Flatbush Diabetes: A Report of Two Cases and a Review of the Literature

Flatbush Diyabet: İki Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Type 2 diabetes is an endocrine and metabolic disorder appearing with insulin resistance and impaired beta cell secretory function. Type 1 diabetes is characterized by the autoimmune destruction of pancreatic beta cells, which leads to absolute insulin deficiency. Diabetic ketoacidosis is considered a cardinal feature of type 1 diabetes. A number of studies have demonstrated that diabetic ketoacidosis also occurs in subjects with type 2 diabetes. Such patients are classified as idiopathic type 1 diabetes, type 1B diabetes, Flatbush diabetes or ketosis-prone type 2 diabetes. The aim of our study was to present two patients, who were diagnosed with ketosis-prone type 2 DM, as well as to discuss the subject in the light of the extant literature and to be able to make general recommendations. *Turk Jem 2009; 13: 56-9*

Key words: Flatbush diabetes, prone to ketosis, classification of diabetes mellitus

Özet

Tip 2 diyabet, insülin rezistansı ve beta hücre sekresyon bozukluğunun birlikte görüldüğü endokrin ve metabolik bir hastalıktır. Tip 1 diyabet ise pankreatik beta hücrelerinin otoimmun dekstrüksiyonu sonucu insülin eksikliği ile karakterizedir. Diyabetik ketoasidoz tip 1 diyabeti belirleyici en önemli özelliklerden birisidir. Bazı çalışmalarda diyabetik ketoasidozun tip 2 diyabetik hastalarda da görüldüğü saptanmıştır. Ketoz veya ketoasidoz tablosu ile başvuran bazı hastalarda hem tip 1 hem de tip 2 diyabete özgü klinik özelliklerin bir arada bulunduğu ve bu hastalarda tanı karmaşası yaşanabileceği bildirilmektedir. Bu hastalar idiyopatik tip 1 diyabet veya tip 1B diyabet veya Flatbush diyabet veya ketozis eğilimli tip 2 diyabet olarak sınıflandırılmıştır. Biz de bu çalışmamızda ketozis eğilimli tip 2 diyabet olduğunu belirlediğimiz 2 olgumuzu sunmayı, konuyu literatür bilgileri eşliğinde tartışmayı ve genel bir değerlendirme yapmayı amaçladık. *Türk Jem 2009; 13: 56-9*

Anahtar kelimeler: Flatbush diyabet, ketozise eğilim, diyabetin sınıflandırılması

Introduction

The clinical, metabolic, and immunological features of some patients with an early diagnosis of type 1 diabetes mellitus (DM), as based on the presence of diabetic ketosis or ketoacidosis at the time of first admission, have been observed to resemble patients with type 2 DM. Generally, autoimmune indicators are not detected in such patients with a strong family history of obesity and diabetes; human leukocyte antigen (HLA) tissue groups, which have a tendency towards type 1 diabetes, are positive at low rates (1). There is a short-term history, characterized by polyuria, polydipsia, and weight loss occurring within 1-4 weeks, as well as acute onset of ketosis or ketoacidosis. A family history, development of the disease and the presence of obesity give rise to the possibility that there is a severe insulin secretory defect together with insulin resistance. In these patients it has been reported that insulin treatment at an early stage improves the glucotoxicity and secretory defect, and usually prevents the recurrence of ketoacidosis (2). In addition, an increase in insulin sensitivity has also been reported in the follow-up of these patients as a result of discontinuation of insulin (2, 3). Ketosis prone type 2 diabetes mellitus, has been identified in many different racial groups, particularly in African Americans (3). The purpose of the present study was to present two patients, who were diagnosed with type 2 DM with a tendency toward ketosis, as well as to discuss the subject in the light of the extant literature and to make general recommendations.

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Case 1

A 39-year-old male patient without any known systemic diseases was admitted to our department with complaints of a dry mouth, polydipsia, and polyuria increasing within the last week. On laboratory analysis, the blood pH was 7.32, and the levels of plasma glucose, ketonuria, and glucosuria were 436 mg/dl, 80 mg/dl, and 1000 mg/dl, respectively. He was hospitalized with the diagnosis of diabetic ketoacidosis. Hemoglobin A1c (Hb A1c) and C-peptide levels of the patient, who had a strong family history of type 2 diabetes in his first-degree relatives, were 12.3% and 1.2 ng/ml, respectively (Table 1). The body mass index (BMI) was 34 kg/m^2, and no precipitating factors for ketoacidosis were detected. Intensive insulin therapy and fluid treatment were initiated. The acidosis was kept under control within the first 12 hours by these treatments, and normoglycemia was achieved. The patient, to whom 1700 mg/day metformin with 1.2 U/kg/day subcutaneous intensive insulin was administered at the 72nd hour of hospitalization, was discharged with recommended exercise, dietary and lifestyle change program. Due to frequent hypoglycemic attacks during his follow-up visits, the insulin dose was gradually decreased to 0.2 U/kg/day, beginning from the ambulatory follow-up performed after 2 weeks. With a decreasing need for insulin during his follow-up visits, insulin treatment was completely discontinued at the end of the 3rd month. Metformin treatment was ceased in the 4th month due to a serious gastrointestinal intolerance; therefore, the patient was then prescribed 1 mg of repaglinide before each of the three main meals. Despite these changes, the hypoglycemic attacks continued. Since his insulin and C-peptide levels during the 5th month were 10 ng/dl and 2.4 ng/dl, respectively, the decision was made to follow him without any medications. During a two-year follow-up without any medications, but with strict lifestyle changes, his blood glucose levels were normoglycemic. An oral glucose tolerance test (OGTT) performed with 75 g of glucose revealed a fasting blood glucose level of 122 mg/dl and a 120th minute blood glucose level of 138 mg/dl. Patients with these findings are diagnosed as having impaired fasting glycemia. He is compliant with follow-up.

Table 1. Demographic, clinical, and laboratory characteristics of the cases

Characteristics	**Case 1**	**Case 2**
Age/Gender	39/Male	74/Female
BMI (kg/m^2)	34	36
Family history for DM	+++	+++
Form of presentation	Ketoacidosis	Ketosis
HbA1c (%)	12.3	10.3
Pre-treatment C-peptide	1.2 ng/ml	2.4 ng/ml
C-peptide at normoglycemic period	2.1	10.7
HLA tissue groups	Not determined	HLA DRB1*11, DRB1*16, A*23, A*31, B*49, B*51
Autoantibody analyses Anti-GAD/anti-islet antibody	Negative	Negative
Duration of antidiabetic medication use	4 months	36 months
Follow-up period without any medication	2 years	2 years
OGTT results during follow-up without medication 0 and 120th	Impaired fasting glycemia 122-138 mg/dl	Impaired glucose tolerance 118-176 mg/dl

OGGT: Oral glucose tolerance test

Case 2

A 74-year-old female patient was admitted to our clinic 4 years ago for the first time with complaints of severe hyperglycemia and ketonuria. Her glucose level and HbA1c were 483 mg/dl and 10.3%, respectively, at the time of admission. Her ketonuria was measured as >80 mg/dl and she had no signs of acidosis (pH, 7.38; Table 1). Ketosis was improved with insulin infusion treatment and with intensive fluid therapy, and normoglycemia was achieved. At the end of 24 hours, 1 U/kg/day subcutaneous insulin treatment was initiated. Because the patient had signs of hypoglycemic attacks at the end of the first year, the insulin dose was gradually reduced to 0.5 U/kg/day. The patient decreased the dose of required insulin according to her blood glucose measurements using home blood-glucose monitoring, and it was observed that her insulin requirement has been increased up to 18 U/day level at the end of the 2nd year. Insulin treatment was ended and oral anti-diabetic treatment was initiated with 1700 mg/day metformin and 2 mg/day of glimepiride. Despite these treatment changes, signs of hypoglycemia were observed; thus, all of her treatments were ended and she was followed without any medications. During this period, the levels of fasting blood glucose, HbA1c, and C-peptide were detected as 90 mg/dl, 6.3%, and 10.7, respectively. Due to psychological compliance problems, a prolonged fasting test for 72 hours was discontinued in the 50th hour without experiencing hypoglycemia. At the end of the test, the blood glucose level was measured as 72 mg/dl, whereas the insulin level was 1.8 IU/mL. She underwent radiological examinations in terms of insulin-secreting pancreatic and non-pancreatic masses, and no pathological findings were detected regarding an insulinoma. She demonstrated no signs of hyper-or hypoglycemia during her two-year follow-up period without any medications but with strict lifestyle changes. She is still being followed with the signs of impaired glucose tolerance (IGT), with a fasting glucose of 118 mg/dL and a 120th minute glucose of 176 mg/dL after an OGTT performed with 75 g of glucose. The summary of the data of both cases is presented in table 1.

Discussion

Currently, diabetic patients are classified into three groups as follows: primary (types 1 and 2), secondary, and gestational. With the exception of secondary and gestational diabetes, the classification of patients with types 1 and 2 DM is not always easy. As with the cases presented in this report, despite having a tendency towards ketosis and an acute severe onset, patients with negative autoimmune markers, components of metabolic syndrome, and a family history for DM, have the characteristics of both groups. Such patients are classified as idiopathic type 1 DM or type 1B DM according to the American Diabetes Association (ADA) classification (1). However, such a classification scheme seems to be inadequate in identifying the clinical, phenotypic, and etiologic differences of such patients. Therefore, the classification of these patients as a different group is adopted by many researchers. For the first time, Winter et al. (2) defined a

group of African American patients in 1987 who presented with severe hyperglycemia or diabetic ketoacidosis with demographic, clinical, and metabolic features similar to type 2 DM, and who were similar to the cases presented herein. Of the patients, 46% were obese and had intermediate insulin secretory responses to a mixed meal tolerance test. This entity was referred to as "atypical diabetes." In subsequent studies, similar entities have been identified, particularly in African Americans and in other ethnic groups, such as Africans, Americans, Japanese, Chinese, Latinos, and Caucasians (3-8). Since these patients have features same as type 1 together with 2 DM, such patients were also referred to as 'type 1B,' 'atypical DM,' 'Flatbush DM,' 'type 1.5 DM,' and ketosis prone type 2 diabetes mellitus (2-4,8,9). The above-mentioned patients presented with diabetic ketoacidosis or severe hyperglycemia; autoimmune markers were not assessed and the relationship with HLA tissue groups were generally not reported either. After the clinical improvement of the initial entity in the patients, it was observed that they were generally not in need of insulin and their glycemic control had been quite close to the normoglycemic targets for years with the help of diet or oral antidiabetic agents. A temporary defect, both in insulin secretion and insulin effect, and improvement and maintenance in the function of beta cells with aggressive treatment for years, has been reported in such patients (2,3,10).

The prevalence of ketosis prone type 2 diabetes mellitus is not known. Among African Americans and Latinos presenting with newly diagnosed diabetic ketoacidosis, the prevalence of type 2 DM is considered to be between 20% and 50% (3,11,12, 13). However, it has been reported that type 2 DM with a tendency towards ketosis is observed in less than 10% of the patients admitted with diabetic ketoacidosis among Asians and Caucasians (8,14,15). In various studies, it was reported that most of the type 2 DM patients with a tendency toward ketosis are obese and middle-aged, and this type of diabetes is observed 2-3-fold more frequently in men. Although this difference among genders is not completely known, it is thought to be related to hormonal factors, body fat distribution, and differences in insulin sensitivity (4,11,16). In such patients, the clinical onset of the disease is typically reported to be acute, and symptoms, such as polyuria, polydipsia, and weight loss, are reported to be lasting less than 4-6 weeks (4,10,12). No triggering factors are identified for diabetic ketoacidosis in such patients (3,10,12). It is observed that, more than 75% of the patients are cases with newly diagnosed DM. Both of the present cases were obese (BMI 34 kg/m^2 and 36 kg/m^2, respectively), had a family history for type 2 DM, and were newly diagnosed diabetic patients. The symptoms of the patients had existed for 1 week, and no trigger factors for ketoacidosis were determined.

In the series reported by Umpierrez et al. (3,10), the mean levels of laboratory parameters were as follows: glucose, 684-720 mg/dl; HCO3, 12-14 mmol/L; pH, 7.22-7.25; and HbA1c, 12% to 14%. The similar values of the present cases are presented in Table 1. In a study investigating the estimation of normoglycemic remission and the clinical progression of these patients, HbA1c values <6.3 mmol/L and fasting blood glucose levels <6.6 mmol/L (120 mg/dL) were accepted as a remission (17). In the mentioned study, 42% of the patients achieved remission after 83 days and stayed in remission for approximately 20 months. No difference had been determined between the patients in terms of age, gender, plasma glucose levels at the time of presentation, changes in BMI, weight changes, and used pharmacologic agents. In the study conducted by Mauvais-Jarvis et al. (4), it was reported that insulin treatment had been discontinued after approximately 14.3 weeks in 76% of sub-Saharan-African patients with diabetic ketoacidosis. Ten years after the initial presentation, 40% of the patients did not have an insulin requirement. In the present cases, insulin treatment was discontinued in the 4th and 36th months, respectively, and the patients did not have any additional insulin requirements during their 2-year follow-up periods. It has been reported that after discontinuation of the insulin treatment, hyperglycemia and ketosis are frequently observed in patients treated with diet alone, whereas the remission period is prolonged in patients on sulfonylurea or metformin treatment, and metformin and sulfonylurea are effective in preventing relapses (4,10,18,19). On the contrary, some researchers have concluded that oral antidiabetic agents are insufficient to maintain remission; they have argued that it is necessary to continue insulin treatment for a long time in such patients (8,11). Obese patients admitted with diabetic ketoacidosis lose weight during this period of time; however, the effect of weight loss on the remission of the disease is not known. This relationship has not been demonstrated in some studies, as well (3,4,13). In the present cases, improvement without a change in weight during follow-up supports this suggestion.

The presence of autoantibodies, such as islet cell antibodies (ICA), anti-glutamic acid decarboxylase (anti-GAD) antibodies, and protein tyrosine phosphatase antibodies have been investigated in patients with ketosis prone type 2 diabetes, and autoantibody positivity has been reported in 0% to 18% of patients (4,10,19). This ratio is similar to the autoantibody positivity ratio in patients with type 2 DM (20). It was reported that, basal or stimulated insulin secretion of patients with type 2 DM and a tendency toward ketosis, was higher in autoantibody-positive patients than in autoantibody-negative patients. In addition, it was also reported that, hyperglycemia recurs more frequently in such patients and the rate of insulin requirements once again is higher as well (21,22). Different results have been obtained in studies investigating the association of HLA tissue groups in patients with type 2 DM and a tendency toward ketosis, and in many studies, such a relationship has not been found in contrast with the relationship which exists in type 1 DM (2,3,4,23). An increase in the frequencies of HLA DR3 and HLA DR4 has been determined in many studies, particularly, in the study conducted by Banerji et al. (24). It was reported that the frequency of HLA was especially increased in autoantibody-positive patients, whereas it was low in autoantibody-negative patients (8). The striking facts in terms of the present cases were the presence of negative ICA and anti-GAD antibodies in both cases and the increased insulin antibody titers at the end of the 3rd year in the 74-year-old female during the time period that the hypoglycemic attacks occurred.

In previous studies, beta cell function was evaluated by intravenous glucose infusion one day after the improvement of ketoacidosis in patients with ketosis prone type 2 diabetes; however, the insulin response was observed to be inadequate (2,3,19). In fact, a 3-fold increase in insulin levels of these patients was observed after their metabolic control had been achieved. In other studies, both basal and post-stimulation C-peptide levels of patients were investigated and significant improvement was observed both in

basal and stimulated C-peptide levels during the course of the follow-up (4,25). Such improvements recorded during the course of the follow-up, gave rise to the consideration that the pathologic state in patients with ketosis prone type 2 diabetes was related to the severe, but reversible damage of beta cells, rather than impairment of the beta cells (26,27). Although the mechanism of this temporary beta cell dysfunction is not known precisely, it is suggested that it may be related to glucotoxicity or lipotoxicity (4,10,28). In various studies, it was demonstrated that chronic hyperglycemia causes impairment in insulin effect and glucose uptake in peripheral tissues. Although the impairment in insulin sensitivity in chronic hyperglycemia is not completely understood, it is considered to be associated with the changes in insulin signaling at the post-receptor level (26,27). During the follow-up of patients with type 2 DM with a tendency toward ketosis, it was demonstrated that the insulin effect and insulin sensitivity significantly improved with the amelioration of glucose metabolism (28). In the present cases, the disappearance of insulin requirement, even at different times, did not require oral antidiabetics, and the return of both cases to the pre-diabetic phase after an OGTT supports those considerations.

It was reported that, during follow-up of patients with type 2 DM with a tendency toward ketosis, insulin treatment has been discontinued after an approximately 9-week follow-up in 70% of the patients (10,12). It was also reported that after discontinuation of insulin treatment, hyperglycemic relapse was seen within approximately 2 months during the follow-up with diet-only treatment, whereas the remission periods might be prolonged up to 24-40 months with low dose sulfonylurea or metformin treatment (4,10,18,19). On the other hand, some researchers suggest that patients should be followed up with low dose insulin treatment after the improvement of the acute event; thus, the insulin response and remission could be maintained for a long time (22). As a result, ketosis prone type 2 diabetes mellitus should be considered, especially in male, obese, middle-aged patients with a strong family history for type 2 DM, as well as with acute onset and severe defects in insulin secretion, in whom generally rapid and significant improvement with aggressive treatment is observed and negative autoantibodies are present, and any relationship with HLA tissue groups is not determined. Since the long-term follow-up and treatmen ts of these patients are different from the ones with type 1 DM, evaluations of such patients should be performed carefully.

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