Published by v|b|z

ORIGINAL INVESTIGATION

Incidence of diabetic ketosis and ketoacidosis in Caucasian adults with type 2 diabetes mellitus: A population-based study

Ivan Kruljac[1], Miroslav Ćaćić[1], Petra Ćaćić[2], Lora Stanka Kirigin[1], Vedran Ostojić[3], Mario Štefanović[3], Milan Vrkljan[1,2]

[1]Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb School of Medicine, Zagreb, Croatia
[2]University of Zagreb School of Medicine, Zagreb, Croatia
[3]Department of Internal Medicine, University Hospital "Sveti Duh", Zagreb, Croatia
[4]Clinical Institute of Chemistry, University Hospital Center "Sestre Milosrdnice", University of Zagreb, Faculty of Pharmacy and Biochemistry, Zagreb, Croatia

Corresponding author:
Ivan Kruljac, MD, PhD, Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb Medical School, Vinogradska Cesta 29, 10000 Zagreb, Croatia, Telephone: 00385992179089, e-mail: ivkruljac@gmail.com

DOI: 10.21040/eom/2017.3.1.2

Received: February 24th 2017
Accepted: March 15th 2017
Published: March 30th 2017

Copyright: © Copyright by Association for Endocrine Oncology and Metabolism. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Funding: None.
Conflict of interest statement: The authors declare that they have no conflict of interest.
Data Availability Statement: All relevant data are within the paper.

Abstract

Aims: We aimed to analyze incidence and characteristics of patients with diabetic ketosis (DK) and diabetic ketoacidosis (DKA) in Caucasian adults with type 2 diabetes mellitus (T2DM).

Methods: Studied population included 261,749 adults. DK criteria included plasma glucose >13.9 mmol/L and ketonuria >2, while in DKA bicarbonate <18 mEq/L or pH<7.30 was also required. Hyperglycemic crises without these criteria were defined as non-ketotic hyperglycemia (NKH).

Results: During a 5-year period, we observed 630 episodes of DK and 215 episodes of DKA. Only 8.6% of DK episodes and 34.4% of DKA were attributed to type 1 diabetes mellitus (T1DM). Patients with T1DM were younger, leaner, majority had newly diagnosed disease, and hyperglycemia was the main cause of admission. Standardized incidence ratio for DK was 48.1 (95% confidence interval [CI] 44.5–52.1) and 17.0 (95% CI 14.9–19.4) for DKA. Incidence for both DK and DKA was increasing with age. In patients younger than 50, the incidence of DK and DKA was similar. However, dramatic rise in the incidence of DK was observed in both sexes after the age of 50. When compared with patients with NKH, the patients with DK had higher serum pH and bicarbonates. Patients with T2DM had a risk of 0.8% for developing DKA and 2.9% for DK over 5-year period.

Conclusions: Our study showed that DK and DKA are not uncommon in Caucasian adults and the majority of episodes were contributed to T2DM. Incidence of DK is far more higher than the incidence of DKA in patients older than 50, who predominantly have T2DM. Moreover, patients with DK have higher serum pH and bicarbonates, both of which imply that DK and DKA are distinct clinical entities in patients with T2DM. Further studies are needed to assess the impact of these clinical entities.

Key words: Diabetic ketoacidosis; ketosis; ketosis-prone diabetes mellitus; type 2 diabetes mellitus; incidence

1. Introduction

Current paradigms suggest that diabetic ketoacidosis (DKA) occurs in patients with type 1 diabetes mellitus (T1DM) [1]. Diabetic ketosis (DK) precedes the development of DKA in T1DM and requires careful self-monitoring, intensified treatment, and often leads to hospitalization. According to the current American Diabetes Association (ADA) guidelines, T1DM in adults is divided into two groups: Immune-mediated diabetes and idiopathic T1DM [2]. Immune-mediated diabetes or latent autoimmune diabetes of adults is characterized by the presence of beta-cell antibodies and progressive deterioration of beta-cell function, which leads to insulinopenia and long-term insulin therapy. On the other hand, the patients with idiopathic T1DM present with episodes of DKA and short-term insulin dependence, which often leads to restoration of beta-cell function and insulin withdrawal [3].

DKA has recently drawn great attention due to several cases of DKA in patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors [4,5], a new class of antidiabetic drugs, and diabetologists have emphasized the importance of identifying these patients early. Furthermore, concerns have been raised regarding the current classification of diabetes mellitus (DM), and the need to update it. Ketosis-prone diabetes or atypical diabetes is a poorly defined subgroup of type 2 diabetes mellitus (T2DM) of unknown pathogenesis and incidence, which predominantly occurs in obese Hispanic and Afro-American middle-aged men in sub-Saharan Africa [6-10]. These patients usually have a strong family history of diabetes, a low prevalence of autoimmune markers, and lack HLA genetic association [11]. This subtype of T2DM has been divided into four categories based on the presence of antibodies and beta-cell function. Interestingly, approximately 75% of patients lack autoimmune markers, which are present in all patients with typical T1DM [11]. Absolute or relative insulin deficiency is the cornerstone of DK and DKA pathogenesis in T1DM [1]. On the other hand, evidence exists that the pathogenesis of DKA greatly differs in T2DM. It has been suggested that DKA in T2DM occurs due to impaired uptake and metabolism of ketone bodies rather than increased synthesis. Moreover, ketone bodies are mostly synthesized from amino acids (mostly leucine) rather than fatty acids, as is the case in T1DM [12]. The exact precipitating factors and regulatory mechanisms remain unknown, and the exact clinical role of DK in patients presenting to emergency departments with hyperglycemic crises has not yet been established. Therefore, determining the incidence of DK and DKA in adults is the first step in the assessment of disease burden and for planning future studies. Thus, we aimed to estimate the incidence of DK and DKA in a well-defined, predominantly Caucasian population.

2. Methods

2.1. Study protocol

This was a population-based, cross-sectional study performed in the emergency department of a teaching hospital. According to official Croatian census from 2011, the study population was comprised 261,749 adults in the City of Zagreb and Zagreb County. All patients within this residential area were admitted to our emergency department in case of hyperglycemic crisis. The primary aim of this study was to estimate the incidence of DK and DKA in a predominantly Caucasian population. A secondary aim was to analyze laboratory findings, hospitalization rates and precipitating factors of DK and DKA in patients with T2DM and T1DM.

We reviewed electronic charts from all patients with plasma glucose (PG) > 13.9 mmol/L at admission between January 1, 2010, and December 31, 2014. DK was defined as PG >13.9 mmol/L, ketonuria >2+ and capillary blood bicarbonate level >18 mmol/L or capillary blood pH >7.30, while DKA was defined as PG >13.9 mmol/L, ketonuria >2+, and capillary blood bicarbonate level <18 mmol/L or capillary blood pH <7.30 [11]. Mild DKA was defined as capillary bicarbonate level 15-18 mmol/L, moderate 10-15 mmol/L, and severe as capillary bicarbonate level <10 mmol/L. Patients with PG >13.9 mmol/L and undetectable ketonuria were classified as non-ketotic hyperglycemia (NKH).

Age, gender, place of residence, readmission and hospitalization rates, the main reason for admission, and laboratory results were obtained for all patients via electronic records. A detailed review of medical history, comorbidities, medication, and physical examination

was performed for all patients with DK and DKA, and for 486 patients with NKH who were age- and gender-matched to patients with DK. Diabetes-specific data (body mass index, duration of diabetes and years on insulin therapy) were obtained for approximately 60% of patients by searching other institutional electronic registries. The review of electronic charts was performed by medical doctors.

2.2. Classification of diabetes

In general, patients were considered to have T2DM if they did not have previously diagnosed T1DM. An additional search of hospital records and Croatian diabetes registry was performed for all patients with newly diagnosed diabetes to classify the patients as T1DM or T2DM. To validate the accuracy of this approach, we reviewed the diabetologist's charts within the first year of diagnosis of diabetes. T2DM was defined based on the presence of at least two of the following characteristics: Age >40 years, body mass index >25 kg/m^2, and adequate glycemic control with oral antidiabetic drugs >1 year. A total of 776 patients were eligible for this analysis; 410 patients with NKH, 267 patients with DK and 99 patients with DKA. Based on the previously described model, 93.7% of patients with NKH, 83.1% of patients with DK, and 64.6% of patients were considered to have T2DM. Similar results were obtained when we classified patients with T1DM as previously established T1DM aged <40 years at initial diagnosis. Therefore, the patients were classified as T2DM if they did not have previously diagnosed T1DM and were 40 years of age or older at the time of initial diagnosis. This classification is also in accordance with Croatian diabetes epidemiological data since T2DM is very uncommon in young adults in Croatia. Moreover, we compared characteristics of patients with T2DM and T1DM presenting with DKA to demonstrate differences between these two types of diabetes and to validate our classification model.

2.3. Statistical analyses

Patient characteristics were assessed using descriptive statistics presented as a mean with standard deviation. Continuous variables were compared with one-way analysis of variance and Bonferroni method was used for *post-hoc* analysis. Categorical variables were analyzed using the Chi-square test. When comparing characteristics between patients with T2DM and T1DM, we used non-parametric statistics; Mann–Whitney test for continuous variables and Fisher exact test. Linear backward stepwise regression analysis was used to analyze the association between several laboratory parameters.

We used two approaches to estimate the incidence of DK and DKA. The primary analysis was performed by calculating crude incidence of visits per 100,000 person years. Age- and gender-adjusted incidence was calculated based on 2013 standard European population [13]. Age- and gender-standardized prevalence ratios are not available in Croatia; therefore, we could not calculate standardized incidence ratios for the specific patient populations with diabetes. To bring our data closer to clinicians, we estimated the prevalence of diabetes in the study population and calculated crude incidence rates of patients with DK and DKA per 100 persons with diabetes over the 5-year period. $P < 0.05$ was considered significant. The statistical analysis was performed with SPSS Version 20.0.

3. Results

3.1. Incidence of DK and DKA

Among 5,088 admissions of which patients had PG >13.9 mmol/L, acid-base status or urine analysis was missing in 1679 admissions and these patients were excluded from further analyses. The characteristics of excluded patients were similar to patients with NKH and only 3.6% of them were admitted for hyperglycemia. A flowchart of patients throughout the study is provided in Figure 1. Among 3409 admissions, we observed 630 episodes of DK in 520 patients, 215 episodes of DKA in 165 patients, and 2562 episodes of NKH in 2041 patients. Only 8.6% of DK episodes and 34.4% of DKA episodes were attributed to T1DM. Approximately, 20% (397/3409) of patients were readmitted for a median of 2 [2,3] times. Among readmitted NKH patients, 14.6% developed ketosis during the next visit, while 50% of patients in the DK group and 28% in the DKA group had NKH at their next visit. The overall age- and gender-adjusted incidence rate for DK was 48.1 (95% confidence interval [CI] 44.5-52.1) and 17.0 (95% CI 14.9-19.4) for DKA (Table 1). Incidence of DK and DKA was approximately 2-fold higher in male than in female patients. Incidence of DK and DKA in the general population increased with

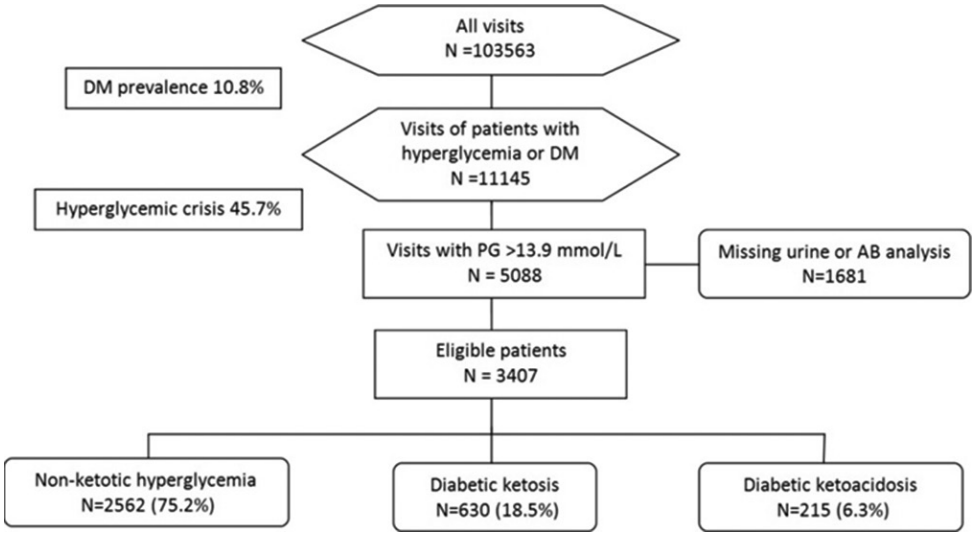

Figure 1. Flowchart of the study population

age (Figure 2). The prevalence of diabetes in Croatia is estimated to 6.8%, of which 7% of patients have T1DM. Thus, we have estimated 17,799 patients with diabetes in our study population (1246 of T1DM and 16.553 of T2DM). After calculating crude incidence rates per patient, approximately 2.9% of patients with T1DM and 0.8% of patients with T2DM will develop at least one episode of DKA. Moreover, 3.0% of patients with T1DM and 2.9% of patients with T2DM will develop DK over the 5-year period.

3.2. Patient characteristics

When compared to NKH group, the patients with T2DM and DK or DKA were characterized by younger age, higher prevalence of male gender, rural residence, and higher rates of newly diagnosed diabetes, with the most common reason for admission being hyperglycemia (Table 2). Patients with DK used more metformin and had higher estimated glomerular filtration rate, capillary blood pH and bicarbonate levels, when compared to both groups (Table 2). Patients in DK and DKA had higher C-reactive protein (CRP) levels and a higher proportion of patients had CRP >50 mg/L, when compared to the NKH group. Interestingly, a lower proportion of patients with DK and DKA had an established diagnosis of infection as the main precipitating factor of hyperglycemic crisis. CRP levels correlated with capillary blood pH and bicarbonates levels in patients with T1DM, however, a similar association in patients with T2DM and DKA was not found. Symptoms were similar in all groups, except for vomiting, which

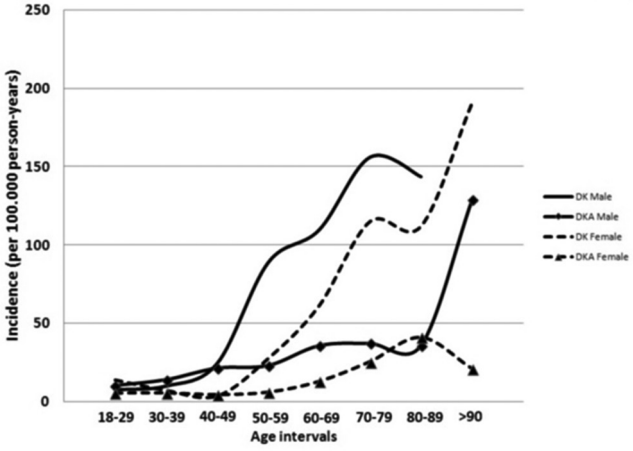

Figure 2. Incidence of diabetic ketosis (DK) and diabetic ketoacidosis (DKA) in males and females in specific age intervals; DK in males full line, DK in females dotted line, DKA in males full line with rhombus, DKA in females dotted line with triangle

was more often reported in patients with DK and DKA. Expectedly, patients with DKA had higher leukocyte counts, serum osmolarity, heart rate and were hospitalized more often (Table 2).

When compared to T1DM, patients with T2DM were older, had higher BMI, blood pressure, used more oral antidiabetic drugs and had lower hospitalization rates (Table 3). In T1DM, patients with DKA had higher male predominance and higher rates of newly diagnosed diabetes. DKA in patients with T1DM was more acidotic, more commonly precipitated with therapy withdrawal and more associated with vomiting at admission. Infection

Table 1. Annual incidence rate of diabetic ketosis and ketoacidosis by gender and age, City of Zagreb and Zagreb County, January 1, 2010-December 31, 2014

Age (years)	Male					Female					Total				
	Person-years†	Ketosis cases (No.)	DKA cases	Ketosis rate	DKA rate	Person-years†	Ketosis cases (No.)	DKA cases	Ketosis rate	DKA rate	Person-years†	Ketosis cases (No.)	DKA cases	Ketosis rate	DKA rate
20-29	105530	8	11	7.6	10.4	108200	15	6	13.9	5.5	213730	23	17	10.8	8.0
30-40	120285	12	17	10.0	14.1	124960	9	7	7.2	5.6	245245	21	24	8.6	9.8
40-49	102335	25	22	24.4	21.5	109230	4	5	3.7	4.6	211565	29	27	13.7	12.8
50-59	108035	96	25	88.9	23.1	130710	36	8	27.5	6.1	238745	132	33	55.3	13.8
60-69	86580	95	31	109.7	35.8	107875	66	14	61.2	13.0	194455	161	45	82.8	23.1
70-79	53765	84	20	156.2	37.2	81730	94	21	115.0	25.7	135495	178	41	131.4	30.3
80-89	19480	28	7	143.7	35.9	43750	49	18	112.0	41.1	63230	77	25	121.8	39.5
90+	1555	0	2	N/A	128.6	4725	9	1	190.5	21.2	6280	9	3	143.3	47.8
Overall (crude rate)	597565	348	135	58.2	22.6	711180	282	80	39.7	11.2	1308745	630	215	48.1	16.4
Age adjusted rate‡				63.8	24.8				39.0	10.9				48.1	17.0

†Person-years were calculated based on 2011 census for the city of Zagreb and Zagreb county. ‡The overall gender-specific incidence rates are age adjusted to the 2013 standard European population. DKA-Diabetic ketoacidosis

Table 2. Characteristics of patients with type 2 diabetes mellitus divided based on the presence NKH, DK, and DKA

	NKH (A) (N=2543)	DK (B) (N=580)	DKA (C) (N=160)
Age (years)	71.0±11.7[BC]	67.0±11.7	65.1±13.8
Male gender % (n)	49.1 (1248)	56.2 (331)[A]	61.0 (100)[A]
Duration of diabetes (years)	12.1±9.7[BC]	9.9±9.5	7.7±8.7
BMI (kg/m^2)	30.8±5.9[C]	29.8±6.3	27.4±6.0
Rural residents % (n)	39.6 (998)	45.1 (263)[A]	46.0 (75)
Readmissions % (n)	20.5 (521)	17.5 (103)	22.0 (36)
Newly diagnosed DM % (n)	8.7 (184)	17.2 (91)[A]	15.8 (23)[A]
Hospitalized % (n)	47.2 (1163)	49.7 (284)	74.5 (120)[AB]
Died % (n)	0.4 (10)	0.5 (3)	0.0 (0)
Admitted due to hyperglycemia % (n)	24.0 (607)[C]	34.5 (202)[C]	44.5 (73)
Serum glucose (mmol/L)	19.9±6.5	20.9±6.7	29.1±12.6[AB]
Leukocytes (10^9/L)	12.0±7.7	11.9±5.5	14.3±6.3[AB]
Hemoglobin (g/L)	131.4±22.9	139.4±19.7[A]	139.4±22.0[A]
CRP (mg/L)	55.9±83.5	71.6±101.1[A]	83.6±115.4[A]
CRP>50% (n)	25.8 (656)	31.4 (182)	39.8 (64)
Plasma osmolarity (mmol/L)	309.9±16.0[B]	305.8±12.3	314.0±20.4[AB]
eGFR (ml/min)*	71.8±34.4	82.6±34.4[AC]	66.9±27.2
HbA1c (%)*	8.5±2.1	8.6±2.2	7.3±1.7[AB]
pH	7.40±0.10	7.43±0.06[AC]	7.31±0.15[AB]
Base excess (mmol/L)	−2.2±5.2	−1.1±3.7[AC]	−11.7±6.7[AB]
Bicarbonate (mmol/L)	21.2±5.1	22.7±3.7[AC]	12.8±4.6[AB]
Cause of hyperglycemia			
Established diagnosis of infectious disease % (n)	20.4 (99)[C]	16.4 (95)	9.4 (15)
Adherence to therapy % (n)	8.4 (41)	8.8 (51)	9.4 (15)
Unknown % (n)	56.0 (272)	54.5 (316)	69.4 (111)
Symptoms			
Polyuria % (n)	18.7 (91)	21.9 (127)	25.6 (41)
Weight loss % (n)	11.3 (55)	10.0 (58)	15.0 (24)
Vomiting % (n)	11.9 (58)	22.9 (133)[A]	30.6 (49)[A]
Abdominal pain % (n)	23.3 (113)	27.6 (160)	33.1 (53)
Systolic BP (mmHg)	141.8±25.1	140.8±25.6	136.4±28.2

(*Contd...*)

Table 2. (*Continued*)

	NKH (A) (N=2543)	DK (B) (N=580)	DKA (C) (N=160)
Diastolic BP (mmHg)	83.0±13.1	83.0±13.3	80.2±14.3
Heart rate (beats/min)	88.7±21.6	93.8±21.3	101.3±21.0[AB]
Treatment			
Sulfonylureas % (n)	31.1 (151)	33.3 (193)	26.9 (43)
Metformin % (n)	22.8 (111)	33.4 (194)[A]	22.5 (36)
Insulin % (n)	24.7 (120)	27.2 (158)	33.8 (54)

OAD-Oral antidiabetic drugs, eGFR-Estimated glomerular filtration rate was calculated with chronic kidney disease epidemiology collaboration formula, HbA1c-Glycated hemoglobin, BMI-Body mass index, A-Significant difference when compared with NKH, B-Significant difference when compared with DK, C-Significant difference when compared with DKA, AB-Significant difference when compared with NKH and DK, AC-Significant difference when compared with NKH and DKA, NKH-Non-ketotic hyperglycemia, DK-Diabetic ketosis, DKA-Diabetic ketoacidosis, CRP-C-reactive protein, BP-Blood pressure. *Analysis performed on 50 subjects with DKA, 305 subjects with DK and 276 patients with NKH.

Table 3. Study population divided based on the presence of DK and DKA. Characteristics of patients were compared between patients with T1DM and T2DM

	DK		DKA	
	T1DM (N=50)	T2DM (N=580)	T1DM (N=55)	T2DM (N=160)
Age (years)	31±14	67.0±11.7†	37±16	65.1±13.8†
Duration of diabetes (years)	9.8±9.3	9.9±9.5	10.6±10.5	7.7±8.7
BMI (kg/m^2)*	24.1±4.2	29.8±6.3†	22.7±3.4	27.4±6.0†
Male gender % (n)	42.0 (21)	56.2 (331)†	69.1 (38)	61.0 (100)†
Rural residents % (n)	43.9 (22)	45.1 (263)	45.5 (25)	46.0 (75)
Readmissions % (n)	18.0 (9)	17.5 (103)	27.3 (15)	22.0 (36)
Newly diagnosed DM % (n)	24.0 (12)	17.2 (91)†	23.6 (13)	15.8 (23)†
Hospitalized % (n)	62.0 (31)	49.7 (284)†	87.3 (48)	74.5 (120)†
Admitted due to hyperglycemia % (n)	58.0 (29)	34.5 (202)†	60.0 (33)	44.5 (73)†
Serum glucose (mmol/L)	24.6±10.2	20.9±6.7†	32.1±14.7	29.1±12.6
Leukocytes (10^9/L)	11.3±6.3	11.9±5.5	16.8±7.4	14.3±6.3†
Hemoglobin (g/L)	143.5±18.4	139.4±19.7†	149.4±20.1†	139.4±22.0
CRP (mg/L)	10.7±22.6	71.6±101.1†	18.2±31.5	83.6±115.4†
CRP>50% (n)	4.0 (2)	31.4 (182)	7.3 (4)	40.0 (64)
Plasma osmolarity (mmol/L)	307.1±13.0	305.8±12.3	315.0±18.9	314.0±20.4
eGFR (ml/min)*	94.6±32.0	82.6±34.4	71.6±25.2	66.9±27.2
pH	7.4±0.1	7.43±0.06†	7.2±0.1	7.31±0.15†

(*Contd...*)

Table 3. (*Continued*)

	DK		DKA	
	T1DM (N=50)	T2DM (N=580)	T1DM (N=55)	T2DM (N=160)
Base excess (mmol/L)	−3.6±5.0	−1.1±3.7†	−17.4±6.6	−11.7±6.7†
Bicarbonate (mmol/L)	20.4±4.8	22.7±3.7†	8.5±4.9	12.8±4.6†
Mild DKA	NA	NA	14.5 (8)	41.9 (67)†
Moderate DKA	NA	NA	30.9 (17)	34.4 (55)
Severe DKA	NA	NA	54.6 (30)	23.7 (38)†
Cause of hyperglycemia				
Established diagnosis of infectious disease % (n)	8.0 (4)	16.4 (95)	0.0 (0)	9.4 (15)
Adherence to therapy % (n)	16.0 (8)	8.8 (51)	23.6 (13)	9.4 (15)†
Unknown % (n)	42.0 (21)	54.5 (316)	56.4 (31)	69.4 (111)
Symptoms				
Polyuria % (n)	44.1 (22)	21.9 (127)†	29.1 (16)	25.6 (41)
Weight loss % (n)	14.0 (7)	10.0 (58)	20 (11)	15.0 (24)
Vomiting % (n)	32.0 (16)	22.9 (133)†	48.6 (27)	30.6 (49)†
Abdominal pain % (n)	38.0 (19)	27.6 (160)	34.5 (19)	33.1 (53)
Systolic BP (mmHg)	128.4±18.7	140.8±25.6†	127.3±22.29	136.4±28.2†
Diastolic BP (mmHg)	79.4±11.8	83.0±13.3	76.5±13.54	80.2±14.3
Heart rate (beats/min)	82.5±17.3	93.8±21.3†	99.1±24.50	101.3±21.0
Treatment				
Sulfonylureas % (n)	6.0 (3)	33.3 (193)†	0.0 (0)	26.9 (43)†
Metformin % (n)	6.0 (3)	33.4 (194)†	3.6 (2)	22.5 (36)†
Insulin % (n)	64.0 (32)	27.2 (158)†	72.7 (40)	33.8 (54)†

DK-Diabetic ketosis, DKA-Diabetic ketoacidosis, CRP-C reactive protein, eGFR-Estimated glomerular filtration rate was calculated with chronic kidney disease epidemiology collaboration formula, BMI-Body mass index, BP-Blood pressure, T1DM-Type 1 diabetes mellitus, T2DM-Type 2 diabetes mellitus. †P<0.05; *Analysis in patients with T1DM performed on 20 DK patients and 25 DKA patients; in T2DM on 305 DK patients and 50 DKA patients

was rarely associated with DKA in patients with T1DM and higher CRP levels in some patients can be explained by severe acidosis.

4. Discussion

To the best of our knowledge, this is the first study that estimated the incidence of DK and DKA in patients with adult-onset DM. Moreover, neither one study has provided sufficient details regarding DK and DKA in patients with T2DM. Hyperglycemic crises are associated with a three times higher incidence of mortality both in elderly and non-elderly patients. The long-term mortality rate of hyperglycemic crises in non-elderly and elderly patients is 14.1% and 36.2%, respectively [14,15]. High mortality rates may also be precipitated by mistreatment as a consequence of inaccurate classification of DM.

This emphasizes the need for improved knowledge and classification of these clinical entities.

DKA is a common acute complication in T1DM although increasing evidence exists that it may occur in T2DM as well. Some authors suggest that this specific type of T2DM should be classified as ketosis-prone T2DM [8]. The previous studies have reported that ketosis-prone T2DM mostly occurs in obese Hispanic and Afro-American middle-aged men, but also in patients in Sub-Saharan Africa. Our study is first to show that DKA and DK are not rare clinical entities in Caucasian Europeans. Moreover, the majority of patients with DKA and especially DK have clinical features of T2DM. Previous studies in the United States have reported that approximately 50% of patients with DKA have T2DM [6,7,9,10]. On the other hand, studies on a Chinese population reported that DKA was far more common in patients with T2DM, where 68% of all patients with DKA had T2DM [16], which is similar to our results. The high prevalence of T2DM in patients with DKA and DK may subject our study to criticism regarding the model used to classify the type of diabetes. Although we did not analyze the antibody status, serum insulin or C-peptide levels to classify the type of diabetes, a similar clinical model was used in previous studies [6,7]. Basically, this model classified all lean patients younger than 40 years as T1DM and obese patients older than 40 years as T2DM. Moreover, if T1DM patients were well controlled with oral antidiabetic drugs for more than 1 year, they were reclassified as T2DM, and patients with T2DM who required constant insulin therapy were reclassified as T1DM. This seems like a reasonable approach, especially from a clinician's perspective. We must also point out that no current clinical guidelines require antibody status or serum C-peptide levels for diabetes classification or for treatment decision-making [17]. The clinical picture alone is usually enough to correctly classify patients with T2DM; therefore, the definition of T2DM used in our study is a reasonable one. Several points support our findings that the majority of patients with DKA and DK really do have T2DM. For instance, the number of admissions due to DKA in the United States has increased over the last decade [18]. Although the type of diabetes was not specified in those reports, the only logical explanation is the fact that DKA occurs both in T1DM and T2DM, and that the prevalence of T2DM is increasing worldwide, while the prevalence of T1DM remains unchanged. Therefore, we can conclude that the overall burden of DKA is mostly attributed to patients with T2DM. Although our study is not powered to analyze the change in incidence, we observed a modest increase in the incidence of DKA in patients with T2DM but not in patients with T1DM. Additional proof that DK and DKA occurred in patients with T2DM lies in the fact that their incidence increased with age, which correlates with the increase in the prevalence of T2DM. Thus, we can conclude that patients with T2DM present to the emergency department with DK and DKA more commonly and the overall incidence is higher in patients with T2DM.

Characteristics of patients with DK and DKA are the second point that needs to be discussed. First of all, there were profound differences in the majority of variables between patients with T1DM and T2DM, which additionally supports our model for diabetes classification. Patients with T1DM were younger, the vast majority of them used only insulin therapy and presented with more severe forms of DKA. Interestingly, infection was a rare precipitating factor of DKA in T1DM. Patients with T2DM presenting with DK and DKA had higher CRP levels suggesting that infection was a more common precipitating factor in T2DM. However, a minority of patients had an established diagnosis of infectious disease after initial workup (laboratory findings, urine analysis, chest roentgenogram, and abdominal ultrasound). The previous studies on pediatric patients with T1DM reported that CRP correlates with the severity of acidosis, independently of the presence of infection [19,20]. We found a similar association in patients with T1DM but not in patients with T2DM. Moreover, patients with DK had higher CRP levels with even higher capillary blood pH and bicarbonate levels and improved renal function, when compared to patients with NKH. Therefore, the clinical impact of CRP in patients with DK and DKA remains elusive.

When discussing only patients with T2DM, patients with DKA were younger than NKH and were more often males, as seen in the previous studies. Studies conducted on

urban populations in the United States have also observed a higher incidence in patients of Afro-American and Hispanic ethnicity [6,7]. The authors concluded that these patients had higher genetic susceptibility for developing DKA. In our study, residents of rural communities had a higher incidence of DKA, which suggests the possibility that socioeconomic status and health-care accessibility may be more important than ethnic determination and genetic variants.

Patients with DK and DKA share similar anthropometric features, which suggest that patients with DK may be at a higher risk of developing DKA. However, if DK precedes DKA in T2DM, one would expect laboratory findings consistent with compensated metabolic acidosis. On the contrary, patients with DK had higher bicarbonate levels when compared with patients with NKH. Moreover, in patients younger than 50, the incidence of DK and DKA was similar, while we observed a dramatic rise in the incidence of DK in both sexes after the age of 50. The majority of patients younger than 50 have T1DM, in which DK usually precedes DKA. Therefore, one could expect that the incidence of DK and DKA in patients with T1DM would be similar. However, patients older than 50 years mostley have T2DM, while the incidence of DK is far more higher. This implies that DK and DKA may be two distinct clinical entities in patients with T2DM. Further prospective studies are needed to elucidate the clinical impact of DK in patients with T2DM. However, the patients who had DK on their first admission were more likely to have DK at readmission. This supports the theory of ketosis-prone diabetes as a distinct subtype of T2DM. Current guidelines lack stringent criteria that distinguish T1DM from T2DM in adults. This issue is beyond the fact whether the patient has positive or negative beta-cell antibodies. Our study does not answer whether adult patients with an episode of DK or DKA should be classified as T1DM or as a specific subgroup of T2DM, but emphasizes the need for a more detailed classification of DM.

Our study has several limitations. The patients were classified as T1DM or T2DM based on clinical characteristics and we did not determine C-peptide or autoantibody status. However, patients with positive autoantibodies at diagnosis may be sufficiently controlled with oral antidiabetic drugs for several years. Thus, therapeutic decision-making regarding the initiation of insulin therapy may not depend on autoantibody status. A relatively high proportion of patients had missing urine analysis or acid-base status and one can raise concerns regarding the incidence of DK and DKA. However, patients with missing data had similar laboratory findings and anthropometric characteristics as patients with NKH. The majority of these patients had mild hyperglycemia, which was found incidentally during patient work-up. Therefore, we can conclude that only a small proportion of these patients may have had DK or DKA. However, the rates of DK and DKA may be only higher than reported in our study. Despite these limitations, we believe that this study provides valuable epidemiologic data on the incidence and characteristics of DK and DKA in a predominantly Caucasian population, which was previously considered to be extremely rare.

In conclusion, our study showed that DK and DKA are not uncommon in Caucasian adults and that the majority of patients presenting with DK and DKA have clinical features of T2DM. Younger age, male gender, and rural residency are associated with DK and DKA. The incidence of DK and DKA increases with age in the general population, due to the higher prevalence of T2DM. Incidence of DK is far more higher than the incidence of DKA in patients older than 50, who predominantly have T2DM. Moreover, patients with DK have higher serum pH and bicarbonates, both of which imply that DK and DKA are distinct clinical entities in patients with T2DM. Further prospective multicenter studies should assess the clinical impact of DK and DKA in patients with clinical features of T2DM. Hopefully, they will answer some important questions: Does DK precede the onset of DKA; do patients with one episode of DK have a distinct type of DM and can these patients be safely treated with peroral antidiabetic agents (for instance SGLT2 inhibitors)?

Author Contributions

IK gave the idea for the study, performed statistical analysis, participated in manuscript drafting and gave the final approval. MĆ and PĆ performed the data acquisition, critically reviewed the manuscript and gave the final

approval. LSK wrote the manuscript and gave the final approval. VO and MŠ designed electronic databases, participated in manuscript drafting and gave their final approval. MV gave advice regarding statistical analyses and data acquisition, critically reviewed the manuscript and gave the final approval.

References

1. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335-43. https://doi.org/10.2337/dc09-9032.
2. American Diabetes Association. Diabetes care. Diabetes Care 2016;39 Suppl 1:S52-9.
3. Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: Ketosis-prone Type 2 diabetes mellitus. Ann Intern Med 2006;144:350-7. https://doi.org/10.7326/0003-4819-144-5-200603070-00011.
4. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. American association of clinical endocrinologists and American college of endocrinology position statement on the association of sglt-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016;22:753-62. https://doi.org/10.4158/EP161292.PS.
5. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849-52. https://doi.org/10.1210/jc.2015-1884.
6. Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V. New profiles of diabetic ketoacidosis: Type 1 vs Type 2 diabetes and the effect of ethnicity. Arch Intern Med 1999;159:2317-22. https://doi.org/10.1001/archinte.159.19.2317.
7. Newton CA, Raskin P. Diabetic ketoacidosis in Type 1 and Type 2 diabetes mellitus: Clinical and biochemical differences. Arch Intern Med 2004;164:1925-31. https://doi.org/10.1001/archinte.164.17.1925.
8. Umpierrez GE. Ketosis-prone Type 2 diabetes: Time to revise the classification of diabetes. Diabetes Care 2006;29:2755-7. https://doi.org/10.2337/dc06-1870.
9. Musey VC, Lee JK, Crawford R, Klatka MA, McAdams D, Phillips LS. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. Diabetes Care 1995;18:483-9. https://doi.org/10.2337/diacare.18.4.483.
10. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157:669-75. https://doi.org/10.1001/archinte.1997.00440270117011.
11. Maldonado M, Hampe CS, Gaur LK, D'Amico S, Iyer D, Hammerle LP, et al. Ketosis-prone diabetes: Dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003;88:5090-8. https://doi.org/10.1210/jc.2003-030180.
12. Patel SG, Hsu JW, Jahoor F, Coraza I, Bain JR, Stevens RD, et al. Pathogenesis of $A^{+}ß^{-}$ ketosis-prone diabetes. Diabetes 2013;62:912-22. https://doi.org/10.2337/db12-0624.
13. Methodologies and Working Papers: Revision of the European Standard Population Report of Eurostat's Task Force; 2013.
14. Huang CC, Weng SF, Tsai KT, Chen PJ, Lin HJ, Wang JJ, et al. Long-term mortality risk after hyperglycemic crisis episodes in geriatric patients with diabetes: A national population-based cohort study. Diabetes Care 2015;38:746-51. https://doi.org/10.2337/dc14-1840.
15. Kao Y, Hsu CC, Weng SF, Lin HJ, Wang JJ, Su SB, et al. Subsequent mortality after hyperglycemic crisis episode in the non-elderly: A national population-based cohort study. Endocrine 2016;51:72-82. https://doi.org/10.1007/s12020-015-0669-8.
16. Tan H, Zhou Y, Yu Y. Characteristics of diabetic ketoacidosis in Chinese adults and adolescents -- a teaching hospital-based analysis. Diabetes Res Clin Pract 2012;97:306-12. https://doi.org/10.1016/j.diabres.2012.05.004.
17. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in Type 2 diabetes: A patient-centered approach: Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79. https://doi.org/10.2337/dc12-0413.
18. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), and Hyperglycemic Hyperosmolar State (HHS). South Dartmouth (MA): MDText. com. Inc.; 2000.
19. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, Konstantopoulos I, et al. Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM). Endocr J 2011;58:1045-53. https://doi.org/10.1507/endocrj.EJ11-0024.
20. Dalton RR, Hoffman WH, Passmore GG, Martin SL. Plasma C-reactive protein levels in severe diabetic ketoacidosis. Ann Clin Lab Sci 2003;33:435-42.