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ORIGINAL ARTICLE

Dorđević M. Diabetic
ketoacidosis. Halo 194. 2021;
27(3):84-90.**A ONE-YEAR ANALYSIS OF DIABETIC KETOACIDOSIS***Milan ĐORĐEVIĆ*

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<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 evaluate patients hospitalized with DKA and analyze their findings.**Methodology** The retrospective study included 63 patients with DKA. Data has been obtained from medical histories and patient logs at the Clinic of Endocrinology, Clinical Centre Nis.**Results** The following results were obtained: 31.74% of the patients were male with an average of 56.25 years of age, while 68.26% of the patients were female with an average of 49.75 years of age. The total age average was 53.71 years. Average glycemic values on admission were 24.36 mmol / l, the pH was 7.14, the bicarbonate level was 11.2mmol/l. The patients had been diagnosed with diabetes for an average of 15.2 years at the time of treatment. Type 2 diabetes was present in 53,97% of the patients, while 46.03% of the patients suffered from Type 1 diabetes. The duration of hospitalization was approximately 7.89 days. The required time for resolving ketoacidosis was 16.21 hours. The time required to begin the administration of the GPI (glucose, potassium, insulin) infusion as a form of therapy was 4.88 hours. After administering the GPI solution, the glycemic value was 10.9 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 diabetic ketoacidosis 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, therapy.**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. Some of the free fatty acids in the liver are re-esterified into triglycerides, which leads to hypertriglyceridemia. In addition to glucagon, the concentrations of adrenaline, cortisol and growth hormone are also increased. Thus, the balance is disturbed, and counterregulatory hormones overcome the effect of small amounts of insulin.

Hyperglycemia leads to glycosuria when the glucose concentration exceeds the threshold for absorption from primary urine. Glycosuria causes osmotic diuresis and dehydration, that is, loss of free water and electrolytes. Hypokalaemia occurs, causing more mineralocorticoids to get secreted and they, in turn, cause further loss of potassium through urine. Potassium is also used to neutralize ketone bodies. All these events lead to hypovolemia, dehydration and hemoconcentration. The most significant disorder in the development of ketoacidosis is ketogenesis. Ketone bodies are moderately strong organic acids, which when present in excess in the blood, 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, 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 leads to serious vital organ function failure with a negative inotropic effect on the myocardium, peripheral vasodilation and systemic hypotension, increased risk of ventricular arrhythmias and worsening of 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].

The patient presents with nausea, vomiting, loss of energy, drowsiness, altered level of consciousness, thirst, abdominal pain, polyuria, polydipsia and a dry mouth. These symptoms exacerbate electrolyte disturbances. Physical findings are warm dry skin, facial flushing, dry lips, dry and coated tongue, the smell of acetone on the breath, hyperventilation, Kussmaul's breathing, hypotension, tachycardia [1,3].

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

Therapy includes fluid replacement, insulin replacement, electrolyte replacement, acid-base disorder correction, elimination of precipitating factors and other measures. Fluid replacement: during the first 2-4 hours of therapy one or more litres an hour of 0.9% sodium chloride solution (about 300mmol/l) are administered on average to treat hypotension, dehydration and hemoconcentration. Over the next 4-8 hours, therapy is continued with half of the initial amount, 250-500 ml per hour. If hypernatraemia (Na >150 mmol/L) is present, a hypotonic 0.45% solution of sodium chloride (75 mmol/l) is administered or, as an alternative, a 5% glucose solution with a corresponding increase in insulin. After 8 to 12 hours of therapy, patients are allowed to take fluid by mouth provided they do not vomit. Intravenous fluid administration is reduced and discontinued. Cardiovascular and kidney functions must be monitored at all times. [2-8].

Insulin replacement: treatment begins with an intravenous injection of 16-20 I.U. of insulin, followed by a continuous IV infusion of 0.1 I.U. of insulin per kg of body weight per hour. The recommended dose is 6 I.U. per hour. Glycemia levels should drop by an average of 3-5 mmol/l every hour. When they reach the level of 12-14 mmol/l, insulin is administered in the dose of 2-4 I.U. per hour in combination with a 5% glucose solution for as long as the patient is in acidosis, i.e. as long as acetone can be detected in the serum and urine. This treatment scheme is continued until the patient starts eating when it is replaced with fast-acting insulin before each meal [2-8].

Potassium replacement: if potassium levels exceed 5.5 mmol/l, there is no need for replacement. Potassium replacement should begin after the first or second litre of infused fluid has been administered or when the patient has reestablished diuresis. If potassium levels are below 2.5 mmol/l, 40 mmol/h of potassium should be administered. If they are below 3.5 mmol/l, 30 mmol/h should be administered and if they are below 5 mmol/l only 10-20 mmol/h.

Potassium levels should be maintained at 4-5 mmol/l. If potassium levels should fall below 3mmol/l, it is recommended to temporarily discontinue insulin pending the correction of potassium levels [2-7].

Bicarbonates should be administered in the following cases: severe acidosis with a pH level below 7 or a serum bicarbonate level below 8mmol/l, life-threatening hyperkalemia with potassium levels above 6.5 mmol/l, cardiogenic shock and general collapse. Initially, 150 mmol/l of sodium bicarbonate is diluted in saline solution and administered for 6 hours. This should be repeated until the pH levels reach 7.0 - 7.1. In other words, 50-100 ml of 8.4% sodium bicarbonate solution is added to 250-1000 ml of 0.45% sodium chloride solution. The infusion rate is 50-100ml of bicarbonate solution every 2 hours. It is recommended to add 10-20ml of potassium to every 100ml of sodium bicarbonate [2-8].

Objective

To examine medical records of all patients hospitalized and treated for DKA in one year and conclude how long it took for arterial blood gas test values to return to normal as a result of treatment based on current therapeutic protocols, therefore resolving the DKA.

Methodology

The retrospective study included 63 patients diagnosed with DKA who were hospitalized and treated at the Clinic of Endocrinology, Clinical Centre Nis in one year. Data was collected from the intensive care unit patient logs and medical histories. Conclusions were drawn using descriptive statistics based on demographic data and laboratory parameters.

Results

Obtained results are shown in Table 1.

The results of the study showed a variety of characteristics in patients suffering from DKA, as well as the fact that patients with Type 2 diabetes mellitus can also develop ketoacidosis, even though it is widely accepted that DKA is hugely prevalent in patients with Type 1. The results of our study, however, showed a slightly higher number of patients with Type 2 diabetes mellitus who had developed DKA during the selected year than those with Type 1. The patients presented with classical DKA symptoms.

Based on the duration of symptoms, we can conclude that the patients' disease had in many cases been long-lasting, untreated and perhaps unrecognized by the attending physician or denied by the patient.

Figure 1 presents the sex and age of patients included in our study. There is a clear prevalence of female patients. Figure 2 presents the distribution of patients according to sex and type of diabetes mellitus.

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 glyceimic 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 %

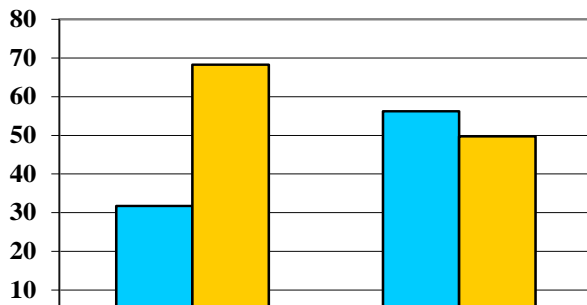


Figure 1. The distribution of patients according to sex and age

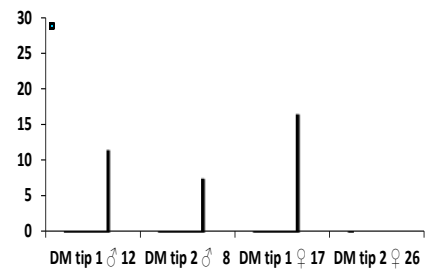


Figure 2. The distribution of patients according to sex and type of diabetes mellitus

The most common precipitating factor for the development of DKA was an infection, followed by the absence of insulin from therapy, while all the other causes are in third place (Figure 3)

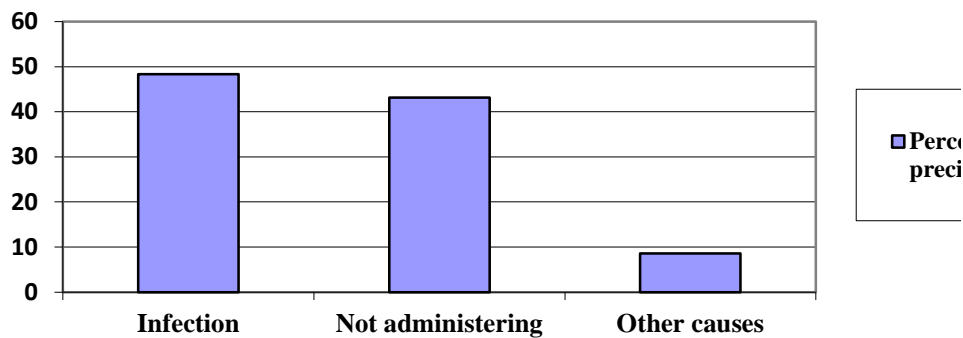


Figure 3. Precipitating factors for DKA

Discussion

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 (26%) was insulin deficiency [1]. Most of the patients with DKA had Type 1 diabetes mellitus. However, patients with Type 2 diabetes mellitus were also at risk of developing DKA as a result of catabolic stress in acute diseases. In our analysis, the percentage of patients with Type 2 diabetes mellitus was 53.97%, while only 46.03% had Type 1 diabetes mellitus. Type 1 diabetes mellitus was more prevalent in men (12 men with Type 1 vs. 8 with Type 2), while Type 2 diabetes mellitus was more common in women (26 women with Type 2 vs. 17 with Type 1 [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. 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]. 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 imbalances [16].

Death from DKA is caused by delayed treatment due to late detection or non-recognition of the disease by the physician, high comorbidity and age. Therefore, if a patient suffers from Type 2 diabetes mellitus, steps must be taken to prevent DKA and, if necessary, introduce additional insulin therapy before serious complications occur. With age, the time needed to resolve the acidosis in patients increases and their

hospitalization lasts longer. The occurrence of DKA does not seem to depend on how long the patient had been diagnosed with diabetes mellitus, especially since this number varied from 1-32 years. Mortality in acute complications of diabetes mellitus, especially DKA, has declined over the years as a result of a better understanding of pathophysiological mechanisms and therapeutic measures [12]. No significant statistical differences were observed in the biochemical parameters of individual groups of patients, which was confirmed in studies by other authors [12].

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, the acidosis is aimed to be resolved in 24 hours and it is recommended that patients return to subcutaneous insulin administration and food intake after 48 hours. Our results show that the average duration of ketoacidosis was 16.21h (3.9-53h). Based on the algorithms, when the glycemic level is 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 h to start with GPI solution therapy and the average measured glycemic level when administering the GPI solution was 10.9 mmol/l. Some patients had developed acidosis with only slightly elevated glycemic values, which was mainly due to comorbidities [7,12].

Literature also describes DKA with euglycemia when glycemic levels are below 11.1 mmol/l. Possible causes of euglycemia are recent insulin use, reduced caloric 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 imbalances [16].

Death from DKA is caused by delayed treatment due to late detection or non-recognition of the disease by the physician, high comorbidity and age. Therefore, if a patient suffers from Type 2 diabetes mellitus, steps must be taken to prevent DKA and, if necessary, introduce additional insulin therapy before serious complications occur. With age, the time needed to resolve the acidosis in patients increases and their hospitalization lasts longer. The occurrence of DKA does not seem to depend on how long the patient had been diagnosed with diabetes mellitus, especially since this number varied from 1-32 years. Mortality in acute complications of diabetes mellitus, especially DKA, has declined over the years as a result of a better understanding of pathophysiological mechanisms and therapeutic measures [12]. No significant statistical differences were observed in the biochemical parameters of individual groups of patients, which was confirmed in studies by other authors [12].

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 if they don't feel well [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 and raising awareness about diabetes and its complications.

Conflict of interest: None declared.

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ORIGINALNI RAD

DIJABETIČNA KETOACIDOZA: JEDNOGODIŠNJA STUDIJA

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Sažetak

Uvod/cilj Dijabetesna ketoacidoza (DKA) predstavlja najučestaliju i najtežu akutnu komplikaciju dijabetesa sa visokom stopom morbiditeta. Cilj rada bio je analizirati kliničko-biohemijske parametre i etiološke uzročnike nastanka DKA bolesnika hospitalizovanih zbog ove bolesti.

Metod rada Jednogodišnjim retrospektivnim ispitivanjem je obuhvaćeno 63 bolesnika sa DKA lečenih po protokolu za ovu bolest. Korišćeni su podaci iz protokola i istorije bolesti DKA bolesnika lečenih u Jedinici za intenzivnu negu Klinike za endokrinologiju KC Niš.

Rezultati Prema polnoj distribuciji, bilo je više žena (68,25%) prosečne starosti 68,25% godina nego muškaraca (31,74%) prosečne starosti 56,25. Prosečne vrednosti glikemije na prijemu bile su 24,36 mmol/l, bikarbonata 11,2 mmol/l i pH 7,14. Procentualna zastupljenost ispitanika obolelih od dijabetesa tip 2 je iznosila 53,97%, dok je sa dijabetesom tip 1 bilo 46,03% bolesnika. Prosečna dužina hospitalizacije je bila 7,89 dana. Vreme potrebno za izlazak bolesnika iz ketoacidoze je 16,21 sati. GIK (glukoza, insulin i kalijum) rastvor je uključen u terapiju tokom 4,88 (2,5-14) sati. Vrednost glikemije pri uključenju GIK rastvora je bila 10,9 mmol/l. Najučestaliji precipitirajući faktor nastanka DKA je infekcija 48,32%, zatim izostanak insulina iz terapije 43,13%, dok su ostali uzroci bili zastupljeni sa 8,55%.

Zaključak U pristupu bolesniku sa DKA treba koristiti aktuelne terapijske algoritme. Obzirom da je broj obolelih od dijabetesa u svakodnevnom porastu, u porastu su i komplikacije ove bolesti što nameće potrebu za intenzivnim javno-zdravstvenim merama prevencije DKA.

Ključne reči: ketoacidoza, acidobazni status, dijabetes, terapija.