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Do obese children with diabetic ketoacidosis have type 1 or type 2 diabetes?

Joey C. Low^a, Eric I. Felner^a, Andrew B. Muir^a, Milton Brown^a, Margalie Dorcelet^a, Limin Peng^b, and Guillermo E. Umpierrez^{c,*}

^aDepartment of Pediatrics, Division of Endocrinology, Atlanta, GA, United States

^bRollins School of Public Health, Atlanta, GA, United States

^cDepartment of Medicine, Emory University, Atlanta, GA, United States

Abstract

Objective—Many obese children with unprovoked diabetic ketoacidosis (DKA) display clinical features of type 2 diabetes during follow up. We describe the clinical presentation, autoimmune markers and the long-term course of obese and lean children with DKA.

Research design and methods—We reviewed the medical records on the initial acute hospitalization and outpatient follow-up care of 21 newly diagnosed obese and 20 lean children with unprovoked DKA at Emory University affiliated children's hospitals between 1/2003 and 12/2006.

Results—Obese children with DKA were older and predominantly male, had acanthosis nigricans, and had lower prevalence of autoantibodies to islet cells and glutamic acid decarboxylase than lean children. Half of the obese, but none of the lean children with DKA achieve near-normoglycemia remission and discontinued insulin therapy during follow-up. Time to achieve remission was 2.2 ± 2.3 months. There were no differences on clinical presentation between obese children who achieved near-normoglycemia remission versus those who did not. The addition of metformin to insulin therapy shortly after resolution of DKA resulted in lower hemoglobin A1c (HbA1c) levels, higher rates of near-normoglycemia remission, and lower frequency of DKA recurrence. Near-normoglycemia remission, however, was of short duration and the majority of obese patients required reinstitution of insulin treatment within 15 months of follow-up.

Conclusion—In contrast to lean children with DKA, many obese children with unprovoked DKA display clinical and immunologic features of type 2 diabetes during follow-up. The addition of metformin to insulin therapy shortly after resolution of DKA improves glycemic control, facilitates achieving near-normoglycemia remission and prevents DKA recurrence in obese children with DKA.

Keywords

Diabetic ketoacidosis; Type 2 diabetes; Hyperglycemic crises; Ketosis-prone diabetes; Atypical diabetes; Obese

Conflict of interest statement

The authors state that they have no conflict of interest.

1. Introduction

Diabetic ketoacidosis (DKA) is the most serious acute hyperglycemic emergency and the leading cause of mortality in children with type 1 diabetes mellitus [1]. According to the Search for Diabetes in Youth Study, more than 25% of children have DKA at diagnosis of diabetes [2]. Most children and adolescents with DKA are lean and have autoimmune type 1 diabetes requiring life-long insulin therapy. In recent years however, several reports have indicated that many obese children and adolescents presenting with unprovoked DKA display clinical, metabolic, and immunological features of type 2 diabetes. Their initial presentation is usually acute with a few days to weeks of polyuria, polydipsia and weight loss. Despite their presentation with ketoacidosis, many obese children with DKA achieve near-normoglycemia remission (defined as the ability to discontinue insulin therapy for >1 week and remaining in good glycemic control with fasting BG < 130 mg/dL, random BG < 180 mg/dL, and A1C < 7%). During the remission period that can last for months to years, patients are controlled by either diet or oral hypoglycemic agents [3–7]. Because of the mixed features of type 1 and type 2 diabetes, this variant of type 2 diabetes is referred to in the literature as diabetes type 1B, idiopathic type 1 diabetes, atypical diabetes, Flatbush diabetes, type 1.5 diabetes, and more recently as ketosis-prone type 2 diabetes (KPDM) [8–12].

We are aware of no studies that systematically describe the various clinical, biochemical and demographic predictors of insulin-dependence among lean and obese children presenting with DKA at the time of diabetes diagnosis. Differentiation between type 1 and type 2 diabetes mellitus is challenging in many children, but the distinction has important implications for both short-term and long-term management. Accordingly, this study determined the clinical and laboratory features of type 1 and type 2 diabetes in obese children presenting with DKA including: (1) the ability of achieving near-normoglycemic remission of insulin dependence and (2) the anthropometric, clinical, autoimmune and metabolic markers that alone, or in combination, predicted short- and long-term insulin remission.

2. Research design and methods

We reviewed the medical records of children who presented with DKA between 1/2003 and 12/2006 to Children's Healthcare of Atlanta (CHOA) which includes the 3 major pediatric hospitals in the city of Atlanta with 474 inpatient beds (Egleston, Scottish Rite, Hughes Spalding hospitals). Children were followed after discharge at the Emory-Children's Center Pediatric Endocrinology Clinic. Patients were identified by ICD-9 codes 250.11 and 250.13.

The inpatient medical records were reviewed to first confirm the diagnosis of DKA [13], then selected to include only those patients with new-onset diabetes. These patients were further selected for body mass index (BMI) ≥ 85th percentile. The following data were extracted: (1) demographic information including age, weight, height, sex, race, BMI, (2) chemical and metabolic profiles to assess severity of DKA including initial serum glucose, blood pH, serum bicarbonate concentration, and (3) immunologic profile (islet cell antibodies and glutamic acid decarboxylase antibodies). Outpatient medical records of these patients who were seen at the Emory-Children's Center Pediatric Endocrinology Clinic for their follow up care were also reviewed to identify the following: (1) ability to achieve near-normoglycemic remission, (2) time from diagnosis to achieve remission, (3) follow-up A1C levels, (4) relapse into insulin dependence (defined as being restarted on insulin therapy at any time during follow-up), and (5) time from remission to relapse into insulin dependence. Other inpatient and outpatient factors such as subsequent DKA episodes, the presence of acanthosis nigricans, and initiation of oral hypoglycemic therapy (metformin) were also

extracted. We obtained similar data for a subset of lean DKA patients with new onset diabetes for comparison. The lean patient data were randomly selected from an alphabetized list of the patients who presented with DKA to Children's Healthcare of Atlanta (CHOA) between 1/2003 and 12/2006.

2.1. Statistical analysis

All data in the text and tables are expressed as means $\pm$ standard deviation (SD). Comparisons between: obese and lean patients, between obese patients with remission and without remission, between remission patients with relapse and without relapse, were conducted using a nonparametric Wilcoxon test for continuous variables and a Fisher exact test for categorical variables. Near-normoglycemia remission was defined as the ability to discontinue insulin therapy for >1 week and remaining with fasting BG < 130 mg/dL, random BG < 180 mg/dL, and A1C $< 7\%$. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SAS (version 9.2; SAS Institute, Cary, NC).

3. Results

Compared to lean children, obese children with DKA were older, had acanthosis nigricans, and were more likely to have a family history of diabetes (Table 1). There was a 3:1 male predominance among obese children with DKA and a female predominance (2:1) among the lean children. In addition, most obese children with DKA (62%) had negative autoimmune markers whereas most (94%) lean children had circulating islet cell (ICA) or glutamic acid decarboxylase (GAD₆₅) autoantibodies.

Half of obese children with DKA achieved near-normoglycemic remission and discontinued insulin therapy within 2.2 ± 2.3 months of follow-up (median 1.25 months), while none of the lean children discontinued insulin therapy. Among the obese children, there were no differences in clinical presentation including age, gender, ethnicity, family history of diabetes mellitus, BMI, admission glucose and acid-base parameters, or A1C level between those children who achieved remission and those who did not (Table 2). Interestingly, we found no differences in the frequencies of autoimmune markers between children who achieved remission (36%) and those who did not (40%).

Compared to children who did not achieve remission, those who discontinued insulin had lower A1C levels both within 6 months ($6.0 \pm 0.9\%$ vs. $7.4 \pm 1.8\%$, $P = 0.056$) and at 12 months ($6.8 \pm 1.4\%$ vs. 12.3 ± 2.3 , $P < 0.01$) of diagnosis. In addition, the remission group experienced fewer subsequent DKA episodes (9%) than the children who did not experience remission (50%, $P = 0.064$). Obese children treated with metformin in combination with insulin were more likely to achieve remission. Among obese children who did not achieve remission, only 10% of them were treated with metformin. In contrast, approximately 75% of children who achieved remission received metformin therapy ($P < 0.01$). Metformin-treated children also had lower A1C levels ($8.2 \pm 3.2\%$ vs. $11 \pm 3.1\%$) 12 months after diagnosis.

Despite this initial favorable response, most obese children who achieved remission (78%) ultimately relapsed into hyperglycemia and required insulin treatment (time to relapse: 19.2 ± 17 months). Patients who relapsed had higher, but not significant, differences in the frequency of positive diabetes mellitus autoantibodies.

4. Discussion

We found remarkable differences in the clinical presentation and long-term course between obese and lean patients presenting with DKA. While most lean patients have autoimmune

type 1 diabetes and require long-term insulin therapy, most obese children with DKA have non-autoimmune diabetes and frequently discontinue insulin therapy during follow-up. The use of insulin in combination with metformin was associated with improvement of glycemic control and higher rate of insulin discontinuation. The near-normoglycemic remission unfortunately is of short duration with nearly 80% of patients relapsing into insulin therapy within 15 months of follow-up.

Diabetes ketoacidosis has long been considered a hallmark of type 1 diabetes, an autoimmune disorder resulting in pancreatic β -cell destruction and associated with the need for chronic insulin therapy. Several studies in children and adults, however, have shown that many type 2 diabetes patients can present with DKA [3,6,7,14]. Winter et al. in 1987 were first to recognize that some young patients may present with symptoms of insulin deficiency, with or without ketoacidosis, but during follow up display clinical and metabolic features of type 2 diabetes [3]. Obesity was present in 46% of their patients, and insulin secretion was intermediate between secretion in non-diabetic control subjects and that in patients with type 1 diabetes. We and others have also reported about half of newly diagnosed adult African Americans with DKA display clinical features of type 2 diabetes, including a high rate of obesity, a strong family history of diabetes, a low prevalence of autoimmune markers, and a lack of predisposing HLA genotypes [8,15–17].

As obesity and type 2 diabetes become more prevalent among children and adolescents, it is critical that physicians differentiate between the types of diabetes in order that they may recommend optimal care. Our study indicates that the development of DKA in children is not synonymous with type 1 diabetes and that obese children presenting in DKA better fit a type 2 diabetes profile. The association of early use of metformin in obese DKA patients facilitated remission of insulin dependence as well as improved glycemic control. Metformin is approved by the Food and Drug Administration (FDA) for use in pediatric patients 10 years of age or older with type 2 diabetes [18]. Metformin, a biguanide oral hypoglycemic agent, acts by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and increasing insulin sensitivity [18,19]. In addition to its use in type 2 diabetes, metformin has been studied as an adjunctive therapy in adolescents with type 1 diabetes [4–6]. Several studies in adolescents and young adults with type 1 diabetes have reported improvement in glycemic control as well as reduction in insulin dosages and hypoglycemic events [19]. In our study; however, we observed that despite the initial favorable response in achieving near-normoglycemia remission, most patients relapsed into insulin dependence within 2 years of follow up. Anticipating the short- and long-term clinical course and outcomes of obese children with DKA will help physicians develop appropriate interventions for preventing progressive β -cell dysfunction and metabolic decompensation in children and adolescents.

Our previous work in adult obese patients with DKA has shown that they have markedly impaired insulin secretion and insulin action at presentation [9,12]. Intensified diabetic management results in significant improvement in β -cell function and insulin sensitivity sufficient to allow discontinuation of insulin therapy within a few months of follow-up. Upon discontinuation of insulin, the period of near-normoglycemic remission may last for a few months to several years, with approximately 40% of these patients continuing in remission 10 years after diagnosis [12,14]. This clinical presentation has been reported primarily in Africans and African Americans, but also in other minority ethnic groups [11,14,20]. This subtype of diabetes is recognized by the American Diabetes Association as idiopathic non-autoimmune type 1 diabetes mellitus or diabetes type 1B and by the World Health Organization as idiopathic type 1 diabetes [21,22]. Despite their presentation with DKA and phasic insulin dependence, recent studies have shown that most patients with this

ketosis-prone diabetes have type 2 diabetes and that β -cell function experiences remarkable recovery at near-normoglycemic remission [23,24].

Several groups have reported on the prevalence of autoantibodies to islet cells, insulin, glutamic acid decarboxylase, and protein tyrosine phosphatase in adult patients with ketosis-prone type 2 diabetes [14]. The rate of positive autoimmune markers has ranged between 0% and 16%. The rate of positive autoantibodies appears to be similar to that reported in subjects with type 2 diabetes presenting with nonketotic hyperglycemia (34–37). During follow-up, diabetes subjects with positive autoantibodies have significantly reduced basal and stimulated insulin secretion compared to those with negative antibodies (43, 44), and are more likely to relapse into hyperglycemia and to become insulin dependent [6].

Limitations of this study include its retrospective design and small sample size from a single institution in the Southeastern United States. In this study the vast majority (95%) of obese children with DKA were African Americans, thus the prevalence and clinical course of ketosis-prone diabetes in children from different ethnic populations needs to be determined in future studies. Of interest, a recent systematic review of 46 studies involving more than 24,000 children in 31 countries reported ethnic minority, ethnic minority, lack of health insurance in the US and delayed treatment as factors associated with DKA at diagnosis of type 1 diabetes in children and young adults {Usher-Smith, #314}. In addition, although the acute treatment of DKA is well standardized in our facility, subsequent management such as how and when to initiate combination of insulin and oral hypoglycemic therapy (metformin) in obese children was not standardized. In addition, as compared to their adult counterparts, glycemic goals in children and adolescents may be less stringent [25]. This may be important in the frequency and duration of the insulin remission phase, as indicated by previous studies that showed intensified glycemic control may help preserve β -cell function [26,27].

In summary, despite their presentation with DKA, many obese children with newly diagnosed diabetes display features of type 2 diabetes including the presence of obesity, acanthosis nigricans, negative autoimmune markers, and discontinuation of insulin therapy during follow-up. The addition of metformin at or shortly after presentation helped achieve near-normoglycemic remission and improved long-term glycemic control in obese patients. Our study confirms previous observations of the wide spectrum of clinical presentation of type 2 diabetes.

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Table 1

Clinical features of obese and lean children with DKA.

Variable	Obese	Lean	P
N, %	21	20	
Age, years	14 ± 1.9	10.7 ± 4.3	<0.01
Male gender, %	71	40	0.064
African American, %	95	25	<0.01
Family history of DM, %	95	63	0.02
BMI, kg/m ²	31.4 ± 5.3	16.5 ± 2.1	<0.01
Acanthosis Nigricans, %	71	0	<0.01
Blood glucose, mmol/L	40.8 ± 23	40.3 ± 23	>0.99
Bicarbonate, mequiv./L	11.4 ± 5.0	10.0 ± 3.0	0.43
A1C at presentation, %	12.3 ± 1.8	11.9 ± 1.9	0.34
Positive DM antibody, %	38	94	<0.01
Metformin treatment, %	43	0	<0.01
A1C at 12 months follow up, %	10.1 ± 3.4	8.0 ± 2.1	0.11
Recurrence of DKA, %	29	10	0.24

Data are presented as mean ± standard deviation.

Table 2

Obese children with DKA, with and without near-normoglycemic remission.

Variable	Remission	No remission	P
N, %	52	48	
Age, years	14.3 ± 2.2	13.7 ± 1.7	0.46
Male gender, %	64	80	0.64
African American, %	100	90	0.48
Family history of DM, %	89	100	0.47
BMI, kg/m ²	32.1 ± 6.0	30.7 ± 4.6	0.50
Acanthosis Nigricans, %	73	70	>0.99
Blood glucose, mmol/L	40.5 ± 16	41.2 ± 29	0.60
Bicarbonate, mequiv./L	10.5 ± 5.7	12.4 ± 4.2	0.23
A1C at presentation, %	12.7 ± 1.5	11.9 ± 2.0	0.42
Positive DM antibody, %	36	40	>0.99
Metformin treatment, %	73	10	<0.01
Time to remission (months)	2.2 ± 2.3	n/a	
A1C at 3–6 months follow up, %	6.0 ± 0.9	7.4 ± 1.8	0.056
A1C at 12 months follow up, %	6.8 ± 1.4	12.3 ± 2.3	<0.01
Recurrence of DKA, %	9	50	0.06

Data are presented as mean ± standard deviation.