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Original Scientific Paper

PRECIPITATING FACTORS AND SYMPTOMS IN PATIENTS WITH DIABETIC KETOACIDOSIS

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SUMMARY – The aim of the study was to determine the most common precipitating factors and symptoms of diabetic ketoacidosis and the possible difference according to age, gender and severity of diabetic ketoacidosis. Medical records from January 1, 2017 until December 31, 2019 were reviewed and patients diagnosed with diabetic ketoacidosis were selected. The study included 52 patients, median age 34 (interquartile range 21-56) years. There was no statistically significant difference between male and female gender. The severity of diabetic ketoacidosis was moderate in the majority of cases (65.4%; p=0.005). The most common precipitating factor was infection (61.7%). In patients with moderate diabetic ketoacidosis, respiratory infections were more common, while gastrointestinal infections were more common in severe diabetic ketoacidosis (33% and 25%, respectively; p=0.03). Nausea (median age 32 years; p=0.004) and vomiting (median age 31 years; p=0.01) were more common in younger age groups, while altered mental status was more common in the older age group (median age 61 years; p=0.001). Infection was the most common precipitating factor. The most common symptoms in younger age groups were nausea and vomiting, and altered mental status in the older age group.

Key words: *Diabetes mellitus; Diabetic ketoacidosis; Infection; Nausea; Vomiting*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by a state of chronic hyperglycemia and a disorder of carbohydrate, protein and fat metabolism. In 2019, the estimated prevalence of DM in the world was 9.3% or 463 million patients[1]. In 2019, 315 298 patients were recorded in the CRODIAB Register of DM Patients, which is 7.7% of the total population of Croatia[2]. DM is characterized by acute and chronic complications. Acute complications include diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), hypoglycemia, and lactic acidosis[3].

Diabetic ketoacidosis is usually associated with DM type 1 (insulin-dependent diabetes), although in some stressful conditions (infection, trauma) and conditions of long-term dysregulation, it can also occur in patients with DM type 2. In the last 20 years, the proportion of patients with DM type 2 in the total number of patients with DKA increased[4]. Pa-

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tients with latent autoimmune diabetes of adulthood (LADA) account for 3%-5% of DKA cases[5,6].

The onset of DKA is associated with some of the precipitating factors, which include infections (pneumonia, urinary tract infections, gastrointestinal infections), omission of insulin therapy or dose reduction, new-onset DM, acute conditions (acute myocardial infarction, cerebrovascular incident, pancreatitis), use of medication with counter insulin action (glucocorticoids, sympathomimetics, thiazide diuretics), administration of sodium-glucose co-transporter 2 inhibitors, and cocaine overdose[7-9].

The most common cause of DKA in patients with type 1 DM is omission of insulin therapy or dose reduction, whereas infections are the most common cause in type 2 DM[10]. In 10% of cases, the cause cannot be determined. In case of infection as a precipitating factor, urinary tract infections and respiratory tract infections are most common[11]. Missed insulin therapy is most common in young people with type 1 DM[12]. DKA as the initial presentation of DM is more common in children, whereas in those older than 18 years it is less common and accounts for about 10% of all causes[5,13].

Diabetic ketoacidosis is a condition that develops rapidly, usually within 24 hours. The first symptoms are polyuria, polydipsia and weight loss. Neurological symptoms can develop, although they are much more common in HHS, and include altered mental status (from somnolence to coma) and focal neurological signs. Other symptoms include abdominal pain that may be accompanied by nausea, vomiting, and hyperventilation. If the condition persists, hyperventilation may progress to shallow breathing with tachycardia and hypotension. Patients may also have acetone odor[7].

Criteria for the diagnosis of DKA according to the American Diabetes Association (ADA) include plasma glucose concentration greater than 13.9 mmol/L, arterial blood pH less than 7.3, bicarbonate concentration less than 18 mmol/L, anion deficiency greater than 10, ketonemia, ketonuria (positive acetoacetate in urine by nitroprusside test), and acute altered mental status[14].

The aim of this study was to determine the most common precipitating factors and symptoms of DKA, the possible difference according to age, gender and severity of DKA, and to compare the data with data in the literature.

Patients and Methods

The research was conducted as a cross-sectional study with historical data at the Osijek University Hospital Center and was approved by the Ethics Committee for Research of the Osijek Faculty of Medicine, Josip Juraj Strossmayer University of Osijek. Data were collected by searching the hospital information system. Data on all patients diagnosed with DKA at the Emergency Department of the Osijek University Hospital Center in the period from January 1, 2017 to December 31, 2019 were reviewed. The anonymity of the patients was ensured by keeping the patients under a unique number. The study included those patients who met the ADA criteria for DKA. A total of 52 patients were included, of which 23 (44%) were male and 29 (56%) were female, mean age 40 (18-85) years.

By searching medical records, basic demographic data on the patient (age, gender), symptoms at admission (nausea, vomiting, abdominal pain, altered mental status), type of DM, cause of DKA, number of days of hospital stay, and treatment outcomes were collected. Of laboratory findings, data on arterial blood gas analysis and acid-base status (pH, bicarbonates, partial pressure of carbon dioxide and oxygen in arterial blood, oxygen saturation), inflammatory parameters (leukocytes, C-reactive protein), liver aminotransferases (aspartate transaminase, alanine transaminase, gamma-glutamyl transpeptidase), renal function (urea, creatinine), electrolyte status (sodium, potassium), serum glucose values and glycosylated hemoglobin values (HbA1c) were collected. Data on the presence of ketones in urine and presence of signs of urinary tract infection were collected as well. Patients were divided into groups by age, gender, and severity of DKA. The following age groups were formed: 18-24, 25-44, 45-65 and >65 years. According to ADA guidelines, mild DKA is characterized by pH values of 7.25-7.3 and bicarbonate values of 15-18 mmol/L. Patients with moderate DKA have a pH of 7.0-7.24 and bicarbonate 10-14 mmol/L, and those with severe DKA have pH <7.0 and bicarbonate <10 mmol/L[14].

Statistical methods

All categorical data collected were expressed as absolute and relative frequencies, whereas numerical data were expressed as median and interquartile range, as distribution within parameters did not follow normal gaussian distribution. Differences between independent sets of numerical data were tested with nonparametric Mann Whitney U test or Mann-Whitney U

test with Conover post-hoc test, whereas differences between categorical data were tested with χ^2-test or Fisher exact test[15]. Statistical analysis was done with MedCalc (19.1.3, MedCalc Software bv) software tool, with statistical significance defined as α=0.05, where all p values were two tailed.

Results

Our study included 52 patients, median age 34 (interquartile range 21-56) years), range 18- 85 years. The largest number of patients belonged to the 18-24 age group (n=19; 36.5%, χ^2-test, p=0.17). There was a similar number of males (n=23; 44.2%) and females (n=29;

Table 1. Admission laboratory tests

	Median	Interquartile range	Min	Max
Glucose (mmol/L)	27.10	21.93-36,68	14.60	62.00
HbA1c* (%)	11.05	9.40-12.33	6.60	15.20
pH	7.19	7.09-7.25	6.88	7.33
pCO_2† (kPa)	2.29	1.62-3.03	0.61	8.35
SpO_2‡ (%)	96.80	95.45-97.95	71.20	100.00
HCO_3§ (mEq/L)	5.85	3.73-8.38	1.80	18.70
Sodium (mmol/L)	130.00	125.75-133.25	118.00	160.00
Potassium (mmol/L)	4.80	4.08-5.40	3.00	6.90
Leukocytes (x10^9/L)	16.85	10.85-20.88	4.20	43.50
Hemoglobin (g/L)	143.50	132.25-155.00	53.00	174.00
CRP (mg/L)	11.75	4.83-44.50	0.50	339.40
Urea (mmol/L)	8.95	5.28-11.65	1.90	81.00
Creatinine (µmol/L)	83.00	63.00-116.25	4.00	1088.00
AST (U/L)	19.00	14.00-25.00	8.00	161.00
ALT (U/L)	24.00	16.75-30.00	5.00	175.00
GGT (U/L)	24.00	15.75-33.00	7.00	270.00
TSH (mU/L)	1.56	0.97-2.42	0.003	5.97

*Glycated hemoglobin; †partial pressure of carbon dioxide; ‡oxygen saturation; §bicarbonates;
CRP = C-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyl transpeptidase; TSH = thyroid-stimulating hormone

55.8%, χ^2-test, p=0.56). Moderate DKA was observed in the largest number of cases (n=34; 65.4%), which was a statistically significant result (χ^2-test, p=0.005). The basic laboratory findings are shown in Table 1.

A possible cause of DKA was found in 47 (90.4%) patients. Infections were reported as the most common cause of DKA (n=29; 61.7%, χ^2-test, p=0.21). Fifteen (51.7%) patients with infection had DM type 2, 13 (44.8%) had DM type 1, and 1 (3.4%) patient had LADA. The respiratory system was the most common site of infection (n=10; 34.5%, χ^2-test, p=0.69), and in other cases the sites of infection were the gastrointestinal system (n=5; 17.2%) and urinary system (n=5; 17.2%). Omission of insulin therapy or dose reduction was a precipitating factor in the development of DKA in 21 (44.7%) patients, of which 17 (81%) had DM type 1, 3 (14%) had DM type 2 and 1 (5%) had LADA. In the 18-24 age group, there were 12 (63%) patients in whom the cause of DKA was omission of insulin therapy or dose reduction. There were 7 (14.9%) patients with newly diagnosed DM. The mean age of patients with newly diagnosed DM was 41 years and

Table 2. Association of age with gender, severity of diabetic ketoacidosis, precipitating factors, type of infection and clinical presentation

		Age median (IQR)	**p**
Gender	Female	49 (20-59.5)	0.43*
	Male	33 (22.3-43.8)	
Severity of DKA	Mild	41.5 (32-61)	0.30†
	Moderate	33.5 (20-55)	
	Severe	32 (20-58)	
Precipitating factor#	0	49 (27-64)	0.13†
	1	33 (25.5-53.3)	
	2	43.5 (31.5-55)	
	3	21 (20-34)	
	4	39.5 (21-61)	
	5	54 (20.8-65.5)	
Type of infection**	0	23 (20-43.8)	0.17†
	1	61 (46.5-71.5)	
	2	39 (32-55)	
	3	56 (23.5-61.5)	
	4	49 (20-58)	
Nausea	No	56 (29.8-64.3)	**0.01***
	Yes	32 (20-49)	
Vomiting	No	55 (34.3-63.3)	**0.004***
	Yes	31 (20-45.3)	
Abdominal pain	No	32 (20.5-55)	0.10*
	Yes	49 (32-66)	
Altered mental status	No	32 (20-50.3)	**0.001***
	Yes	61 (44.8-74.5)	

*Mann-Whitney U test; †Kruskal-Wallis test; ‡difference is between 1-2 and 1-3 (post-hoc Conover); IQR = interquartile range; DKA = diabetic ketoacidosis;
#precipitating factor: 0 – infection; 1 – new-onset diabetes mellitus; 2 – infection + new-onset diabetes mellitus; 3 – omission of insulin therapy or dose reduction; 4 – infection + omission of insulin therapy or dose reduction; 5 – other; **type of infection: 0 – total; 1 – urinary system; 2 – respiratory system; 3 – gastrointestinal system; 4 – other

mean HbA1c was 13.1%. The cause of DKA development was not determined in 5 (9.6%) patients. No statistically significant difference was found between precipitating factors with respect to age, gender, and severity of DKA. However, a statistically significant association was found between the type of infection and the severity of DKA. Gastrointestinal infection was most common in severe DKA, whereas respiratory infection was most common in moderate DKA (Fisher exact test, p=0.03) (Table 2).

A large number of patients presented to the physician with symptoms of nausea (n=35; 67.3%, χ^2-test, p=0.07) and vomiting (n=33; 63.5%, χ^2-test, p=0.17). Abdominal pain was present in 16 (30.8%) patients and 11 (21.2%) patients had altered mental status. A triad of symptoms, i.e., nausea, vomiting and abdom-

Table 3. Association of gender and severity of diabetic ketoacidosis, precipitating factors, type of infection and clinical presentation

		Gender, n (%)			**Severity of DKA, n (%)**				**Total, N (%)**
		Female	Male	p	Mild	Moderate	Severe	p	
Gender	Female	4 (40) 17 (50)			6 (60)	17 (50)	6 (75)	0.47*	29 (55.8)
	Male				2 (25)		23 (44.2)		
Severity of DKA	Mild	6 (21)	4 (17)	0.47*	34 (65.4) 8 (15.4)				10 (19.2)
	Moderate	17 (58)	17 (74)						
	Severe	6 (21)	2 (9)						
Precipitating factor§	0	11 (38)	8 (35)	0.16*	4 (40)	14 (41)	1 (13)	0.39*	19 (36.5)
	1	0	3 (13)		1 (10)	2 (6)	0		3 (5.8)
	2	2 (7)	2 (9)		2 (20)	2 (6)	0		4 (7.7)
	3	8 (28)	7 (30)		2 (20)	8 (24)	5 (61)		15 (28.8)
	4	3 (10)	3 (13)		0	5 (15)	1 (13)		6 (11.5)
	5	5 (17)	0		1 (10)	3 (9)	1 (13)		5 (9.6)
Type of infection¶	0	13 (45)	10 (44)	0.23*	4 (40)	13 (38)	6 (75)	**0.03***	23 (44.2)
	1	5 (17)	0		3 (30)	2 (6)	0		5 (9.6)
	2	4 (14)	6 (26)		3 (30)	7 (21)	0		10 (19.2)
	3	2 (7)	3 (13)		0	3 (9)	2 (25)		5 (9.6)
	4	5 (17)	4 (17)		0	9 (27)	0		9 (17.3)
Nausea	No	9 (31)	8 (35)	0.78†	4 (40)	11 (32)	2 (25)	0.83*	17 (32.7)
	Yes	20 (69)	15 (65)		6 (60)	23 (68)	6 (75)		35 (67.3)
Vomiting	No	11 (38)	8 (35)	0.82†	5 (50)	13 (38)	1 (13)	0.28*	19 (36.5)
	Yes	18(62)	15 (65)		5 (50)	21 (62)	7 (87)		33 (63.5)
Abdominal pain	No	18 (62)	18 (78)	0.21†	6 (60)	24 (71)	6 (75)	0.82*	36 (69.2)
	Yes	11 (38)	5 (22)		4 (40)	10 (29)	2 (25)		16 (30.8)
Altered mental status	No	22 (76)	19 (83)	0.74*	7 (70)	29 (85)	5 (63)	0.25*	41 (78.8)
	Yes	7 (24)	4 (17)		3 (30)	5 (15)	3 (37)		11 (21.2)
		29 (100)	23 (100)		10 (100)	34 (100)	8 (100)		52 (100)

*Fisher exact test; †χ2-test; DKA = diabetic ketoacidosis; §precipitating factor: 0 – infection; 1 – new-onset diabetes mellitus; 2 – infection + new-onset diabetes mellitus; 3 – omission of insulin therapy or dose reduction; 4 – infection + omission of insulin therapy or dose reduction; 5 – other; ¶type of infection: 0 – total; 1 – urinary system; 2 – respiratory system; 3 – gastrointestinal system; 4 – other

inal pain, was found in 10 (19.2%) patients. Nausea (median age 32 years; Mann-Whitney U test, p=0.004) and vomiting (median age 31 years; Mann-Whitney U test, p=0.01) were more common in younger age groups, and altered mental status in older population (median age 61 years; Mann-Whitney U test, p=0.001) (Table 3). In our study, there were 12 (23.1%) patients who did not have any of these symptoms.

Diabetes mellitus type 1 was diagnosed in 29 (55.8%), DM type 2 in 20 (38.5%), and LADA in 3 (5.8%) patients (χ^2-test, p=0.001). Recurrent ketoacidosis has been reported in 6 patients with median age of 20 (interquartile range 19-21) years. The ratio of male to female patients with recurrent ketoacidosis was 1:2.67. Fatal outcome was recorded in 1 (1.9%) patient.

Discussion

This study presents the precipitating factors and symptoms in patients admitted to the Emergency Department of Osijek University Hospital Center due to DKA. A review of the literature found no research on the incidence and precipitating factors of DKA in this region. This research provides an insight into the basic characteristics, clinical presentation and the most common causes of DKA and can thus help in early identification of these patients.

In our study, no significant difference was found between the number of male and female patients (χ^2-test, p=0.56), as reported in other studies[16]. Mild DKA was found in 10 (19.2%), moderate in 34 (65.4%), and severe in 8 (15.4%) cases, which makes a statistically significant difference (χ^2-test, p=0.005). Compared to the study from Spain, there were significantly more cases of moderate DKA and fewer severe cases[5]. This can be explained with a smaller number of patients in our study. No statistically significant association of the precipitating factor with the severity of DKA was found. Mild to moderate DKA was most often caused by an infection, while severe DKA was most often related to a newly diagnosed DM associated with infection. A statistically significant difference was found between the type of infection and the severity of DKA (Fisher exact test, p=0.03). Gastrointestinal infections were more common in severe DKA leading to further loss of fluids and electrolytes. On the other hand, respiratory infections were more common in moderate DKA.

In recent years, there has been an increase in the number of patients with DM. Research at a university hospital in Zagreb has shown that there is an increase in the number of cases and hospitalizations due to DKA, while there are no published data for Osijek University Hospital Center so far[2,17]. Due to the increase in the number of patients with type 2 DM, the number of patients with DKA in patients with type 2 DM is also increasing[18]. Of the total number of patients in our study, 38.5% had type 2 DM. In a study from China, the percentage of patients with type 2 DM was 68%, which can be explained by the fact that the autoimmune form of DM is less common in the Asian population, but also that recurrent cases of DKA are more common in patients with type 1 DM[19].

In our study, there were 6 patients with recurrent DKA, most often in the 18-24 age group. These data are consistent with data from the literature where it is stated that the highest risk of DKA is at the age of 13 to 25 years[20]. Apart from younger age, important risk factors for recurrent DKA are female gender and DM type 1[4,13]. The male to female ratio of patients with recurrent DKA was 1:2.67. In a study by Randall *et al*. the characteristics of patients with recurrent DKA were observed. In 78% of patients with recurrent DKA, the precipitating factor was omission of insulin therapy or dose reduction. One-third of these patients stopped taking their insulin without giving any reason to stop. In their study, patients with multiple episodes of DKA were more likely to have lower body weight, longer duration of DM, DM was detected at an earlier age, and had abused drugs in the past. Furthermore, 46% of patients suffered from depression[21].

In addition to patients with type 1 and type 2 DM, patients with LADA were also included but in a significantly smaller number (χ^2-test, p=0.001). These patients were more often diagnosed as type 2 DM in the past, although the cause of this condition is autoimmune β-cell destruction. These patients require insulin therapy earlier than patients with type 2 DM. In addition, they are more likely to have higher HbA1c values, i.e., poorer regulation of DM, which predisposes them to DKA[22]. In a study in Spain, the percentage of patients with LADA type was 3.7%, which is slightly less than the figure obtained in this study (5.8%)[5]. The difference in these results could be explained by the smaller number of patients in our study. All patients in that study had insufficiently regulated DM (HbA1c >7%) and high plasma glucose levels (>25 mmol/L)[5].

In our study, the most common precipitating factors were infections and omission of insulin therapy or

dose reduction, which is consistent with previous studies[5,13,14,17,23]. Infections were more frequent (61.7%), which can be explained by the fact that the observed patients were older than 18 years. Ahuja *et al*. found in their study that infection as a precipitating factor occurred in 15% of cases of DKA in the population younger than 18 years, while in the population older than 18 years it appeared in 56% of cases, which is in line with our results[24]. Type 2 DM increases the risk of infections, which results in more patients with DM type 2 for whom infection is a precipitating factor[25]. In a study from Thailand, 82% of patients with infection had type 2 DM, which is a much higher number than that obtained in this study (52%)[26]. A possible explanation is better control of patients with type 1 DM in our region and consequently a smaller percentage of those for whom the precipitating factor is omission of insulin therapy or dose reduction, but a higher percentage of those with infection. In the same study, the most common site of infection was the gastrointestinal system due to the high prevalence of infections transmitted by contaminated food and water in their region. A study in Pakistan found that the urinary system was the most common site of infection, but only patients with type 2 DM were included in their study[27]. These results deviate from the results of our study, which identified respiratory system as the most common site of infection in patients with DKA. Our result (34% of respiratory infections) can be compared with the situation in developed countries. For example, a study in Spain showed that 38% of patients had respiratory infections, 22% had gastrointestinal infections, and 19% had urinary tract infections[5].

Omission of insulin therapy or dose reduction was detected as the cause of DKA in 21 (44.7%) cases. These data coincide with data obtained in other studies[4,5]. In a study by Barski *et al.*, omission of insulin therapy or dose reduction was a precipitating factor in 50% of cases. Among them, 96% patients had type 1 DM, which makes a statistically significant difference[10]. Omission of insulin therapy or dose reduction is a common cause of DKA in young adults with type 1 DM. Wolf *et al*. investigated the precipitating factors and clinical characteristics of DKA in young adults[12]. In their study, the precipitating factor was omission of insulin therapy or dose reduction in 58% of cases, which is in line with our results (63%). In our study, the median age of patients who discontinued insulin therapy or reduced the dose was 21 years. It has been shown that adolescents and young adults are more likely to have poorer glycemic control, most often due to improper diet and lack of self-control, as well as non-adjustment of insulin dose to glycemic values. In addition, the period of young adulthood marks the transition from pediatric to adult endocrinologist leading to a change of physician and approach to treatment. These patients may stop coming to check-ups for psychological reasons, which are extremely important for good control of their disease. A study was conducted in the United Kingdom in 2014, which found that 1 in 5 young adults had symptoms of depression or anxiety, which are conditions associated with poor glycemic control[28-30]. In our study, psychiatric comorbidities and the reasons for irregular insulin use were not investigated. To improve control and quality of life in these patients, insulin pump therapy may be introduced which attempts to mimic the physiological secretion of insulin by combining continuous low doses and prandial bolus of insulin. This allows for adjustment in insulin delivery to variations in daily insulin requirements. Studies have shown that using an insulin pump as opposed to multiple daily injections leads to improved quality of life, better control, and fewer microvascular complications[31]. On the other hand, in a large randomized REPOSE trial, the use of an insulin pump *versus* multiple daily injections did not lead to significantly better glycemic control and better psychosocial status of the adult patients enrolled in that study[32]. Insulin pump is associated with a higher risk of developing DKA due to pump failure or catheter occlusion. However, in the 2019 meta-analysis, no significantly increased risk of DKA was found compared to multiple daily insulin injections[33]. In our study, three (6%) patients had an insulin pump, of which one patient had LADA and two patients type 1 DM. None of these patients had a pump failure that would lead to DKA. Their mean HbA1c was 8.8% indicating unregulated glycemia.

The first presentation of DM as DKA was found in 7 (14.9%) cases, of which 4 (7.7%) cases were associated with infection as a precipitating factor. Compared to the work from France in which there were 27.9% of newly detected cases, in our hospital this number is significantly lower[34]. In a study by Jurić *et al*., newly detected DM accounted for 11% of all causes of DKA, which is consistent with our result[17]. Most of them belonged to the 40-60 age group. The mean age of patients with newly diagnosed DM in our study was 41

years. Most commonly, type 1 DM which manifests with DKA, first appears in the pediatric population that was not the subject of this study. In addition, an increasing number of newly diagnosed type 2 DM presenting with DKA may explain the mean age of patients obtained in this study, but at the same time indicates the need of early detection and timely and appropriate treatment of diabetes[35].

The most common symptoms that patients had at the time of arrival were nausea and vomiting, which is consistent with other studies[13,36]. Ahuja *et al*. found a more frequent incidence of altered mental status in women and the elderly, which is consistent with the results of our study[24]. In the elderly, this symptom is more common due to the higher frequency of other comorbidities and higher number of medications taken by the elderly population, which often include medications that act as central nervous system depressants. Altered mental status in DKA occurs due to the combined influence of serum hyperosmolarity, dehydration and acidosis. Serum pH and hyperosmolarity are the most important predictors of altered mental status[37]. Delaying a visit to the doctor and not conducting regular glucose self-monitoring in the elderly may explain the more frequent occurrence of altered mental status and emphasizes the need to start therapy early. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain are common in DKA. Studies have shown that, like altered mental status, these symptoms are associated with severe acidosis. In the study by Umpierrez and Freire, 75% of patients with severe DKA presented with abdominal pain, while 13% of patients with mild DKA had abdominal pain. There was no association between glycemic levels and degree of dehydration with the existence of abdominal pain as a symptom. The pathogenesis of these reversible gastrointestinal symptoms is not fully understood and is believed to be multifactorial. Nausea and vomiting can be attributed to increased ketone body concentrations and acidosis that cause a central neurogenic response, but also to gastric atony due to acute hyperglycemia. Elevated levels of glucagon and catecholamines may also have a negative effect on gastrointestinal motility. Abdominal pain can occur due to intestinal ischemia which occurs due to large fluid loss and metabolic acidosis. Also, in that study, the incidence of abdominal pain in DKA as an indicator of a serious surgical event in the abdomen was observed. In 6% of cases, surgical intervention was required, and in others these symptoms resolved after correction of metabolic acidosis[38].

In our study, the incidence of DKA was lowest in winter (n=9, 17%), which is in contrast to the study from Taiwan. Chin-Li *et al*. examined the relationship between ambient temperature and the incidence of DKA over a period of 14 years and showed that the number of cases of DKA was inversely proportional to ambient temperature[39]. We also noticed that in our study, patients most often (n=13, 25%) reported to the emergency room on Thursday.

The disease ended favorably in 51 (98.1%) cases, and 1 (1.9%) case had a fatal outcome. These figures coincide with a study from Australia and New Zealand in which 1.4% of cases had a fatal outcome[40].

Our research studied the incidence of DKA, precipitating factors, leading symptoms and age groups at risk, thus enabling better care planning for people with diabetes and can help in the early detection of DM and DKA. It emphasizes the importance of identifying patients with recurrent ketoacidosis and planning to take additional measures to protect these patients. The limitations of our study are related to the relatively small number of patients and only inclusion of patients examined in the Emergency Department, which includes most but not necessarily all patients.

Conclusions

In our study, most patients were in the 18-24 age group. There was no gender difference. In most cases, patients had moderate DKA. The most common precipitating factor were infections and most common among them were respiratory infections. There was no statistically significant difference in precipitating factors of DKA according to age, gender and degree of DKA. On sub-analysis of infections, respiratory infections were a significantly more common type of infection in patients with moderate DKA, whereas gastrointestinal infections were more common in severe DKA. The most common symptoms were nausea and vomiting. They were more common in younger age groups, whereas altered mental status was more common in elderly patients. No statistically significant difference was found in DKA symptoms according to gender and severity of DKA.

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Sažetak

PRECIPITIRAJUĆI ČIMBENICI I SIMPTOMI U BOLESNIKA S DIJABETIČKOM KETOACIDOZOM

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Cilj istraživanja je bio utvrditi najčešće precipitirajuće čimbenike i simptome dijabetičke ketoacidoze te postoji li razlika s obzirom na dob, spol i stupanj dijabetičke ketoacidoze. Pregledana je medicinska dokumentacija od 1. siječnja 2017. do 31. prosinca 2019. godine te su izdvojeni bolesnici s dijagnozom dijabetičke ketoacidoze. U istraživanje je uključeno 52 bolesnika. Medijan dobi bio je 34 godine (interkvartilni raspon 21-56 godina). Nije postojala statistički značajna razlika muškog i ženskog spola. U najvećem broju slučajeva radilo se o umjerenom stupnju dijabetičke ketoacidoze (65,4%; p=0,005). Najčešći precipitirajući čimbenik bila je infekcija (61,7%). Kod umjerenog stupnja najčešće se radilo o respiracijskim infekcijama, a u teškom stupnju o gastrointestinalnim infekcijama (33% i 25%; p=0,03). U mlađim dobnim skupinama češće su se pojavljivale mučnina (medijan dobi 32 godine; p=0,004) i povraćanje (medijan dobi 31 godina; p=0,01), a u starijoj dobnoj skupini poremećaj svijesti (medijan dobi 61 godina; p=0,001). Infekcije su bile najčešći precipitirajući čimbenik dijabetičke ketoacidoze. Najčešći simptomi u mlađim dobnim skupinama bili su mučnina i povraćanje, a u starijoj dobnoj skupini poremećaj svijesti.

Ključne riječi: *Šećerna bolest; Dijabetička ketoacidoza; Infekcija; Mučnina; Povraćanje*