Research article

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Predictors and Trend of Ketoacidosis Hospitalization Rate in Type 2 Diabetes Mellitus Patients from 2006 to 2015 in Abruzzo Region, Italy

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Abstract

Aims. This study aimed to assess the trend of hospitalizations for DKA in adult patients with type 2 diabetes mellitus and its associated factors.

Design. A retrospective cross-sectional study was performed. Data were collected from hospital discharge records (HDRs) of patients (age ≥18) with either primary or secondary discharge diagnosis for DKA and type 2 diabetes from 2006 to 2015 in Abruzzo region. Age-adjusted hospitalization rates were computed by gender and standardized on the regional population in 2006. A logistic regression model was implemented using presence of DKA as dependent variable.

Results. We identified 160,366 HDRs with type 2 diabetes. Out of them, 1611 (1.00%) were due to DKA. The hospitalization rates for DKA increased both for male +115.9 and female +142.8%, from 2006 to 2015. The most significant predictors of DKA were age 18-44 (aOR=4.17), uncontrolled diabetes (aOR=1.79), trauma (aOR=1.38), any infection (aOR=1.68), liver disease (aOR=1.29), fluid and electrolyte disorders (aOR=2.09), psychosis (aOR=1.69).

Conclusions. Trends of DKA in adult patients with type 2 diabetes has been increasing in both male and female. Multimorbidity is an open challenge for public health, therefore better coordination is needed among different specialist consultants to reduce the occurrence of this preventable complication. ***Clin Ter 2020; 171(1):e53-58. doi:10.7417/CT.2020.2189***

Key words: *Ketoacidosis, Type 2 diabetes, Multimorbidity, Inpatient diabetes*

Introduction

Diabetic ketoacidosis (DKA) is considered as one of the most serious hyperglycemic emergency occurring in patients with diabetes (1). DKA was long considered a key clinical feature of type 1 diabetes but, in recent years, an increasing number of ketoacidosis cases have also been reported in subjects with type 2 diabetes (2).

In the USA 34% of DKA episodes occur in patients with type 2 diabetes (3). American and European retrospective studies show that approximately 20% to 30% of DKA patients had type 2 diabetes (4,5). The prevalence of DKA in type 1 and type 2 diabetes pediatric patients is well documented (6,7) but only five papers describe the epidemiology of DKA in European adult populations and they mostly focus on type 1 diabetes (8). Although in patients with diabetes the male-female ratio is roughly equal, women may be more likely to develop diabetic ketoacidosis than men (9).

Associated conditions such as infections, trauma, and drugs (corticosteroids, thiazides, sympathomimetic agents and atypical antipsychotic) are well-known trigger factors for DKA (10).

While in the pediatric population specific programs have been established to reduce hospitalizations for DKA in high-risk patients, there is a need for similar programs to involve adults too (11).

Moreover, DKA hospitalization has been increasing worldwide because of unknown causes (11). Unlike this global trend, in Italy Lombardo et al. report a reduction in hospitalization but recording hyperglycemic complications as a whole and without discriminating the diabetes type (12).

Therefore, the trend of hospitalizations for DKA in type 2 diabetes adult patients in Italy remains unknown. In this study, we compute the trends of hospitalization rates for DKA by gender and assess the predictors of DKA in hospitalized adult patients with type 2 diabetes in Abruzzo region, Italy, in the period 2006-2015.

Methods

This is a population-based cross-sectional study carried out in Abruzzo region. Abruzzo is an Italian central region bordering the Adriatic Sea with approximately 1,300,000 inhabitants. It is organized in four Local Heath Authorities which manage four third level hospitals. The study includes all hospitalizations of diabetic patients occurred from January 1, 2006 to December 31, 2015 in hospitals of Abruzzo region. Data were collected from all hospital discharge records (HDR), using the hospital information system. Each HDR includes admission and discharge dates,

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discharge status (categorized as "discharged," "transferred" or "death"), presence of trauma, demographic information (birthplace, residence, gender, and age) and up to 6 discharge diagnoses (1 principal and 5 secondary diagnoses) coded according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM). The HDR of all adult diabetic patients (age ≥ 18) were extracted and identified using the principal or the secondary diagnostic codes 250.x. Only patients with a diagnostic code referred to type 2 diabetes were included identifying 250.00, 250.02, 250.x.0, 250.x.2 where x=1- 9 in any diagnosis. We selected cases of DKA using the principal or secondary diagnostic codes 250.10 or 250.13. We excluded patients with diagnostic code for diabetic coma (250.3), as the code do not distinguish between hypoglycemic and DKA-related coma. We identified patients with uncontrolled diabetes by primary or secondary diagnostic code 250.x2 where x=0-9, renal complications by 250.4x, ocular complications by 250.5x, neurological complications by 250.6x and peripheral vascular complications 250.7x. Moreover, comorbidities were expressed using the Elixhauser's Comorbidity index using the encoding proposed by Quan et al. (13). Since the Elixhauser's Comorbidity index does not include any type of infective disease, we extracted these conditions by primary or secondary diagnostic code 001-139. In the ICD-9-CM low tract respiratory infections (LTRI) are defined separately from other infective diseases, so we identified LTRI coded as 480.xx-486.xx.

Statistical Analysis

Quantitative variables were expressed as median and interquartile range (IQR). Qualitative variables were summarized as frequency and percentage.

Hospitalization rates for DKA were computed every year by gender as the ratio between the number of HDR with DKA codes in any diagnosis and the Abruzzo resident population per 100,000, standardized by age on the regional population in 2006. A logistic regression model was implemented as follows: presence of diabetic ketoacidosis was considered as dependent variable and each available factor was used as independent variable (univariate analysis). In the multivariable analysis, a stepwise logistic regression model with backward selection was performed: all covariates with p-value <0.10 were included. Adjusted odds ratios (adjORs) with their 95% confident intervals (95%CIs) were computed to measure the association among factors at the baseline and presence of ketoacidosis. Statistical significance was set at $p < 0.05$. The data were analyzed using the statistical software Stata® version 15 (14).

Ethical Approval

The present study was carried out in conformity with the regulations on data management of the Regional Health Authority of Abruzzo and with the Italian Law on privacy (Art. 20_21 DL 196/2003) published on the Official Journal n. 190 of 14 August 2004. Data were encrypted before the analysis at the regional statistical office, where each patient was assigned a unique identifier. This identifier eliminated the possibility of tracing the patient's identity. The use of these data does not require specific written informed consent from the patients.

Results

During the study period, a total of 72,621 type 2 diabetes patients (median age of 73.23; IQR: 64.31-80.52) produced 160,350 HDRs. The number of hospitalization for type 2 diabetes mellitus in Abruzzo in the study period and the patients' characteristics are shown in Table 1. DKA diagnosis was present in 1611 cases, 895 males (55.56%). Age-adjusted hospitalization rates for DKA per 100,000 residents increased both for male +115.9% (13.3/100,000 in 2006 vs 28.36/100,000 in 2015) and female +142.8% (7.68/100,000 in 2006 vs 18.65/100,000 in 2015). Every year, the ratio between males and females (ratio M/F) was in favor of males, as shown in Table 2.

The most significant factors associated with DKA were age 18-44 (adjOR=4.17; 95%CI: 3.27-4.31), uncontrolled diabetes (adjOR=1.79; 95%CI: 1.60-2.01), trauma (adjOR=1.38; 95%CI: 1.13-1.68), any infection (adjOR=1.68; 95%CI: 1.22-2.33), liver disease (adjOR=1.29; 95%CI: 1.09-1.53), fluid and electrolyte disorders (adjOR=2.09; 95%CI: 1.09-1.53), and psychosis (adjOR=1.69; 95%CI: 1.25-2.30). The multivariable logistic regression results are shown in Table 3.

Table 1. Hospitalizations for type 2 diabetes in Abruzzo, 2006-2015

Discharge	
N	160,350
Ketoacidosis in any diagnosis, n (%)	1611 (1.00)
Duration of stay, median (IQR)	7 (4-13)
Age distribution (years)	
18-44	2233 (1.39)
45-64	29,981 (18.70)
65-84	102,779 (64.10)
≥85	25,357 (15.81)
Rehospitalizations in the study period, n (%)	87,729 (54.71)
Patients	
N	72,621
Female, n (%)	34,324 (47.26)
Age, median (IQR)	73.23 (64.31-80.52)
Age categories	
18-44	1494 (2.06)
45-64	16,165 (22.26)
65-84	44,382 (61.11)
≥85	10,580 (14.57)
Citizenship	
Italians	71,317 (98.20)
Foreigners	1304 (1.80)

Table 2. Age-adjusted hospital admission rate for DKA/100,000 residents in Abruzzo 2006-2015

Year	Males *	Females *	Ratio M/F
2006	13,13	7,68	1,70
2007	21,23	9,07	2,34
2008	12,51	7,02	1,78
2009	8,18	5,48	1,49
2010	14,24	10,64	1,33
2011	12,27	9,24	1,32
2012	18,23	12,32	1,47
2013	22,85	14,97	1,52
2014	24,73	17,18	1,43
2015	28,36	18,65	1,52
Δ%**	+115,9	+142,8	

* Standardized by age on 2006 Abruzzo's population
**Relative percentage variation from 2006 to 2015

Discussion

The present study aimed at estimating the trends of hospitalization rates for DKA by gender and the predictors of DKA in hospitalized adult patients with type 2 diabetes in Abruzzo region, Italy, in the period 2006-2015.

In this study we assess that age adjusted hospitalization rates for DKA per 100,000 residents increased both for male +115.9%, and female +142.8%. A previous nationwide study conducted in Italy from 2001 to 2010 showed a decreased hospitalization rate for acute diabetic complications (12) but this study aimed to estimate the hospitalization trend for both acute hyperglycemic complications (ketoacidosis/hyperosmolarity) and not by diabetes type. However, it could be misleading to directly apply to the DKA the trend identified in people with any acute hyperglycemic complication and without distinguishing by diabetes type (15).

Consequently, our trend could be in contrast with the national one because our data refer to a single Italian region and consider only DKA occurrence in type 2 diabetes patients.

The results describe an association between DKA and some predictors as younger patients, uncontrolled diabetes, trauma, any infection, fluid and electrolyte disorders, liver disease and psychosis. These evidences are consistent with the scientific literature, which suggest how younger subjects with poor glucose control might be the group mostly contributing to the increase in DKA hospitalization rates among people aged <45 years (6,16,17). Also infections and trauma are known and frequent causes for the development of DKA in diabetic patients (10,18,19). Indeed patients with type 2 diabetes and poor metabolic control can develop DKA under stressful conditions such as trauma or infection (3).

The association between DKA and fluid and electrolyte disorders is consistent with the scientific literature. DKA patients usually present signs of dehydration, moreover have a total-body potassium deficit of ~3-5 mmol, also promoted by insulin therapy through the movement of potassium back into the intracellular compartment (10,20). In a previous study, Kamata et al. (21) showed that DKA in patients with type 2 diabetes is often associated with a more severe dehydration than in patients with type 1 diabetes, and the fluid electrolyte disorders require a greater volume of replacement fluids and potassium supplementation to resolve it. As suggested by Barski et al. (22), patients with DKA and type 2 diabetes have higher levels of plasma glucose that can presumably lead to more severe glycosuria and dehydration, compared to type 1 diabetes patients. As for the association between DKA and liver disease, it is known that diabetes is observed in up to 30% of patients with cirrhosis and diabetes can be either an underlying type 2 diabetes mellitus or the consequence of alterations directly related to an impaired liver function (23). Moreover, the incidence of acute liver failure appears to be increased in patients with diabetes (24). The difficulty of glycemic management in hepatopathic patient with diabetic comorbidity is also very well known (25) and there are not clear guidelines for the medication use in diabetic patients with cirrhosis, particularly in the early stage (26).

This study also highlights psychosis (including schizophrenic psychosis, episodic mood disorders, delusional disorders and other non-organic psychoses) as predictor of DKA. Other studies conducted on administrative data showed an association among acute diabetic complications and psychosis without distinguish between different subtypes such as diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome and hypoglycemia (27,28). The development of ketoacidosis in the psychotic patient could be linked to both antipsychotic therapy and the inadequate treatment of diabetes. Hence, as regards therapy, atypical antipsychotic drugs, particularly olanzapine and clozapine, are risk factors of DKA (29), although we should not exclude a potential pathogenic link suggested by the report of abnormal glucose regulation among individuals with schizophrenia that predate the introduction of antipsychotic therapy (30). Furthermore, in these patients the presence of a treatment gap allows to the increase of diabetes related morbidity (31). It has also been described how sedentary lifestyle, poor diet, and low medication adherence can play a role in the development of acute complications in these patients (31).

The results of this study should be considered in the light of some limitations. Firstly, HDRs lack of clinical information such as laboratory results, drug therapy and symptoms. This can lead to unmeasured confounders hampering the multivariate analysis. Secondly, the misclassification of outcomes and the potential underestimation of their frequencies may still be a possibility. Thirdly, there is not a linkage with outhospital mortality registry, drug prescription database or other recorded information, lacking important features involved in the pathogenesis and management of DKA. Particularly, the drug therapy could be linked to DKA onset. In addition, the design of a cross-sectional study is limited in assessing temporal relationship between exposure and outcome, and it cannot demonstrate the existence of a causal relationship between risk factors and DKA.

Table 3. Predictors of DKA in for type 2 diabetes

	DKA n(%)	**OR (95%CI)**	**adjOR (95%CI)**
Total sample	1611		
Gender			
Male	895 (55.56)	Ref.	
Female	716 (44.44)	0.93 (0.84-1.03)	
Age categories			
18-44	109 (6.77)	5.48 (4.35-6.91)	4.17 (3.27-5.31)
45-64	382 (23.71)	1.37 (1.17-1.62)	1.31 (1.10-1.55)
65-84	885 (54.93)	0.92 (0.80-1.07)	0.97 (0.84-1.12)
≥85	235 (14.59)	Ref.	Ref.
Citizenship			
Italians	1574 (97.70)	Ref.	Ref.
Foreigners	37 (2.30)	1.70 (1.22-2.36)	1.12 (0.80-1.57)
Controlled diabetes			
Yes	1185 (73.56)	Ref.	Ref.
Not	426 (26.44)	1.70 (1.52-1.90)	1.79 (1.60-2.01)
Diabetes complications			
Renal	12 (0.74)	0.31 (0.18-0.56)	0.24 (0.13-0.42)
Ocular	6 (0.37)	0.14 (0.06-0.32)	0.11 (0.05-0.26)
Neurological	6 (0.37)	0.33 (0.15-0.75)	0.25 (0.11-0.56)
Peripheral vascular	4 (0.25)	0.02 (0.00-0.06)	0.02 (0.00-0.06)
Trauma	113 (7.01)	1.43 (1.18-1.74)	1.38 (1.13-1.68)
Comorbidities			
Infection (All)	70 (4.35)	1.71 (1.34-2.18)	1.68 (1.22-2.33)
Low respiratory tract infection	82 (5.09)	1.29 (1.03-1.62)	1.13 (0.90-1.42)
Congestive heart failure*	137 (8.50)	0.57 (0.48-0.68)	0.65 (0.54-0.78)
Cardiac arrhytmias*	108 (6.70)	0.57 (0.47-0.70)	0.67 (0.55-0.82)
Valvular disease*	54 (3.35)	0.73 (0.56-0.97)	0.91 (0.69-1.20)
Pulmonary circulation disorders*	11 (0.68)	0.96 (0.52-1.74)	
Peripheral vascular disorders*	51 (3.17)	0.49 (0.37-0.65)	0.89 (0.67-1.18)
Hypertension, uncomplicated*	293 (18.19)	0.50 (0.44-0.57)	0.52 (0.46-0.59)
Hypertension, complicated*	186 (11.55)	1.21 (1.04-1.41)	1.11 (0.95-1.30)
Paralysis*	4 (0.25)	1.06 (0.39-2.86)	
Other neurological disorders*	27 (1.68)	1.20 (0.82-1.76)	
Chronic pulmonary disease*	162 (10.06)	0.87 (0.73-1.02)	0.90 (0.76-1.06)
Hypothyroidsm*	23 (1.43)	1.00 (0.66-1.51)	
Renal failure*	134 (8.32)	0.87 (0.73-1.04)	
Liver disease*	158 (9.81)	1.72 (1.45-2.03)	1.29 (1.09-1.53)
Peptic ulcer disease excluding bleeding*	3 (0.19)	1.03 (0.33-3.22)	
AIDS/HIV*	1 (0.06)	0.41 (0.05-2.92)	
Solid tumor without metastasis*	126 (7.82)	0.98 (0.82-1.18)	
Metastatic cancer*	28 (1.74)	0.87 (0.60-1.27)	
Lymphoma*	14 (0.87)	1.53 (0.90-2.60)	
Rheumatoid arthritis/collagen vascular diseases*	13 (0.81)	0.83 (0.48-1.43)	
Coagulopathy*	5 (0.31)	0.86 (0.35-2.08)	

Obesity*	53 (3.29)	0.80 (0.33-1.93)	
Weight loss*	5 (0.31)	1.21 (0.50-2.93)	
Fluid and electrolyte disorders*	61 (3.79)	2.46 (1.90-3.19)	2.09 (1.09-1.53)
Blood loss anemia*	20 (1.24)	1.48 (0.95-2.38)	1.38 (0.88-2.16)
Deficiency anemia*	46 (2.86)	1.14 (0.85-1.54)	
Alcohol abuse*	7 (0.43)	2.95 (1.39-6.27)	1.74 (0.81-3.73)
Drug abuse*	1 (0.06)	1.35 (0.18-9.71)	
Psychoses*	45 (2.79)	2.38 (1.76-3.22)	1.69 (1.25-2.30)
Depression*	18 (1.12)	1.02 (0.64-1.63)	

In conclusion, in Abruzzo region the trend of DKA in adult patient with type 2 diabetes is increasing in both male and female.

Our study points out some well-known DKA predictors. While some of them are acute conditions such as trauma, infections and hydro-electrolytic disorders, others are chronic conditions such as liver disease and psychosis. These results are remarkable in terms of prevention, whereas hospital admissions for acute diabetic complications are often avoidable and should be considered as a sentinel health events of inadequate outpatient care. In order to reduce the DKA trend a patient-centered, a holistic approach to diabetes management is needed. Multimorbidity is an open challenge for public health and often to multimorbid patients are dispensed fragmented and ineffective treatments. Indeed, different comorbidities require the coordination of different specialist consultants to meet specific health needs.

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