes for a long time or had been ignoring the fact that they had diabetes. Death from DKA comes as a result of late detection because the symptoms have not been recognized by the attending physician, high comorbidity and advanced age. Therefore, it is necessary to work on preventing the occurrence of DKA, especially in T2DM patients by introducing additional insulin therapy if necessary in a timely manner. With age, the time needed for patients to recover from acidosis increased, and their stay at the hospital was longer.

Time passed since the patient had been diagnosed with diabetes was not significant for the occurrence of DKA, based on the fact that this number oscillated in the study between 1 and 32 years. Mortality in acute complications of diabetes, especially in DKA, has declined over the years due to a better understanding of pathophysiological mechanisms and therapeutic measures [12]. No significant differences were observed in biochemical parameters for individual groups of patients, which was confirmed in studies by other authors [12].

Based on data published by the Institute of Endocrinology, Diabetes and Metabolic Diseases in Belgrade for the period between 1993 and 1999, the incidence of DKA was 31%. The main cause was insulin deficiency (26%) [1]. Most of the patients with DKA had T1DM.

However, patients with T2DM were also at risk of developing DKA as a result of catabolic stress in acute disease. In our analysis, the percentage of patients with T2DM was 53.97%, while only 46.03% had T1DM. T1DM was more prevalent in men (12 men with T1DM vs. 8 with T2DM), while T2DM was more common in women (26 women with T2DM vs. 17 with T1DM [5]. Contrary to popular belief, DKA is more common in adults than in children [4,6]. Precipitating factors for the development of DKA include infections, newly diagnosed diabetes and inadequate therapy (figure 2). Cardiovascular (myocardial infarction) and central nervous system (apoplexy) diseases can also cause ketoacidosis. Many other causes, such as acute mental and physical stress (bone fractures), poisoning (alcohol and narcotics) and certain diseases (pancreatitis, Cushing's syndrome, acromegaly) can affect the occurrence of ketoacidosis [1-3]. Simultaneous occurrence of several etiological factors is usually encountered. It could be concluded that 40% of DKA cases are caused by infection, 30% by cardiovascular disease, 20% by inadequate therapy, and for 10% the cause is unknown [1-3]. Our results showed that the most common precipitating factor for DKA was an infection, followed by the absence of insulin from therapy, while other causes appeared in the third place (Figure 3).

According to current treatment protocols for DKA, acidosis is aimed to be resolved within 24 hours and it is recommended that patients return to subcutaneous insulin administration and food intake within 48 hours. Our results show that patients suffered from ketoacidosis for an average of 16.21h (3.9-53h).

Based on treatment algorithms, when glycemia values are below 12mmol/L (11-14mmol/L), a 5% glucose solution should be administered along with potassium as needed, and insulin (IV or SC).

It was found that it took an average of 4.88 hours to start with GIK solution therapy and the average measured glycemia when administering the GIK regimen was 10.9 mmol/L. Some patients had developed acidosis with only slightly elevated glycemia, which was mainly due to comorbidities [7,12].

Literature also describes DKA with euglycemia when glycemia values are below 11.1 mmol/L. Possible causes of euglycemia are recent insulin use, reduced calorie intake, higher alcohol consumption, chronic liver disease and glycogen storage disorders, as well as pregnancy [13]. Euglycemia can mislead clinicians into delaying the diagnosis and thus delaying treatment for this emergency [13]. Algorithms for treating DKA vary from country to country. Some authors have compared therapeutic protocols in the US and the UK [14]. Despite being preventable, DKA is quite a common condition at hospital admission.

Many patients may develop DKA while hospitalized [15]. A huge effort is being made to improve treatment, standardize care and reduce morbidity and mortality [14,15]. Treatment of DKA is further complicated by the constant need for reevaluation of the patient's condition and timely responses in correcting electrolyte disbalances [16].

In prevention, emphasis should be placed on educating the public and health workers and raising awareness about diabetes mellitus and its complications. Prevention of DKA is possible not only through appropriate patient education and improving the level of healthcare but also by improving communication between the patient and general practitioners. The most important thing is to advise patients not to stop taking insulin and to seek medical help whenever feel ill [12,15].

Conclusion

Current therapeutic algorithms are used to treat patients with ketoacidosis. To resolve the DKA, it is necessary to normalize certain parameters. Our one-year analysis presented us with treatment options and the patients' symptomatology. Since the incidence of diabetes mellitus is on the rise, its complications are also becoming more frequent which is why prevention is much needed. In prevention, emphasis should be placed on educating the public and health workers, as well as raising awareness about diabetes and its complications.

Conflict of interest: None declared.

References:

1. Nacionalni vodič dobre kliničke prakse za dijagnostikovanje i lečenje dijabetes mellitus-a, 2012. Dostupno na URL: https://www.zdravlje.gov.rs/view_file.php?file_id=529&cache=sr
2. American Diabetes Association: Diabetes Care. 2021; 44 (Suppl 1): S111-S124. <https://doi.org/10.2337/dc21-S009>.
3. American Diabetes Association. Diabetes Care. 2020; 43(Suppl 1): S14-S31. doi: 10.2337/dc20-S002.
4. Bettencourt-Silva R, Aguiar B, Sá-Araújo V, Barreira R, Guedes V, Marques MJ, et al. Diabetes-related symptoms, acute complications and management of diabetes mellitus of patients who are receiving palliative care: a protocol for a systematic review. *BMJ Open*. 2019; 9(6): e028604. doi: 10.1136/bmjopen-2018-028604. PMID: 31203247.
5. Cashen K, Petersen T. Diabetic Ketoacidosis. *Pediatr Rev*. 2019; 40(8): 412-420. doi: 10.1542/pir.2018-0231. PMID: 31371634.
6. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism*. 2016; 65(4):507-21. doi: 10.1016/j.metabol.2015.12.007. PMID: 26975543.
7. Norhammar A, Mellbin L, Cosentino F. Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor. *Eur J PrevCardiol*. 2017; 24(3 suppl): 52-60. doi: 10.1177/2047487317709554. PMID: 28618910.
8. Dhatariya KK. Defining and characterising diabetic ketoacidosis in adults. *Diabetes Res ClinPract*. 2019; 155: 107797. doi: 10.1016/j.diabres.2019.107797. PMID: 31344382.
9. Stoner GD. Hyperosmolar Hyperglycemic State. *Am Fam Physician*. 2017;96(11):729-736. PMID: 29431405.
10. Rewers A. Acute Metabolic Complications in Diabetes. In: Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, et al, editors. *Diabetes in America*. 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018. CHAPTER 17. PMID: 33651551.

11. Choi BC, Shi F. Risk factors for diabetes mellitus by age and sex: results of the National Population Health Survey. *Diabetologia*. 2001; 44(10): 1221-31. doi: 10.1007/s001250100648. PMID: 11692170.
12. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. 2021 May 9. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. PMID: 25905280.
13. Modi A, Agrawal A, Morgan F. Euglycemic Diabetic Ketoacidosis: A Review. *Curr Diabetes Rev*. 2017; 13(3): 315-21. doi: 10.2174/1573399812666160421121307. PMID: 27097605.
14. Dhatariya KK, Vellanki P. Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemic Hyperosmolar State (HHS): Novel Advances in the Management of Hyperglycemic Crises (UK versus USA). 2017; 17(5): 33. doi: 10.1007/s11892-017-0857-4. PMID: 28364357.
15. Evans K. Diabetic Ketoacidosis: Update on management. 2019; 19(5): 396-398. doi: 10.7861/clinmed.2019-0284. PMID: 31530688.
16. Thomovsky E. Fluid and Electrolyte Therapy in Diabetic Ketoacidosis. *Vet Clin North Am Small Anim Pract*. 2017r; 47(2): 491-503. doi:10.1016/j.cvsm.2016.09.012. PMID: 28017407.

ORIGINALNI RAD

JEDNOGODIŠNJA ANALIZA DIJABETESNE KETOACIDOZE

Milan Đorđević

Služba hitne medicinske pomoći, Dom zdravlja Jagodina, Srbija

Sažetak

Uvod/Cilj Dijabetesna ketoacidoza (DKA) predstavlja učestalu i najtežu akutnu komplikaciju dijabetesa. To je težak metabolički poremećaj sa visokom stopom morbiditeta. Cilj rada je bio ispitati pacijente hospitalizovane zbog DKA, analizirati njihove parametre, kao i precipitirajuće faktore za nastanak DKA.

Metod rada Retrospektivnim jednogodišnjim ispitivanjem je obuhvaćeno 63 pacijenata sa DKA. Istraživanje je sprovedeno korišćenjem deskriptivne statistike na osnovu demografskih podataka (pol i starost) i laboratorijskih nalaza (glikemija, pH vrednosti i bikarbonati).

Rezultati Od 63 pacijenta 20 pacijenata (31,74%) su muškarci, a 43 (68,26%) su žene. Prosečna starost muškaraca je 56,25 godina $\pm$ 18,25 SD, a prosečna starost žena 49,75 godina $\pm$ 14,42 SD. Ukupan prosek godina je 53,71 $\pm$ 15,58 SD. Ukupan broj obolelih od dijabetesa tipa 1 je 29 (46,03%) i to 12 muškaraca i 17 žena. Ukupan broj obolelih od dijabetesa tipa 2 je 34 (53,97%), od čega 8 muškog i 26 ženskog pola. Vrednosti glikemije (u mmol/L) na prijemu su 24,36 $\pm$ 7,68 SD; PH 7,14 $\pm$ 0,12 SD; bikarbonata (mmol/L) 11,2 $\pm$ 3,76 SD. Ketonska tela su merena kvalitativno u uzorcima urina označenim od + do +++, i stoga nisu uključena u statistiku. Pacijentima je dijagnostikovao dijabetes u proseku 15,2 $\pm$ 8,3 SD godina pre hospitalizacije, i njihova hospitalizacija je trajala 7,89 $\pm$ 2,87 SD dana. Potrebno vreme za rešavanje ketoacidoze (u satima) je 16,21 $\pm$ 12,02 SD. Vreme (u satima) potrebno za primenu GIK (glukoze, insulina i kalijuma) režima kao oblika terapije je 4,88 $\pm$ 2,33 SD. Nivo glikemije u krvi pri prelasku na GIK rastvor je 10,9 $\pm$ 0,32 SD. Najčešći precipitirajući faktor za DKA je infekcija 48,32%; izostanak insulina u terapiji 43,13%, dok su ostali uzroci zastupljeni sa 8,55%.

Zaključak Lečenje pacijenata sa DKA zasniva se na aktuelnim terapijskim algoritmima. Naša jednogodišnja studija prezentuje karakteristike DKA pacijenata i način njihovog zbrinavanja. Kako je incidence dijabetes melitusa u porastu, sve su češće i komplikacije ove bolesti zbog čega je prevencija neophodna.

Ključne reči: ketoacidoza, acidobazni status, dijabetes, parametri, elektroliti.