

## Characteristics of Ketosis-onset Diabetes in Tunisian Population

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### Abstract

Different types of diabetes can be presented by a ketosis (DK) or ketoacidosis (DKA). The objectives of this study were to analyze the characteristics of patients with newly diagnosed diabetes revealed by DK or DKA and discuss the different types of diabetes particularly ketone prone type 2 diabetes.

**Subjects and methods:** Retrospective study including 288 patients with new ketosis onset diabetes; 178 men, mean age: 35.5 years. We analyzed clinical, biological, therapeutic and subsequent clinical course data. Diabetes was classified according to clinical, biological and follow-up data.

**Results:** It was a DKA in 39 cases (13.5 %). Patients were classified as type 1 in 62.2% of cases and ketosis type 2 diabetes in 34.7 % of cases. As compared to type 1 diabetes, ketosis type 2 diabetes patients had a more advanced age, higher body mass index and waist circumference, and less frequent DKA. After the acute episode, 60% of ketosis type 2 diabetes was treated with insulin and half of them had associated metformin. After a mean follow-up of 2.4 years, 52% of ketosis type 2 diabetes patients were treated with oral hypoglycemic agents.

**Conclusion:** Ketosis type 2 diabetes is a relatively new entity accounting for about one third of all new cases of DK or DKA in our population.

**Keywords:** Diabetic ketoacidosis; Ketosis prone type 2 diabetes; Type 1 diabetes

### Introduction

Ketosis is a frequent and potentially life-threatening complication of diabetes. It may occur in known diabetic patients or it may be a circumstance of diabetes diagnosis. Ketosis onset diabetes is generally considered and treated as type 1 diabetes. However, type 2 diabetes may be revealed by ketosis or keto-acidosis [1-4]. Classification of diabetes at the time of ketosis is important for a better long term management. The aim of this study was to analyze clinical, biological and subsequent clinical course data of subjects who have had a ketosis (DK) or ketoacidosis onset diabetes (DKA) and to discuss the different types of diabetes and especially ketosis-prone type 2 diabetes.

### Research Design and Methods

We performed a retrospective analysis of all 288 patients referred for ketosis or ketoacidosis new onset diabetes to the endocrinology and diabetology department at Tunisian university hospital La Rabta from 1st January 2000 to 31th October 2005. They were 178 males (61.8%) and 110 females (38.2%) with a mean (SD) age of 35.5 (17.1) years.

We analyzed patient's medical records

- Clinical data - Age, gender, consanguinity, family history of diabetes, known personal hypertension, dyslipidemia, auto-immune disease, clinical history (symptoms of hyperglycemia, their duration, precipitating factor), physical examination (general condition, temperature, Kussmaul breathing, symptoms of dehydration, state of consciousness, blood pressure, weight, height, waist circumference (WC), glucosuria, acetonuria).
- Para clinical data - Blood glucose, sodium, potassium, urea, creatinine, pH or bicarbonates, complete blood count, erythrocyte sedimentation rate, cyto-bacteriological examination of urine, chest radiography.
- Diabetes vascular complications (history of cerebro vascular or

cardiac attack, blood pressure, peripheral pulses, neurological examination, optic fundus, electrocardiogram, proteinuria or microalbuminurie)

- Anti diabetic treatment prescribed initially and at follow-up.

Classification of diabetes was based on initial clinical and biological data (family history of diabetes, abdominal obesity, severity of polyuria and polydipsia, weight loss before DKA, duration of symptoms, severity of DKA, presence of vascular complications) and subsequent clinical course to last follow-up (weight, need for exogenous insulin). Patients were divided into two major groups; type 1 diabetes and ketosis type 2 diabetes.

Ketoacidosis is defined by hyperglycemia  $> 2.5\text{g/l}$ , presence of urinary ketone  $\geq ++$  using Keto-Diastix Bayer<sup>®</sup> ketone and glucose reagent strips for urinalysis and arterial  $\text{pH} < 7.30$  or venous  $\text{HCO}_3^- < 15 \text{ mmol/L}$ . Ketosis was defined by the presence of hyperglycemia and urinary ketone without acidosis.

Data management and analysis were made using Epi-Info 6 statistical package. We used CHI 2 test for discontinued variables and Student's test for continues variables. The difference was considered significant if  $p < 0.05$ .

### Results

The study concerned 288 subjects with a sex ratio of 1.61 and a

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mean (SD) age of 35.5 (17.1) years [11-89 years]. Female were older than males (mean (SD) age of 38.7(18.6) vs 33.5(15.7) years,  $p = 0.03$ ). Family history of diabetes was reported in 57.3 % of cases. Parental Consanguinity was present in 36 % of cases. Hypertension was known in 28 subjects (9.7%), dyslipidemia in 24 (8.5 %) and an auto-immune disease in 5 patients (celiac disease in 1 case, Grave's disease in 1 case, hypothyroidism in 2 cases and vitiligo in 1 case). Polyuria and polydipsia were reported by 278 patients (96.9 %) during a mean (SD) period of 49.8 (93.5) days [4 days-2 years]. Weight loss was reported in 234 patients (81.5 %) by an average (SD) of 7.1 (7.7) Kg. Mean body mass index (BMI) (SD) was 23.6 (5.8) Kg/m<sup>2</sup>. Females had a mean BMI significantly higher than men (mean BMI (SD) 25.1 (6.2) vs 22.6 (5.2) Kg/m<sup>2</sup>,  $p = 0.0003$ ). Obesity (BMI  $\geq 30$  Kg/m<sup>2</sup>) was noted in 22 females (12.3%) and 12 males (10.9%). Overweight (BMI = 25 – 29.9 Kg/m<sup>2</sup>) was noted in 28 females (15.7%) and in 37 males (33.6%). Abdominal obesity was noted in 57 females (32%) (WC  $\geq 80$  cm) and in 34 males (30.9 %) (WC  $\geq 94$  cm). It was a DKA in 39 cases (13.5 %) and a DK in 249 cases (86.5 %). Precipitating factor was an infection in 41.3 % of cases, an emotional stress in 4.5% of cases and was not determined in the other cases. According to clinical and biological data, diabetes was classified as type 1 diabetes in 179 cases (62.2 %), ketosis type 2 diabetes in 100 cases (34.7 %) and other types in 9 cases (Figure1).

The comparison of clinical data between patients classified as type 1 diabetes and those classified as ketosis type 2 diabetes showed that type 1 diabetes patients were younger, more frequently of male gender (Figure 2,3), DKA was more frequent, BMI and WC were lower. The frequency of family history of diabetes didn't differ between the two groups (Table 1). Microvascular complications were present in 30 (30%) ketosis type 2 diabetes patients: retinopathy in 6 cases (6 %), peripheral neuropathy in 21 cases (21 %) and nephropathy in 7 cases (7%). Hypertension was present in 28 cases (28%), cerebro-vascular attack in 4 cases (4%), coronary heart disease in 7 cases (7%) and peripheral artery disease in 4 cases (4%).

At discharge, insulin therapy was prescribed in all type 1 diabetes patients and in 60 (60%) ketosis type 2 diabetes patients in whom 30 associations with metformin. The others were treated with oral anti-diabetic agents (Figure 4). All ketosis type 2 diabetes patients presenting with DKA were treated with insulin. Among the 73 ketosis type 2 diabetes patients followed at the office, during a mean follow-up period (SD) of 2.4 (1.1) years, 28 patients were under oral drugs and 10 over the 45 patients (22.2 %) initially treated with insulin were switched to oral drugs after a mean period of 14.7 months. Thus, 52%

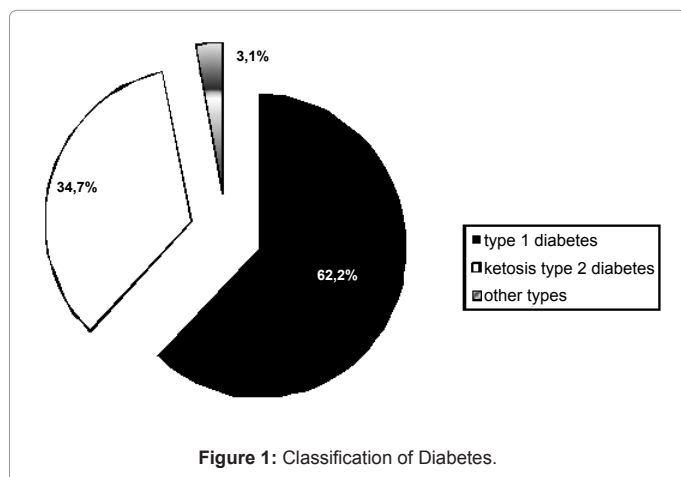


Figure 1: Classification of Diabetes.

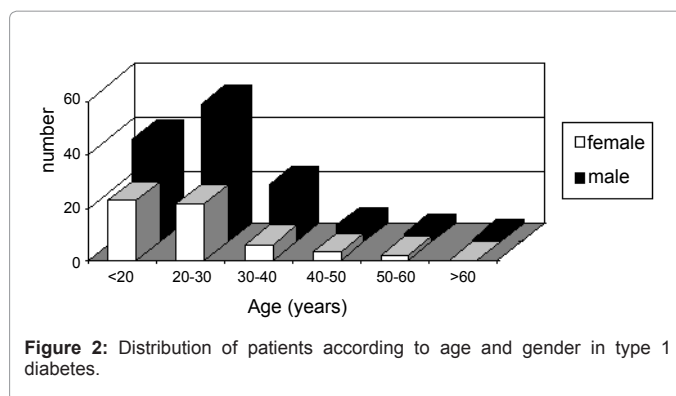


Figure 2: Distribution of patients according to age and gender in type 1 diabetes.

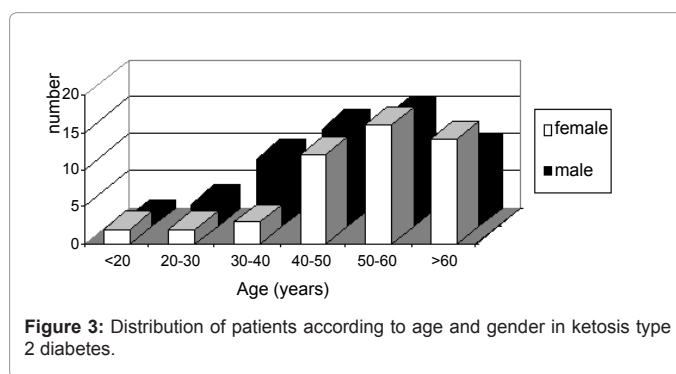


Figure 3: Distribution of patients according to age and gender in ketosis type 2 diabetes.

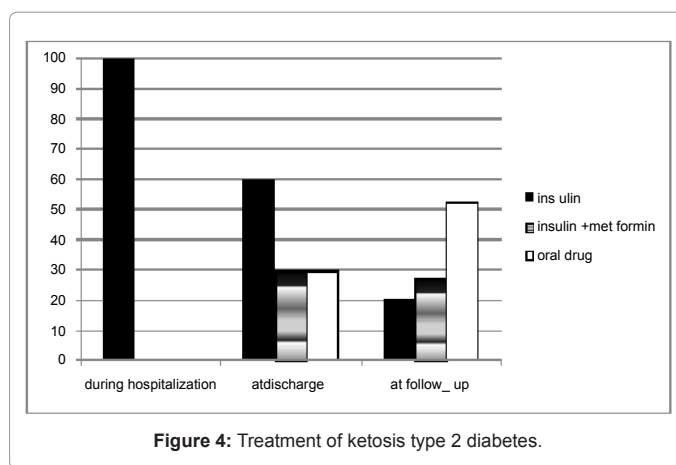


Figure 4: Treatment of ketosis type 2 diabetes.

of ketosis type 2 diabetes patients followed at the office were treated with oral drugs.

## Discussion

Type 1 diabetes is characterized by a deficiency in insulin secretion and has generally an acute clinical presentation, whereas type 2 diabetes is characterized by an insulin resistance and is a latent disease that can be asymptomatic for years. However, type 2 diabetes can be expressed by a ketosis in the presence of a precipitating factor but ketosis is not a classic initial presentation of the disease. Type 2 diabetes generally occurs in patients with family history of diabetes, abdominal obesity and can be associated with hypertension and dyslipidemia and complicated by micro and macroangiopathy. Whereas, type 1 diabetes generally appears in younger subjects with normal weight and is presented with a marked polydipsia and polyuria, an important weight

	All patients (n=288)	Type 1 diabetes (n = 179)	Ketosis type 2 diabetes (n = 100)	P (type 1 vs ketosis type 2 diabetes)
Age (years)	35.5 (17.1)	25.9 (10.0)	51.4 (14.6)	0.000000
Gender ratio (male/female)	1.61	2.2	1.04	0.005
Ketoacidosis	13.5	17.3	8.0	0.02
Family history of diabetes	57.3	56	65	NS
Known hypertension	9.7	0	28	0.0000000
Infection	41.3	36.8	49.0	0,04
Weight loss (Kg)	7.1 (7.7)	6.9 (6.7)	7.6 (9.5)	NS
Weight variation	-12	-13	-11	NS
BMI (Kg/m <sup>2</sup> )	23.6 (5.8)	20.8 (4.1)	28.5 (5.1)	0.000000
Obesity	11.8	2.8	29	0.000000
Overweight	22.2	8.9	46	0.000000
Waist circumference (cm)	85.8 (15.4)	78.1 (12.1)	98.1 (12.2)	0.000000
Abdominal obesity (TT> 94cm in men and >80cm in women)	31.6	12.8	65	0.0000000

Values are mean (standard deviation) or percentage

**Table 1:** Clinical characteristics of patients according to the type of diabetes.

loss and a ketoacidosis. Type 2 diabetes can be treated with oral agents but type 1 diabetes necessitates insulin therapy. We used a series of these arguments for the classification of our diabetic patients. Thus, 37.8% of cases with presenting DK and DKA revealed ketosis prone type 2 diabetes. This particular form of diabetes was reported in some populations such as those of black African origin and some ethnic minorities. In African Americans, Umpierrez [1] noted that 74 % of patients with inaugural DK or DKA had ketosis type 2 diabetes. On the same way, Nyenwe et al. [2] and Pinerio-Pilona & Raskin [3] noted a frequency of 60 %. In Koreans [4], this sub-type of diabetes represented 43% of inaugural DK or DKA. Ketosis type 2 diabetes represents one over 8 cases of diabetes in black American people from African origin [2,5-8] but is rarely described in Asiatic and white populations [9]. Our population is particular as it is a mixture of Arab and Berber races and mostly originates from rural areas that migrated to the capital city of Tunis.

Mean age of patients with ketosis type 2 diabetes was 51.4 years in our study and varied from 33 to 53 years in the literature [5,10]. All studies agree that type 1 diabetes appears at an earlier age. However, age is not sufficient to distinguish between the two types of diabetes as the two types can occur at any age.

Male gender was more frequently described in this sub type of diabetes (gender ratio varying from 1.5 to 3) but this was not the case in our study (gender ratio was 1.04) [8,11]. Family history of diabetes was as frequent in the two types of diabetes in our population (56% and 65%) and is explained by the high prevalence of diabetes in our general population [12]. So, the presence of type 2 diabetes in relatives doesn't exclude type 1 diabetes. Family history of diabetes in ketosis type 2 diabetes was also common in other populations varying from 60 to 84% [10,13].

Hypertension was present in 28 % of our ketosis type 2 diabetes patients which is close to that noted in other studies like that of Pinerio-Pilona et al. [11]. DKA was less frequent (8%) than DK in our ketosis type 2 diabetes. Tanaka et al. in Japan [14] reported 45.8 % of DKA in ketosis type 2 diabetes and explained this high frequency of DKA by a pancreatic glucotoxicity secondary to an excess of absorption of soft drinks. On the other hand, ketosis type 2 diabetes represented 20.5% of all cases of DKA in our study. So, the severity of a DKA doesn't exclude ketosis type 2 diabetes.

Obesity is a classic feature of type 2 diabetes and is the main cause of insulin resistance. BMI in our ketosis type 2 diabetes was significantly

higher than in type 1 diabetes (mean (DS) BMI of 28.5 (5.1) Kg/m<sup>2</sup> vs 20.8 (4.1) Kg/m<sup>2</sup>, p=0.0000) and varied from 26 to 37Kg/m<sup>2</sup> in different series [2,8]. 29 % of our ketosis type 2 diabetes patients were obese and 46 % were overweight. The frequency of obesity in ketosis type 2 diabetes varied from 20.6 % in the study of Mauvais Jarvis et al. [13] to 55% in the study of Banerji et al. [15] and 81.5% in that of Pinerio-Pilona et al. [11].

Different precipitating factors can lead to hyperglycemic crisis. Infectious diseases are the most common cause occurring in 30 à 50 % of cases [16]. A precipitating infectious cause was found in 36.8% of our type 1 diabetes patients and 49% of ketosis type 2 diabetes. Balasubramanyam et al. [7] reported that half of ketosis type 2 diabetes presented by DKA had no identifiable precipitating factor. Glucotoxicity and lipotoxicity might be implicated in the insulinopenia causing DKA in ketosis type 2 diabetes [2,14,17,18]. Glucotoxicity can be secondary to an excess of soft drinks taken to satisfy thirst [19]. Sobngwi suggested the role of human herpes virus 8 (HHV-8) in the pathogenesis of ketosis type 2 diabetes [20].

Distinguishing type 1 from ketosis type 2 diabetes is generally easy. A young age, a normal weight, the absence of a precipitating factor, the severity of ketoacidosis and the presence of an autoimmune disease are in favour of type 1 diabetes. Whereas, an overweight, the presence of hypertension or of vascular complications and the possibility of treatment with oral drugs are in favour of ketosis type 2 diabetes [5,10].

However, there are some situations where it is difficult to distinguish between the two types of diabetes with only these clinical data. So, the search for the presence of pancreatic auto antibodies and the evaluation of the secretory capacity of beta cells by the dosage of C-peptide can be helpful. Unfortunately, these biological parameters are not routinely available in our country. A Tunisian prospective study concerning 63 cases of ketosis onset diabetes occurring after 30 years of age revealed that pancreatic auto-immunity was present in 36.5% of cases and that Beta-cell functional reserve was preserved in 54%. With these data diabetes can be classified by the Aβ scheme based on the presence or absence of β-cell autoantibodies (A+ or A-) and β-cell functional reserve (β+ or β-) [21].

Ketosis type 2 diabetes is a sub type of diabetes that is intermediate between type 1 diabetes and type 2 diabetes. It is characterized by an acute initial presentation with severe hyperglycemia and ketosis indicating an acute insulinopenia as type 1 diabetes, but it concerns older and more corpulent subjects without auto-immune markers

[15]. After the acute episode, it has the clinical course of classical type 2 diabetes and can be treated without insulin [10]. This sub type of diabetes had been named differently as 'flatbush diabetes' [15] or 'ketosis prone type 2 diabetes' [6,13].

After the acute episode, 60% of our ketosis type 2 diabetes patients were treated with insulin. It was the case in 61% in the study of Pinero-Pilona et al. [3], 42.8% in that of Banerji et al. [15] and 47% in that of Maldonado et al. [21], where as in only 31.8% of patients in the study of Hsin Yu et al. [22] and 24.3% in the study of Mauvais-Jarvis et al. [13].

A re-evaluation of beta cell secretion's capacity might indicate the necessity of continuing insulin therapy. The management of our patients was only based on clinical data, and 52% of our ketosis type 2 diabetes followed at the office was treated with oral hypoglycaemic drugs. In the study of Pinero-Pilona et al. [11], 39 % (21/54 cases) of DKA were treated with oral drugs after a mean follow-up of 12 months. Mauvais-Jarvis et al. [13] described a remission of diabetes in 75.7 % of African sub-Saharan patients presented with DK or DKA, after a period of 14.3 months of insulin therapy. Forty percent of patients didn't necessitate insulin therapy during a follow-up of 10 years. It has been reported that treatment with oral hypoglycaemic drugs can extend the duration of the remission phase and prevent ketosis relapse [13,23]. This reversible dysfunction of beta cells is variable [24]. This remission is different from 'the honey moon' of type 1 diabetes that has a shorter duration. So, insulinopenia observed in the acute phase is transient in this subtype of diabetes. An initial insulin therapy can relieve glucotoxicity and restore beta cell function. The patients can later be treated with oral drugs like classic type 2 diabetes [25].

In conclusion, ketosis or ketocidosis generally reveals type 1 diabetes but can also reveal ketosis prone type 2 diabetes. Based on clinical data, 34.7% of our ketosis or keto-acidosis onset diabetes was ketosis prone type 2 diabetes. In 52% of whom insulin therapy was subsequently withdrawn. This sub type of diabetes has been described in different populations especially in ethnic minority groups. It is characterized by a transient insulinopenia that is reversible after a short period of insulin therapy improving beta cell function.

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