RESEARCH ARTICLE

Lower residual beta-cell function among diabetic children with familiar disposition

Abstract

Objective: Type 1 Diabetes (T1DM) is an autoimmune, multifactorial disease that causes dysregulation of blood glucose and may result in severe complications. The disease still causes long-term complications whereby the treatment is not at its optimum. This study investigates the impact of Family History of T1DM (FHD) on children and adolescents with T1DM by analyzing differences in Diabetic Ketoacidosis (DKA); HbA1c at onset; and HbA1c and residual insulin secretion 3-6 years after the onset of T1DM. Method: 342 children with a diabetes duration of 3-6 years and onset before the age of 15 years participated in the study with blood samples and a mixed meal test. Student t-tests and χ^2 were used in the statistical analysis.

Results: The key finding is, that children with FHD have lower stimulated c-peptide after 3-6 years after onset compared to the controls without FHD (p=0.048). Subjects with FHD have significantly lower levels of HbA1c at the onset of T1DM (p=0.005) and less frequent DKA at onset (p=0.004). No difference in HbA1c 3-6 years after onset was found.

Conclusion: The lower stimulated c-peptide in subjects with FHD suggests that they have a lower beta-cell function and that they have a more aggressive form of diabetes than children without FHD. Less DKA and lower HbA1c at onset are a result of earlier diagnosis. The study is the largest of its kind but still, it was limited by a small study population whereby further studies are needed to investigate the impact of first-degree relatives with T1DM on metabolic control.

Keywords: C-peptide, diabetes type 1, hemoglobin A1c, residual beta-cell function, familiar disposition, diabetic ketoacidosis, dysregulation.

Abbreviations: T1DM: Type 1 Diabetes; FHD: Family History of T1DM; RBF: Residual Beta-Cell Function; DKA: Diabetic Ketoacidosis

Introduction

In Type 1 Diabetes (T1DM) cell-mediated mechanisms gradually destruct β-cells in the islets of Langerhans in the pancreas, and concurrently, the endogenous insulin production decreases [1]. The rate of β-cell destruction varies between individuals. A proportion of People with Diabetes (PWD) have Residual β-Cell Function (RBF) and endogenous insulin production several years after the onset of T1DM [2]. RBF can be estimated as c-peptide in blood. C-peptide derives from the cleavage of proinsulin into insulin and c-peptide [3].

The onset of T1DM can present subtle symptoms such as increased thirst and diuresis, weight loss, and fatigue but in some cases, the initial symptoms proceed, and Diabetic Ketoacidosis (DKA) occurs. DKA is a result of delayed diagnosis of T1DM and, thus, earlier diagnosis reduces the incidence of DKA [4,5]. The risk of DKA at the onset of T1DM is increased at a younger age [5-7]. Other risk factors for DKA at onset are low socioeconomic status and delayed treatment initiation [4].

Long-term complications of T1DM include retinopathy, kidney failure, heart and blood vessel disease, and stroke [8]. The risk of these complications is correlated with glycemic control which is monitored by measurement of HbA1c. A high HbA1c is associated with an increased risk of long-term complications [9]. It is remarkable that poor glycemic control during puberty can cause significant complications during the first years of adulthood, whereby identifying and controlling factors that influence HbA1c in adolescence are important [10]. The cause of increased HbA1c during adolescence

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is multifactorial where, among others, behavior and physiological changes impact HbA1c [9].

Genetics plays a significant role in T1DM. More than 60 loci are identified as risk genes for T1DM and the Human Leukocyte Antigen (HLA) haplotype has the greatest impact accounting for about 50% of genetic susceptibility for T1DM [11,12]. Around 10% of PWD have a Family History of T1DM (FHD) [13,14]. It has been observed that PWD with FHD has a different presentation of T1DM than non-related PWD, such as differences at onset and in HbA1c levels [5,7,13,15].

Based on existing literature, our clinical experience, and the pathogenesis of T1DM, we hypothesize that PWD having a first-degree relative with T1DM differ with regards to the incidence of DKA at the onset of diabetes and that they have more aggressive destruction of β-cells resulting in increased HbA1c and lower RBF years after onset as compared to PWD without first-degree relatives with T1DM. To scrutinize this hypothesis, we identified a cohort of Danish children and adolescents with T1DM, divided them into two subgroups: i) with and ii) without first-degree relatives with T1DM, and analyzed their data on DKA at the onset of T1DM, HbA1c at onset and 3-6 years after onset, and the proportion of people with RBF in each subgroup.

Material and methods

Study design

Patients: The study is a cross-sectional study conducted as a post hoc analysis of data from a study on the risk of hypoglycemia and diabetes control stratified on RBF [2]. Please refer to reference 2 for a detailed description of the study design and data collection. In short, participants in the current study were identified from DanDiabKids, which is a national Danish database including all children and adolescents with the onset of T1DM before the age of 15 years. PWD for more than 3 years but less than 6 years were invited. A total of 348 out of 564 agreed to participate of which six participants had incomplete data hence the study includes 342 patients. There was no difference in HLA-subtype distribution.

Mixed meal test for c-peptide response

Please refer to reference 2 for a detailed description of this test. In short, after an overnight fast, the study subjects omitted their morning insulin dose and ingested a standardized liquid breakfast meal (6 ml/kg body weight; maximum, 360 mL; Boost drink/Sustacal, 237 ml containing 33 g carbohydrates, 15 g protein, 6 g fat, and 240 kcal). After 90 min, a blood sample was collected and meal-stimulated c-peptide concentration was analyzed. All PWD, except for one with high RBF, had postprandial blood glucose >11.2 mmol/l. Subsequently, an appropriate insulin dose was administered.

Family history

Family history is defined as at least one natural 1st degree relative to T1DM (referred to as "FHD"). Today DanDiabKids includes all children and adolescents with T1DM before the age of 18.

HbA1c

HbA1c at the onset of T1DM (hereafter referred to as "HbA1c at onset") was measured no later than one week after onset. Forty-five PWD did not meet the criterion hence data of HbA1c at onset includes 297 PWD. HbA1c 3-6 years after onset of T1DM (hereafter referred to as "HbA1c 3-6 years after onset") were measured within one month before the participation in the project. HbA1c is given in both IFCC and DCCT scales in the Tables for the use of comparison with the existent and future literature.

Diabetic ketoacidosis

DKA at the onset of T1DM was defined as plasma glucose >11 mmol/l and bicarbonate <15 mmol/l and/or pH <7.3. DKA was analyzed as a dichotomous variable as DKA at onset, yes, or no.

Puberty

Pubertal status was identified through PWD records. Pubertal status was defined as a dichotomous variable as pre-pubertal or pubertal.

Statistical analysis

Data was analyzed in "STATA" (College Station, TX: StataCorp LLC) with an unpaired student t-test for continuous and normally distributed data. X^2 was applied when appropriate and Fisher's exact test was applied if a population or expected outcome was <5. As the null hypothesis on RBF concerned a lower proportion of PWD with a stimulated c-peptide above 200 pmol/l,

a one-sided p-value was used when testing this hypothesis. The median was used instead of the mean value when data were not normally distributed (age and duration of T1DM). Data are presented as mean ± standard deviation or Confidence Interval (CI) if indicated. P-values <0.05 were considered statistically significant. The following was analyzed: DKA at onset, HbA1c at onset and 3-6 years after onset, and meal stimulated c-peptide secretion. Confounders were investigated such as age at onset, gender, insulin dose, puberty, and duration of T1DM.

Results

In total 342 children and adolescents were included in the analysis of whom 10.2% had FHD. Gender distribution, age at onset, pubertal status, duration of T1DM, and total insulin doses are listed in **TABLE 1**.

A total of 124 PWD (36.3%) had DKA at the onset. **TABLE 2** shows the difference in DKA at onset between PWD with and without FHD. Five (14.3%) PWD with FHD had DKA at onset compared with 119 (38.8%) PWD without FHD, making PWD without FHD more likely to have DKA at onset, p=0.004.

TABLE 3 shows HbA1c at onset and 3-6 years after onset. The mean HbA1c at onset was 11.1% (± 2.2). PWD without FHD had a mean HbA1c at the onset of 11.2% (± 2.2) compared with 10.1% (± 2.3) for PWD with FHD, p=0.005. HbA1c 3-6 years after onset was similar in PWD both with and without FHD, HbA1c 8.6% (± 1.6) versus 8.3% (± 1.3), p=0.16.

DKA at onset did not predict higher HbA1c 3-6 years after onset (p=NS). Mean HbA1c 3-6 years after onset was 8.3% (95% CI 8.11;8.47) without DKA at onset and 8.4% (95% CI 8.18;8.65) with DKA at the onset. C-peptide response to a mixed meal test **(TABLE 4)**.

TABLE 1. Characteristics of the study population.

	Total	Without family history	Family history	p
N (%)	342	307 (89.8)	35 (10.2)	
Gender (f/m) (%)	169 (49.4)/173 (50.6)	149 (48.5)/158 (51.5)	20 (57.1)/15 (42.9)	NS
Age at onset (median)	9.15	9.16	9.05	NS
Pre-pubertal/pubertal (%)	133 (39.5)/204 (60.5)	118 (39.1)/184 (60.9)	15 (42.9)/20 (57.1)	NS
Duration of T1DM (median)	4.24	4.31	4.12	NS
Exogenous insulin dose (SD) (units/kg bodyweight/day)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)	NS
Diabetic ketoacidosis at onset of type 1 diabetes				

TABLE 2. Diabetic ketoacidosis at onset.

	Without family history (%)	Family history (%)	Total (%)	p-value
Without diabetic ketoacidosis	188 (61.2)	30 (85.7)	218 (63.7)	0.004
Diabetic ketoacidosis	119 (38.8)	5 (14.3)	124 (36.3)	
Total	307 (100)	35 (100)	342 (100)	
HbA1c at onset and 3-6 years after onset				

TABLE 3. HbA1c at onset and 3-6 years after onset.

	Total (SD)	Without a family history of T1DM (SD)	Family history of T1DM (SD)	p-value
n	342	307	35	
Onset of T1DM				
HbA1c (DCCT)*	11.1 (± 2.2)	11.2 (± 2.2)	10.1 (± 2.3)	0.005
HbA1c (IFCC)*	97.8 (± 24.5)	99.2 (± 24.1)	86.4 (± 25.3)	
3-6 years after onset of T1DM				
HbA1c (DCCT)	8.3 (± 1.3)	8.3 (± 1.3)	8.6 (± 1.6)	0.16
HbA1c (IFCT)	67.6 (± 14.6)	67.2 (± 14.3)	70.9 (±17.1)	

*Only data from 297 patients due to exclusion criteria

TABLE 4. C-peptide response to a mixed meal test.				
C-peptide	**Total**	**Without a family history of T1DM**	**Family history of T1DM**	**p-value**
<200 pmol/l	315	280	35	0.048
>200 pmol/l	27	27	0	
Total	342	307	35	

In total, 27 PWD had a c-peptide response >200, and 315 had a response <200 pmol/l. All subjects with a c-peptide response >200 pmol/l were among the 307 subjects without FHD, whereas none of the 35 subjects with FHD had a meal stimulated c-peptide >200 pmol/l, p=0.048.

Discussion

Children and adolescents with T1DM and FHD had a decreased risk of DKA at onset and an initially lower HbA1c at onset. After 3-6 years of T1DM, children and adolescents with FHD had lower RBF as compared to children and adolescents without FHD. FHD did not impact age at onset, pubertal status, total daily insulin dose, duration of T1DM, and HbA1c at the time of participation in this trial.

■ Residual insulin secretion 3-6 years after diagnosis

The most remarkable finding in the present study was, that stimulated c-peptide was lower in subjects with FHD than in the subjects without predispositions to T1DM which suggests faster destruction of beta cells and thereby explains why their HbA1c is similar to the HbA1c of their peers even though they started out with a lower HbA1c at the onset. In our study, all children and adolescents with a stimulated c-peptide >200 pmol/l in the mixed meal test belonged to the group without FHD. Although the hypothesis, that PWD with first-degree relatives with T1DM have lower RBF, is supported by this finding, we acknowledge that the data set is relatively small and the hypothesis should be tested in a larger study population. Our study is, however, the largest one of its kind hitherto.

■ DKA at the onset

In the present study 38.8%, without FHD had DKA at onset compared with 14.3% with FHD. This confirms previous findings of an association between FHD and DKA at onset [5-7,14-16] where FHD is a protective factor against DKA at the onset. This might be a result of the parents' awareness of T1DM because they have more knowledge about disease onset and symptoms of T1DM from their own or other children's diseases and they also have blood glucose measuring equipment available.

Greater knowledge in families with FHD give rise to earlier diagnosis and thereby less DKA and lower HbA1c at onset, whereby greater knowledge in the population could lead to a further reduction in DKA and a lower HbA1c at onset for both patients with and without FHD. Lower incidence of DKA at onset was observed in populations with a higher prevalence of T1DM [4,7] for instance in Finland, where the incidence of DKA at onset is 19.4% [17] compared with one-third in other developed nations [5-7,16]. The difference in incidences of DKA at onset could be caused by differences in access to healthcare, child supervision, or schooling in different regions and countries [4]. Another causal factor could be that higher prevalence in the population results in greater awareness of T1DM in the general public and by healthcare professionals leading to T1DM being diagnosed in earlier stages. Educational campaigns on awareness and symptoms of T1DM have been observed to reduce the incidence of DKA at onset [5,15,16], but it does not make a sufficient reduction of DKA at onset compared with the severity of the condition, [15] whereby knowledge about other factors that reduce the risk are important. Given that awareness campaigns are protective against DKA, it supports the hypothesis that the lower incidence of DKA at onset in children and adolescents with FHD is most likely a result of greater knowledge in these families.

It has been suggested that family disposition has a greater impact on the risk of DKA at onset than HLA-subtype [7,14]. This is supported in the present study where no difference in HLA-subtype was observed between the two groups.

Low age at onset is one of the greatest risk factors for DKA at onset [5-7], but no difference in age at onset between subjects with and without FHD was observed in this study.

At the onset, 36.3% had DKA which is similar to other findings [5-7]. A more recent study

by Fredheim et al. [15] found a remarkably lower incidence of DKA at onset in children and adolescents at 17.9%, but the latter study used a different definition of DKA at onset and this difference can by definition cause a lower incidence of DKA at the onset [18].

Furthermore, a small proportion of the variation can be caused by time differences in the two studies as the Fredheim et al. [15] study is from 2012 and the present study is from December 2005 to June 2007 where the incidence was a little lower [18,19].

Other studies suggested that there is only an association between DKA at onset and FHD if FHD is defined as a sibling with T1DM and not parents and/or siblings with T1DM [16]. This is said to reflect that parents with T1DM do not remember the experience of their own onset many years ago. It may be easier for the parents to recognize symptoms of T1DM at the onset if one of their other children has T1DM. Recent experience with the disease then leads to an earlier diagnosis reducing the risk of DKA at the onset [16]. However in this study having first-degree relatives with T1DM is protective even though it both includes parents and siblings, but it is possible that having siblings with T1DM is more protective than having a parent with T1DM. Further studies are needed to investigate this.

■ HbA1c at onset and 3-6 years after onset

The discussion on the lower risk of DKA at onset also applies to lower HbA1c at onset in the group with FHD. Both findings can be the result of an earlier diagnosis in subjects with FHD.

The association between FHD and HbA1c 3-6 years after onset was not statistically significant in the present study, but Sorensen et al. [2] found that children and adolescents with RBF had significantly lower HbA1c 3-6 years after onset.

Fredheim et al. [15] found an association between FHD and higher HbA1c during follow-up hence the difference in the two studies can reflect differences in follow-up time. Furthermore, Fredheim et al. [15] use any type of diabetes as FHD increasing the number of related children and adolescents. Increasing the study population in the present study by including T2DM as FHD moves the tendency towards higher HbA1c 3-6 years after onset towards a statistically significant result (data not shown).

Family support impacts glycemic regulation and results in lower HbA1c over time [20]. A hypothesis that needs to be investigated is that parents with T1DM may theoretically tend to pass on the responsibility of T1DM to their children early and thereby be less supportive, although we have no indications of this being the case in our study population. Likewise, we have no data showing children and adolescents with FHD to be more likely to have a need for independence from their parents because the parents have followed their children closely due to greater knowledge of T1DM, treatment, and complications, and this could also be the subject for future investigations. Another hypothesis is that fear of hypoglycemia can cause higher HbA1c over time because the fear leads to less glycemic control [21] The fear of hypoglycemia could be greater in patients with FHD if hypoglycemia is more frequent in this population. Hypoglycemia was observed more frequently in children and adolescents with low RBF in this dataset [2]. As low RBF and FHD are associated, this could be a plausible explanation for the more deteriorated HbA1c in the FHD group from onset to the time where the study was performed.

Fredheim et al. [15] suggest that children and adolescents with DKA at onset are more likely to have higher HbA1c years after onset. The same findings were made by Duca et al. [5]. This correlation was not observed in the present study and other studies [22]. The effect of DKA at onset and HbA1c 3-6 years after onset is suggested to be a result of the reduced β-cell function in subjects with DKA [15] which is estimated by IDAA1c in Fredheim et al. [15]. This is a less accurate estimation of RBF than c-peptide measurements and is only validated up to 12 months after diabetes debut. It is possible that the difference in Fredheim et al. [15] is non-significant if RBF was measured as meal-stimulated c-peptide. The association between DKA and HbA1c years after onset in Fredheim et al. could reflect an increase of HbA1c with age and during puberty [9,10].

■ Strengths and weaknesses

DanDiabKids includes all children and adolescents with T1DM with onset before the

age of 15 years in Denmark and all of them were invited to study. To our knowledge, the present study has a clear strength as it is the largest one to investigate standardized meal-stimulated c-peptide in children and adolescents and to report a larger and clinically relevant c-peptide response in a larger proportion of those with T1DM who do not have a first-degree relative with type T1DM. Those who chose not to participate could induce bias but no differences between nonparticipants and participants were observed [2]. Furthermore, 20% of participants and non-participants did not have complete information available in the registry [2]. At the onset, 13.2% of the participants did not have a registered HbA1c at the onset that fulfilled the inclusion criterion. This can induce a bias if these HbA1c levels differ from the included data. Another weakness in the study is the size of the data set whereby a reliable difference can be overlooked as statistically insignificant.

Conclusion

Most remarkable, RBF was reduced in subjects with FHD. At the onset of diabetes, FHD was associated with a lower incidence of DKA and a lower level of HbA1c. After 3-6 years of T1DM, FHD had no effect on HbA1c. Future studies are warranted to investigate the RBF in larger cohorts of PWD with FHD and should explore the underlying mechanisms that connect RBF to inherited factors.

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Conflict of interest

No conflicts of interest to declare

Ethics approval statement

The National Ethics Committee approved the study protocol.

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