Journal of Diabetes and Its Complications 30 (2016) 55–60

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Ketoacidosis at diagnosis in childhood-onset diabetes and the risk of retinopathy 20 years later

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ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form 14 October 2015
Accepted 16 October 2015
Available online 20 October 2015

Keywords:
ketoacidosis
childhood-onset diabetes
retinopathy
nephropathy
C-peptide
HbA1c

ABSTRACT

Aims: To investigate on the relationship between severity of ketoacidosis, an important risk factor for C-peptide preservation, and long-term microvascular complications in childhood-onset type 1 diabetes mellitus (T1DM).
Methods: 230 childhood-onset diabetic patients (177 pre-pubertal), aged 7.0 ± 3.8 years followed for at least 15 years after their diagnosis, were enrolled. Clinical and laboratory data at diagnosis, and C-peptide levels in a subset of patients, were compared with the severity of retinopathy and nephropathy, after a mean of 19.6 ± 3.8 years of disease. Digital retinal photographs were taken in all patients, and centrally graded. Repeated measurements of HbA1c and microalbuminuria for the whole duration of diabetes were collected in over half of the cases.
Results: Out of 230 patients, those with the lowest age at diagnosis had the most severe DKA and clinical conditions ($p < 0.05$), and lower C-peptide levels ($p < 0.0001$) at diagnosis. There was a significant relationship between pH and clinical severity ($r = -0.783$, $p < 0.0001$), and between pH and C-peptide levels ($r = 0.278$, $p < 0.05$). The severity of ketoacidosis had no relationship with subsequent lifetime HbA1c values and long-term microvascular complications. In logistic regression analysis, the only variables that independently influenced severity of retinopathy were lifetime HbA1c ($B = 0.838$, $p < 0.001$), duration of disease ($B = 0.208$, $p < 0.005$) and age at diagnosis ($B = 0.116$, $p < 0.05$).
Conclusions: The degree of metabolic derangement at diagnosis is not associated with retinopathy and nephropathy in childhood-onset T1DM. Age at diagnosis seems to be an important variable to be considered when evaluating the long-term effects of residual beta-cell function.

1. Introduction

The occurrence of DKA in children with newly diagnosed type 1 diabetes mellitus (T1DM) is still high, especially in younger children (Mortensen et al., 2010; Szypowska & Skórka, 2011; Dabelea et al., 2014) and has not significantly changed over time sometimes despite

Conflict of interest: The authors have no conflict of interest to disclose. No funding was secured for this study. There are no financial relationships relevant to this article to disclose.
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http://dx.doi.org/10.1016/j.jdiacomp.2015.10.009
1056-8727/

the efforts of information programs (Fritsch et al., 2013). Younger age, lack of private health insurance, ethnic minority status and no family history of T1DM are independently predictive of DKA (Dabelea et al., 2014; Kligensmith et al., 2013). While there is no doubt on the fact that DKA is acute life-threatening complication, data about its relationships with future long-term complications are lacking. The identification of this relationship may be relevant, since the degree of metabolic derangement at diagnosis may partly reflect the degree of the residual beta-cell function (Mortensen et al., 2010; Fernandez-Castagñer et al., 1996; Bowden et al., 2008) that, according to some authors (Sjöberg et al., 1987; Steffes et al., 2003; Panero et al., 2009), is, in turn, associated with the risk of late complications. In contrast, other authors refute the hypothesis of this link (Klein et al., 1995; Jensen et al., 2011), or, at most, its effects would be indirectly mediated by improved metabolic control (Nakanishi & Watanabe, 2008; Giordano et al., 2011). Even more uncertain is the future of the patients with younger age at diagnosis and low levels of C-peptide (Szypowska & Skórka, 2011; Barker et al., 2014), since they are little represented in the various studies, despite the fact that T1DM in this age range is increasing (Patterson et al., 2012). In a previous study of our group (Salardi et al., 2012) we reported that, if diabetes is diagnosed in infant or toddlers and the prepubertal duration is the longest, the patients seem to be protected against the risk of microvascular complications.

In the present study we aimed to verify whether the severity of metabolic derangement at diagnosis in childhood-onset T1DM is predictive of long-term micro-vascular complications 20 years later. The majority of cases included in the study were prepubertal children and to our knowledge, a long-term outcome in a higher number of very young children has not been reported in other studies.

2. Materials and methods

This is a multicenter retrospective cohort study involving 11 pediatric units in Italy with current cross-sectional data on retinal and renal complications.

The patients were recruited among those who were diagnosed with T1DM as children between 1981 and 1992 and were included in the study according these criteria: each participating centre has attempted to trace all cases of T1DM who had been diagnosed between 1981 and 1992, i.e., with at least 15 years of disease, and who had been transferred to adult care at the time of study. If year by year at least 60% of the original cohort was tracked down, then all tracked patients, with diagnosis in that year, were included in the study. Otherwise, if the percentage of the tracked patients was lower, all the participants with onset in that year, tracked from that centre, were excluded.

In total, 230 Caucasian patients (115 males/115 females, 177 prepubertal (77%) defined by Tanner stage), aged 7.0 ± 3.8 years at diagnosis (range 0.8–14.9 years; n.84 aged <5 years) were enrolled. All patients but six showed at least one autoantibody at diagnosis among ICA, and anti-insulin antibodies, and the diagnosis was confirmed during follow-up by the clinical course of the patient and the insulin requirement leading to total insulin dependence within 2 years. The few cases without autoantibodies or with wide fluctuations in the need for insulin were screened for possible mutation in the glucokinase, HNF1A and HNF4A genes, and found negative. Ninety-nine patients were diagnosed between 1982 and 1989 and 131 between 1990 and 1992. Over this time period most patients changed insulin regimens switching from 2 to 3 or more daily insulin injections and from human insulin to analog insulins starting from 1984. Mean diabetes duration was 19.6 ± 3.8 (range 15–28.5), being 20 years or more in 80 cases. Patients were recalled between 2007 and 2009 to perform retinal photography and to retrieve clinical and laboratory data at diagnosis and during follow-up from existing clinical records. A subset of this cohort has been studied in our recent study (Salardi et al., 2012).

2.1. At diagnosis

Severity of disease at onset was categorized according to pH levels and clinical presentation (Table 1): grade 1 (n = 22) asymptomatic and/or serendipitous diagnosis; grade 2 (n = 102) polyuria and polydipsia together with good general clinical conditions; grade 3 (n = 71) severely compromised clinical conditions with Kussmaul' respiration and manifest signs of dehydration; grade 4 (n = 34) impaired consciousness to coma. Ketoacidosis was defined as capillary pH ≤ 7.30. Glycemic values were available in all but 11 patients, capillary pH value in 178 patients, basal fasting C-peptide levels in 117 and C-peptide levels after glucagon or test meal stimulation in 70 of them, performed only in some centers. The cases who had C-peptide measurements were not different from those who did not have, as regards the clinical and laboratory features at diagnosis. C-peptide measurements were performed during the first admission between the 3rd and the 7th day after the diagnosis, once the acute metabolic derangement was resolved. C-peptide was measured by radioimmunoassay using kits (Bio-Rad, Richmond, CA and Technogenetics, Lisophase, Milan, Italy) with lower limits of detection varying between 0.03 and 0.10 nmol/L. To compare data from different laboratories, we arbitrarily assigned scores to the C-peptide levels reported (Table 1): score 1 (n = 23) undetectable or below 0.03 nmol/L, the lowest limit of detection of the kits, and also of the C-peptide RIA used in the DCCT; score 2 (n = 32) between 0.03 and 0.10 nmol/L, i.e. under the lower limit of detection of some other kits; score 3 (n = 29 cases) minimal secretion between 0.11 and 0.20 nmol//L; score 4 (n = 33 cases) moderate secretion, above 0.20 nmol/L, as used in the DCCT (Kligensmith et al., 2013) as cutoff for stimulated C-peptide.

2.2. Follow-up

Repeated measurements of HbA1c for the whole duration of diabetes were available for 135 patients (Table 2). HbA1c had been measured by different methods (Bio-Rad minicolumn, high-performance liquid chromatography, or DCA 2000 analyzer). To compare results from different laboratories, the values were transformed into percentages of HbA1c above the upper normal reference value of each laboratory. Values were averaged throughout the entire duration of disease (excluding the value at diagnosis) and also in separate clusters for the years 0–5, 5–10,10–15, 15–20, and 20–25.

Digital retinal photographs were taken in mydriasis of two 50° fields per eye, one centered on to the macula and the other nasally to the disc, according to the EURODIAB protocol (Aldington et al., 1995). The pictures were centrally graded in the Diabetic Retinopathy Centre of the Department of Medical Sciences at Turin University by a trained reader. The pictures were graded according to a 5 degree severity scale based upon the American Academy of Ophthalmology simplified classification (Wilkinson et al., 2003), from no diabetic retinopathy (DR) (grade 1), to mild nonproliferative DR (2), moderate nonproliferative DR (3), severe nonproliferative DR (4), and proliferative DR (5). For statistical purposes, all patients with grades 3, 4 and 5 were grouped together as moderate-to-severe DR.

Data on repeated measurement of urinary albumin excretion (UAE) during follow-up and at the time of retinal photography were available in 168 patients. Microalbuminuria was defined as UAE between 30 and 300 mg/24 h or as albumin excretion rate (AER) ≥20 μg/min; macroalbuminuria as UAE >300 mg/day or AER >150 μg/min.

This study was performed in accordance with the Declaration of Helsinki as revised in the year 2000 and approved in the participating centers by an institutional review board regulating non-interventional