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Diabetic ketosis during hyperglycemic crisis is associated with decreased all-cause mortality in patients with type 2 diabetes mellitus

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Abstract

Purpose: Patients with type 2 diabetes mellitus (T2DM) have impaired ketogenesis due to high serum insulin and low growth hormone levels. Evidence exists that ketone bodies might improve kidney and cardiac function. In theory, improved ketogenesis in diabetics may have positive effects. We aimed to assess the impact of diabetic ketosis (DK) on all-cause mortality in patients with T2DM presenting with hyperglycemic crisis.

Methods: We analyzed 486 patients with DK and 486 age- and sex-matched patients with non-ketotic hyperglycemia (NKH) presenting to the emergency department. Cox proportional hazard models were used to analyze the link between patient characteristics and mortality.

Results: During an observation time of 33.4 months, death of any cause occurred in 40.9% of the NKH group and 30.2% of the DK group (hazard ratio in the DK group, 0.63; 95% confidence interval 0.48 - 0.82; P = 0.0005). Patients with DK had a lower incidence of symptomatic heart failure and had improved renal function. They used less furosemide and antihypertensive drugs, more metformin and lower insulin doses, all of which was independently associated with decreased mortality. Plasma glucose and glycated hemoglobin levels were similar in both groups.

Conclusions: Patients with hyperglycemic crisis and DK have decreased all-cause mortality when compared to those with NKH. DK might be a compensatory mechanism rather than a complication in patients with hyperglycemic crises, but further prospective studies are warranted.

Key words: type 2 diabetes mellitus; ketosis; ketogenesis; mortality; heart failure; kidney disease

Introduction

Type 2 diabetes mellitus (T2DM) is associated with impaired ketogenesis [1]. Even non-diabetic obese subjects tend to have lower serum non-esterified fatty acids and ketone bodies [2]. Hyperinsulinemia seems to directly suppress ketogenesis in the liver, but growth hormone and glucagon may have an important role in ketogenesis [3–5]. On the other hand, some patients with clinical features of T2DM may develop diabetic ketoacidosis. This is a poorly defined and elusive clinical entity also known as ketosis-prone type 2 diabetes [6]. It occurs predominantly in obese middle-aged men of Hispanic and Afro-American ethnicity and autoimmunity markers are usually absent [6]. Whether an incidental finding of diabetic ketosis (DK) without acidosis in Caucasians could be referred to as ketosis-prone T2DM is unknown. Similarly, the clinical significance of DK in patients presenting to the emergency departments with hyperglycemic crises is unknown and treatment guidelines for such patients are lacking.

On the other hand, there is an ongoing debate on the EMPA-REG OUTCOME trial results. Empagliflozin, an inhibitor of sodium–glucose cotransporter 2 (SGLT2) was the first anti-diabetic drug that reduced mortality in patients with type 2 diabetes mellitus (T2DM) with high cardiovascular risk factors [7]. The underlying mechanisms are being speculated, but neither one hypothesis included ketone bodies. SGLT2 inhibitors induce profound glycosuria, and consequently, increased ketogenesis [8]. We aimed to assess the role of ketone bodies in patients with T2DM. We analyzed clinical and laboratory characteristics and all-cause mortality rates in patients with T2DM presenting to our emergency department with diabetic ketosis (DK) and non-ketotic hyperglycemia (NKH).

Methods

Patients

This was a single-center, retrospective, cross-sectional study performed in the emergency department of a teaching hospital. We reviewed electronic charts from all patients with plasma glucose (PG) > 13.9 mmol/L at admission between January 1st 2010 and December 31st 2014. DK was defined as PG >13.9 mmol/L, ketonuria >2+ and a capillary bicarbonate level >18 mmol/L or capillary blood pH >7.30. Patients with PG >13.9 mmol/L and undetectable ketonuria (<1+) were classified as non-ketotic hyperglycemia (NKH). Patients were considered to have T2DM if they were not diagnosed with T1DM prior to or after admission or if they were older than 40 years at diagnosis, because T2DM in young adults is rare in our population. Patients younger than 40 years, patients diagnosed with type 1 diabetes mellitus and patients with malignant diseases were excluded.

Patient data including past medical history, comorbidities, medication and physical examination was obtained from the emergency department charts. Diabetes-specific data (glycated hemoglobin, body mass index, renal function) was obtained from different institutional electronic registries and was only analyzed in patients that attended a regular diabetologist visit six months prior or six months after admission. Mortality data was obtained from the Croatian Department of Public Health.

Statistical analyses

Patient characteristics were assessed using descriptive statistics presented as a mean with standard deviation. Independent continuous variables were compared using the t-test or Mann-Whitney test when appropriate and categorical variables using the Chi square test. Cox

proportional hazard models were used to analyze the link between patient characteristics and mortality, and to adjust for potential confounding factors. Backward conditional stepwise approach was used to determine variables independently associated with survival. P values <0.05 were considered significant. The statistical analysis was done using SPSS Version 20.0.

Results

Among 103,563 admissions over the five-year period, there were 5,088 admissions in which patients had PG >13.9 mmol/L. Acid-base status or urine analysis was missing in 1,679 admissions and these patients were excluded from further analyses. Among 3,409 admissions, we observed 630 episodes of DK in 520 patients, 215 episodes of DKA in 165 patients, and 2,562 episodes of NKH in 2,041 patients. Only 8.5% (44) of patients with DK had the diagnosis of type 1 diabetes mellitus and they were excluded from the study. First admissions of 486 patients with DK and 486 age- and sex-matched patients with NKH were included in the study. There were no differences in age and gender between the groups, but patients in the DK group had a slightly shorter duration of diabetes (Table 1). During an observation time of 33.4 months, death of any cause occurred in 199 patients (40.9%) in the NKH group and in 147 (30.2%) in the DK group (hazard ratio in the DK group, 0.63; 95% confidence interval, 0.48 to 0.82; P = 0.0005). Mortality risk was even lower after adjustment for duration of diabetes (HR 0.442, 95% CI 0.30-0.65, P<0.001) (Figure 1). All 46 patients in the NKH group who were readmitted had NKH at their next visit. Similarly, 91.0% (40/44) of patients with DK, had DK on their next visit. Patient characteristics are presented in table 1. Patients with DK had higher hospitalization rates, a higher incidence of newly diagnosed T2DM and acute coronary syndromes, but lower

incidence of symptomatic heart failure and cardiac arrhythmias. The duration of the leading symptom at admission was longer in patients with NKH. Dyspnea was more frequent in the NKH group, while vomiting was more frequent in DK group. Patients with DK had higher estimated hemoglobin, estimated glomerular filtration rate (eGFR), capillary pH and bicarbonate, leukocytes and C-reactive protein levels, and lower potassium levels. Plasma glucose at admission and HbA1c six months prior or after the admission were similar in both groups. Patients with DK used less furosemide, calcium channel blockers, beta-blockers and less antihypertensive agents despite the fact that both groups had similar blood pressure at admission. Patients with DK used metformin more frequently and needed lower insulin doses to achieve similar HbA1c levels. Interestingly, the association between DK and mortality diminished after adjustment for metformin use. Patients with DK had lower serum hemoglobin and potassium levels, higher leucocytes, C-reactive protein and higher estimated glomerular filtration rate (eGFR). However, in backward conditional stepwise analysis, only advanced age (HR 1.05, 95% CI 1.01 - 1.09, P=0.011), male gender (HR 5.744, 95% CI 1.73 - 19.08, P=0.004), eGFR (HR 0.98, 95% CI 0.97 - 0.99, P=0.004) and symptomatic heart failure (HR 6.48, 95% CI 2.17 - 19.34, P=0.001) were independently associated with mortality. In a stepwise multivariate analysis that included all medication, mortality was increased in patients taking sulfonylureas (HR 1.89, 95% CI 1.30-2.76, P=0.001), insulin (HR 1.54, 95% CI 1.03-2.31, P=0.037), furosemide (HR 1.60, 95% CI 1.07-2.41, P=0.023), calcium antagonists (HR 1.43, 95% CI 1.00 – 2.05, P=0.049), and decreased in patients taking metformin (HR 0.66, 95% CI 0.44-0.99, P=0.043).

Discussion

To the best of our knowledge, this is the first study that compared survival rates in patients with and without DK presenting with hyperglycemic crises. Similar to our study, previous studies have shown high mortality rates after hyperglycemic crises [9], emphasizing the need for prevention and proper treatment.

In patients with T1DM, DK precedes the development of diabetic ketoacidosis and requires prompt management and self-monitoring. However, little is known about DK in patients with T2DM. Our study showed that patients with DK have decreased all-cause mortality when compared with patients with NKH. Previous studies have shown that patients with T2DM have impaired ketogenesis, which is associated with high serum insulin levels which directly suppress ketogenesis in the liver [4,5]. High insulin levels also inhibit growth hormone and glucagon secretion, both of which may contribute to suppressed ketogenesis [4]. In our study, patients with DK used more metformin and required lower insulin doses, both of which may be associated with lower serum insulin levels and improved ketogenesis. In a multivariate model that included metformin and ketonuria, the link between DK, metformin and survival diminished. This suggests that metformin plays important role in improving ketogenesis in patients with T2DM. Previous studies also showed decreased mortality in patients taking metformin and increased mortality in patients taking sulfonylureas and insulin irrespectively of blood glucose control and duration of diabetes [10–12]. Improved ketogenesis can also be attributed to physical activity, type of diet, adenosine 5'-monophosphate-activated protein kinase (AMPK) activity and expression of the Foxa2 gene [13,14], although these factors were not analyzed in our study.

Positive ketone bodies can also be attributed to excessive vomiting, which was more common in the DK group.

In terms of the link between ketogenesis and decreased mortality, it is important to mention that due to this study's restrospecive and cross-sectional design, no association means causality, and this decreases the strength of any conclusions. Heart failure and kidney disease is the leading cause of death in diabetics. In our study, symptomatic heart failure, furosemide use, and estimated glomerular filtration rate were independently associated with mortality as well. Interestingly, patients with DK had less symptomatic heart failure, used less furosemide and antihypertensive drugs and had higher eGFR at admission, when compared with patients with NKH. In patients with diabetes, ketone bodies are more efficient fuel sources than glucose since insulin is not required for their utilization. Therefore, proper ketogenesis in acute hyperglycemic crisis may be lifesaving, because it supplies the myocardium with a sufficient amount of energy. Indeed, previous studies have found that hypertrophied and failing hearts shift to ketone body utilization [15][16]. Moreover, ketone bodies have protective effects on the kidney and infusion of exogenous ketone bodies improves kidney function in healthy subjects and in patients with diabetes [17][18][19].

In the end, we would like to correlate our results with the results of the EMPA-REG outcome trial. SGLT-2 inhibitors are the most potent stimulators of ketogenesis by promoting profound glycosuria, carbohydrate depletion, and consequent rise in serum glucagon and decrease in serum insulin levels [8]. Several cases of normoglycemic ketoacidosis have been described in patients treated with SGLT-2 inhibitors [20]. Empagliflozin was the first anti-diabetic drug that reduced mortality in patients with T2DM and high cardiovascular risk factors. Empagliflozin did not reduce the incidence of myocardial infarction or stroke, but reduced hospitalization rates for

heart failure, death from cardiovascular causes, and decreased the progression of kidney disease [7,21]. Although our study cannot be directly compared to the EMPA-REG trial, we observed that patients with DK and patients treated with empagliflozin had similar outcomes in terms of lower heart failure rates and kidney disease. Unfortunately, the EMPA-REG trial did not assess dynamics of ketogenesis.

Our study has several limitations due to its retrospective and cross-sectional design. Ketone body status was determined only during the acute hyperglycemic crisis. Patient follow-up and repeated ketone body measurement would improve the power of the study. Furthermore, the diagnosis of T2DM was based on whether or not the diagnosis of type 1 diabetes mellitus was made prior or after the hyperglycemic crisis, and antibody status and beta-cell function were not assessed. However, in our Croatian population, T2DM is uncommon in young adults; therefore, we set an arbitrary cut-off of 40 years at initial diagnosis to reduce the chances of including patients with type 1 diabetes. The fact that both groups had similar body mass index, duration of diabetes and proportion of patients requiring insulin therapy suggests that we successfully recruited patients with T2DM.

In conclusion, type 2 diabetic patients with hyperglycemic crisis and DK have decreased all-cause mortality when compared to those with NKH. As our findings are retrospective and cross-sectional, further prospective studies are needed to explore the possibility that DK may be a protective factor in patients with hyperglycemic crises.

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Table 1. Differences in anthropometric characteristics, medical history, physical examination and laboratory results between patients with non-ketotic hyperglycemia (NKH) and diabetic ketosis (DK).

	NKH N = 486	DK N = 486	P value*
Age (years)	66.8 ± 12.3	67.1 ± 11.6	0.770
Male gender n (%)	56.2 (273)	55.1 (268)	0.759
Duration of diabetes (years)	11.5 ± 9.7	9.8 ± 9.6	0.047
BMI (kg/m^2) †	30.8 ± 5.9	30.0 ± 6.3	0.234
Hospitalized n (%)	41.9 (204)	50.5 (238)	0.035
Readmissions n (%)	9.3 (46)	9.1 (44)	0.961
Newly diagnosed diabetes n (%)	15.2 (74)	21.6 (105)	0.013
Reason for admission			
Acute coronary syndrome n (%)	4.7 (23)	16.1 (78)	<0.001
Symptomatic heart failure n (%)	5.8 (28)	0.8 (4)	<0.001
Hyperglycemia n (%)	36.4 (177)	38.9 (189)	0.506
Symptoms and physical examination			
Weight loss n (%)	11.3 (55)	10.9 (53)	0.961
Polyuria n (%)	18.7 (91)	23.3 (113)	0.100
Abdominal pain n (%)	23.3 (113)	27.2 (132)	0.184
Vomiting n (%)	11.9 (58)	23.1 (112)	<0.001
Dyspnea	19.5 (95)	5.5 (27)	<0.001
Duration of symptoms (days)	11.9 ± 39.6	5.2 ± 13.7	<0.001
Systolic blood pressure (mmHg)	141.8 ± 25.1	141.2 ± 25.8	0.815
Diastolic blood pressure (mmHg)	83.0 ± 13.1	83.2 ± 13.2	0.881
Heart rate (beats/min)	88.7 ± 21.6	93.1 ± 20.9	0.026
Sinus rhythm n (%)	80.0 (389)	88.3 (429)	<0.001
Laboratory findings			
Plasma glucose (mmol/L)	20.4 ± 6.4	20.6 ± 6.2	0.517
HbA1c (%) †	8.5 ± 2.1	8.6 ± 2.2	0.772
Leucocytes (10^9/L)	10.9 ± 5.8	11.8 ± 5.3	0.008
Hemoglobin (g/L)	133.1 ± 23.5	140.0 ± 19.5	<0.001
eGFR (ml/min) †	73.4 ± 34.9	82.1 ± 34.1	0.023
Sodium (mmol/L)	134.8 ± 5.4	134.5 ± 4.4	0.312
Potassium (mmol/L)	4.4 ± 0.7	4.2 ± 0.5	<0.001
CRP (mg/L)	48.2 ± 82.0	71.4 ± 100.6	<0.001
pH	7.40 ± 0.10	7.43 ± 0.06	<0.001
Bicarbonates (mmol/L)	21.2 ± 5.1	22.7 ± 3.7	<0.001

Medication			
Metformin n (%)	22.8 (111)	34.5 (168)	<0.001
Sulfonylureas n (%)	31.1 (151)	34.8 (169)	0.246
Insulin n (%)	24.7 (120)	25.1 (122)	0.987
Insulin dose (units)	57.2 ± 43.8	42.7 ± 19.6	0.004
Statins	20.2 (98)	18.1 (88)	0.463
Furosemide n (%)	21.0 (102)	9.5 (46)	<0.001
Thiazides	24.5 (119)	24.3 (118)	1.000
ACE inhibitors	44.2 (215)	42.2 (205)	0.560
Beta-blockers	35.6 (173)	19.3 (94)	<0.001
Calcium channel blockers	36.2 (176)	16.7 (81)	<0.001
Number of antihypertensives			
0	28.8 (140)	35.3 (173)	0.023
1	27.0 (131)	35.8 (174)	0.004
2	23.9 (116)	20.0 (97)	0.162
3	15.2 (74)	8.2 (40)	0.001
4	4.9 (24)	0.6 (3)	<0.001

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; ACE - angiotensin-converting-enzyme

*continous variables are compared with t-test or Mann-Whitney test when appropriate and categorical variables with Chi-square test;

† analysis performed on 305 subjects with diabetic ketosis and 276 patients with NKH.

Figure 1. Shown are the cumulative hazards of the all-cause mortality adjusted for duration of diabetes in patients with non-ketotic hyperglycemia (red line) and diabetic ketosis (blue line). Hazard ratios are based on Cox regression analyses.