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Familial Type 1 Diabetes Mellitus – Gender Distribution and Age at Onset of Diabetes Distinguish between Parent-Offspring and Sib-Pair Subgroups

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Abstract

Background—Familial type 1 diabetes mellitus (T1D) comprises parent-offspring and sib-pair subgroups.

Objective—To compare the demographic and clinical characteristics in the two subgroups at diagnosis and evaluate the differences between index cases and second affected family members.

Methods—Retrieved from our institutional registry of new T1D cases for the years 1979 to 2008 were a cohort of 194 familial cases (87 parent-offspring, 107 sib-pairs) ; 133 sporadic cases matched by age, gender, and year of diagnosis were selected as controls. Extracted from their medical files were demographic data, family background, clinical and laboratory findings.

Results—The parent-offspring subgroup was characterized by male preponderance ($p=0.009$). At diagnosis parents were significantly older than their offspring ($p<0.001$); probands were significantly younger than their affected siblings ($p=0.03$). Clinical symptoms and metabolic decompensation were similar in the familial subgroups. Diabetic ketoacidosis (DKA) rate and HbA1c levels were lower in second affected family members in both parent-offspring ($p=0.05$ and $p<0.001$) and sib-pair subgroups ($p<0.001$, for both parameters). Consanguinity and T1D were more frequent in the extended family of familial than sporadic cases ($p<0.001$ and $p=0.012$, respectively) with no difference between the two sub-groups.

Conclusions—The genetic background for T1D would appear to differ not only between familial and sporadic cases but also between parent-offspring and sib-pair subgroups. Whereas differences in age of onset are attributable to both genetic and environmental factors, the less severe clinical manifestations in second affected family members may result from increased awareness or a less aggressive disease process.

Keywords

Type 1 Diabetes Mellitus; familial; parent-offspring; sib-pairs; presentation

Introduction

Type 1 diabetes (T1D) is an autoimmune disease resulting from destruction of pancreatic beta-cells. It is well known that interplay between genetic susceptibility and environmental

factors constitutes the fundamental element in development of the disease (1). The genetic contribution is amply suggested by the relatively high degree of familial clustering among patients with T1D: approximately 10–15% of T1D patients have affected first-degree relatives, whether parents, offspring or siblings. The prevalence of T1D among first-degree relatives has been found to be approximately 5%, significantly higher than that in the general population – 0.4% (1,2–4). The main genetic determinants, responsible for 40% of the genetic susceptibility, map to the major histocompatibility complex (MHC), in particular DR and DQ. (5). Moreover, genes outside the MHC, including the insulin gene, PTPN22, and CTLA-4, have also been linked to disease risk to varying degrees (6–9). As for environmental factors such as infections and diet (10), these of course may also be shared within the same family.

The clinical and genetic characteristics of T1D cases with and without affected family members have been previously studied with varying results. Some investigators found a similarity of presenting features, i.e. age at onset, sex ratio, seasonality, and secular trend, in familial and sporadic T1D patients (11,12), whereas others reported differences between the two groups (13–16). The findings of Veijola et al suggest the existence of different genotypes in familial and non-familial diabetic patients (15). It should be noted that in most of these studies there was no separation of the familial cases into parent-offspring and sib-pair subgroups when comparing them to the sporadic T1D patients.

In the past 30 years (1979–2008) 2099 children and adolescents with newly diagnosed T1D were treated in our tertiary center at the Schneider Children's Medical Center of Israel. Of these 194 had at least one first-degree relative with T1D, including 87 patients of the parent-offspring and 107 of the sib-pair subgroups. In this retrospective study, we evaluated the parent-offspring group separately from the sib-pair group and compared them to age and gender-matched sporadic T1D controls. The objectives of the study was twofold: 1) to compare demographic data, family medical history, presenting symptoms, frequency of diabetic ketoacidosis (DKA), and laboratory findings at diagnosis of T1D between the parent-offspring and sib-pair groups; 2) to compare these characteristics in the index cases to those in the second affected family members.

Patients and Methods

Patients

Survey of the institutional registry of diabetes of our National Center for Childhood Diabetes for all cases of familial T1D diagnosed and followed between 1979 and 2008 yielded 92 multiplex families including 194 patients. All families met the following inclusion criteria: T1D in two or more first-degree relatives; T1D diagnosed after the age of 6 months. Excluded from the study were patients with type 2 diabetes mellitus, genetic defects of beta-cell function (MODY syndromes, mitochondrial DNA mutations, and Wolfram syndrome), drug- or chemical-induced diabetes, cystic-fibrosis-related diabetes, genetic syndromes associated with diabetes and insulin resistance/insulin deficiency (Prader-Willi syndrome, Down syndrome, Turner syndrome, Klinefelter syndrome).

The study population was categorized into two groups (Figure 1): 39 parent-offspring families (87 patients) and 53 sib-pairs families (107 patients). In 8 families there were more than two T1D patients – 7 families with a parent and 2–3 affected offspring and 1 family with 3 affected siblings. Among the sib-pairs there were 5 twin-pairs – one monozygotic and 4 dizygotic. The control population was also extracted from the institutional registry. We were able to retrieve only 133 sporadic T1D patients who matched the familial cases by age, gender, and year of diagnosis, and remained uniplex till December 2008.

Sixty four patients of the sib-pairs (38 Ashkenazi Jews, 22 non-Ashkenazi Jews, and 4 Israeli Arabs) also participated in the European Type 1 Diabetes Genetics Consortium (ET1DGC) study analyzing the genetic basis of T1D in affected sib-pair families. Their DNA was analyzed for typing of HLA class II (DR, DQ, and DP). As DNA analysis was not performed in our sporadic T1D patients, we used genetic data of sporadic Israeli Jewish T1D patients from the population-based Israeli series, for comparison of the frequency of the common susceptibility alleles in the HLA class II region (DRB1* 0301, DRB1*0402, and DRB1*0405; DQA1* 0301, DQB1* 0201 and DQB1*0302) in the familial and sporadic cases (70 Ashkenazi Jews, 95 non-Ashkenazi Jews) (17). The Ashkenazi and non-Ashkenazi Jews were analyzed separately due to the difference in distribution of susceptibility alleles in these ethnic groups. We did not analyze the Israeli Arabic patients as HLA typing was performed only in 4 familial patients, all belonging to one family.

The Familial T1D study protocol and the ET1DGC study protocol were approved by our Institutional Review Board.

Methods

Our institutional diabetes registry records every new-onset diabetic patient referred to our clinic. The registry is consecutive and includes demographic data (date of diagnosis, date of birth and gender). For each familial case, we randomly assigned the next age- and gender-matched, consecutively-diagnosed patient with sporadic T1D. Extracted from the medical files of each patient were additional demographic data : the family history, including ethnicity, consanguinity, documentation of T1D and of autoimmune disease (thyroiditis, celiac, pernicious anemia, and others) in first- and second-degree relatives; presenting symptoms – polyuria/polydipsia, weight loss, malaise, concurrent infection - and duration of symptoms; presence or absence of DKA and HbA1c levels at diagnosis; presence of pancreatic autoantibodies [islet cell antibodies (ICA), insulin autoantibodies (IAA) and glutamic acid decarboxylase autoantibodies (GADA)]. Severity of DKA was defined as follows: mild - pH 7.2–7.3, serum bicarbonate 10–15; moderate - pH 7.1–7.2 serum bicarbonate 5–10; severe - pH<7.1, serum bicarbonate<5. HLA class II (DR, DQ, and DP) results were obtained from the ET1DGC.

Laboratory Analysis

Between the years 1978 – 1994 metabolic control was assessed using HbA1 levels measured with ion-exchange chromatography (Glyc-Affin GHb, Isolab Inc., Akron, Ohio, USA). After 1994 evaluation of metabolic control was based on capillary HbA1c values measured using an automated immunochemical technique (DCA 2000; Siemens Medical Solutions Diagnostics, Tarrytown, NY); the 95% confidence limits (mean $\pm$ 2 SD) are 4.3% to 5.7%. The conversion equation between HbA1 and HbA1c is $HbA1c = 2.409 + 0.617*(HbA1)$.

Until 1984 islet cell autoantibodies (ICA) were determined according to the method of Bottazzo et al. using a standard indirect immunofluorescence assay performed on sections of frozen human blood group O pancreas (18). The results were expressed in Juvenile Diabetes Foundation units (JDF U); detection limit was >20 JDF U. Since 1984 ICA has been determined by RIA using ³⁵S-LA-2 and human serum; detection limit 0.085. Our laboratory has participated in the international workshops on the standardization of ICA methods, in which its sensitivity was 70%, specificity 97%. Insulin autoantibodies (IAA) were measured by a modification of the liquid phase radioimmunoassay originally described by Palmer et al. (19). The cutoff limit for antibody positivity background was >112 nU/ml. GAD autoantibodies (GADA) were quantified with a radioligand assay as described by Petersen et al. (20). The results were expressed in relative units (RU), which represent the specific binding as a percentage of that obtained with a positive standard serum. The cutoff limit for

antibody positivity was >1 GAD Units. Our laboratory has participated in the international workshops on the standardization of GADA methods, in which its sensitivity was 76%, specificity 99%.

Genotyping methods

HLA analysis was performed in a central laboratory affiliated with the ET1DGC. The HLA genotyping was performed with a PCR-based sequence-specific oligonucleotide probe system as previously described (21). HLA genotyping data are presented at a 4-digit level (i.e., DRB1*0101) so that synonymous polymorphisms, which are documented in the 5th and 6th digits, are not reported.

Statistical Methods

All analyses were done using the BMDP program (22) and the results are expressed as mean $\pm$ SD or number (percentage). For continuous variables (number of children in the families of studied patients, HbA1C levels), comparisons between groups were made using analysis of variance (ANOVA). Discrete variables (gender, consanguinity, T1D, and autoimmunity in family members, clinical symptoms, presence and severity of DKA and pancreatic auto-antibodies) were compared using Pearson's chi square or Fisher's exact tests as appropriate. Continuous variables not having Gaussian distribution were analyzed using the Mann-Whitney U-test, with multiple comparisons. Logistic regression was applied to determine variables significantly associated with prediction of familial cases and DKA. A p-value of < 0.05 was considered significant.

Results

Prevalence of T1D (Figure 2)

Although there has been a continuing and pronounced rise in the number of new T1D patients referred to our institution in the past 3 decades (397 new cases between 1979–1988, 592 between 1989–1998, and 1110 between 1999–2008) the percentage of familial patients has remained quite constant, with a prevalence of approximately 9% of the new T1D patients per year (parent-offspring - ~4.0%, sib-pairs- ~5.0%).

Demographic data and family history (Table 1)

Mean age at diagnosis was significantly older in the parent-offspring subgroup ($p=0.04$). Gender distribution revealed a male preponderance (64.4%) in the parent-offspring group, and a slight female predominance (55.1%) in the sib-pairs ($p=0.009$). These two parameters were not analyzed in the sporadic group as the patients were age and gender matched. With regard to ethnicity, there was no difference between the two subgroups, and the ethnic distribution of the familial cases resembled that of the sporadic controls: Ashkenazi Jews – 48.5% vs. 52.6 %, non-Ashkenazi Jews - 44.3% vs. 44.4%, and Muslim Arabs – 7.2% vs. 3%. Consanguinity was reported only in the familial cases (6.7%, $p=0.001$). While the finding of a positive history for both T1D and autoimmune disease in the extended family was similar in the two familial subgroups, it was more prevalent in the familial ($p=0.012$) than in the sporadic cases. T1D in more than 2 members of the extended family was reported in 12.6% of the familial group but only in 2.3% of the sporadic group ($p=0.001$). The frequency of autoimmune disease in extended families was higher among the patients with familial T1D than among the sporadic cases but the difference did not reach statistical significance ($p=0.06$).

Clinical characteristics at diagnosis (Table 1)

At presentation the rate of occurrence of polyuria, polydipsia, weight loss, malaise and concomitant infections was comparable in the two familial subgroups as well as in the sporadic group. Although duration of symptoms before diagnosis was similar in familial and sporadic patients, it was significantly shorter in the parent-offspring group ($p<0.001$).

The prevalence of DKA and levels of HbA1c were similar in the parent-offspring and sib-pair subgroups; these parameters were significantly lower in the familial patients than in the sporadic T1D patients ($p=0.006$ and $p=0.025$, respectively). The distribution of severity of DKA was comparable in the familial and sporadic groups: mild DKA - 36% vs. 33%, moderate DKA - 43% vs. 40%, severe DKA - 21% vs. 27%.

Clinical features at presentation - comparison between the index case and the second-affected family members (Table 2)

Male preponderance was found in both parents and their affected offspring but not in probands and their affected siblings. The mean age at onset of diabetes of the affected offspring was significantly younger than that of the affected parent ($p<0.001$), whilst age at onset of diabetes of affected sibling was significantly older than that of the proband ($p=0.03$).

In the parent-offspring group, the duration of symptoms before diagnosis of diabetes was significantly shorter in the offspring than in the parents ($p<0.001$). Weight loss and malaise were less frequent in the offspring than in the affected parent ($p=0.005$ and $p=0.004$, respectively). In the sib-pair group the duration of symptoms before diagnosis of diabetes and the frequency of reported symptoms at onset were similar in probands and affected siblings; malaise was less frequently reported in affected siblings ($p=0.024$). The prevalence of DKA was lower in affected offspring and affected siblings than in index cases ($p=0.05$ and $p<0.001$, respectively). HbA1c levels at presentation were also significantly lower in affected offspring and affected siblings than in affected parents and probands ($p<0.001$ for both groups). It is of note that no significant difference in BMI-SDS was found between the index case and the second affected family member in either of the parent-offspring and sib-pairs groups.

Islet cells auto- antibodies at presentation

Positive pancreatic auto-antibodies were found in a similar distribution and with a comparable absolute number in the parent-offspring and sib-pairs subgroups. Comparison between familial and sporadic cases revealed a similar percentage of positive ICA (71.9% vs. 70.3 %) and GADA (47.8% vs. 39.8%) while IAA was detected in a significantly higher percentage in familial compared to sporadic cases (67.5% vs. 46.3%, respectively, $p=0.006$). The presence of 3 positive auto-antibodies was significantly higher in familial than in sporadic patients (26.5% vs. 15.7%, respectively, $p=0.036$).

HLA class II typing

Among the 64 patients who underwent HLA typing, in both Ashkenazi and non-Ashkenazi Jews the percentage of susceptibility alleles for T1D in the HLA class II region was higher in the familial cases than in the population-based sporadic T1D cases but the difference did not reach statistical significance, probably due to the small number of subjects tested. In the familial vs. sporadic Ashkenazi population the frequencies of susceptibility alleles were: DRB1* 0301- 50% vs 40%; DRB1*0402 -68.4% vs. 60%; DQA1* 0301- 81.6% vs. 61.4%, ($p=0.05$); DQB1* 0201- 65.8% vs. 57.1%; DQB1*0302 - 73.7% vs. 64.2%. In the familial vs. sporadic non-Ashkenazi population the frequencies of susceptibility alleles were: DRB1* 0301- 81.8% vs. 65.2%; DRB1*0402 - 36.4% vs. 30.5%; DRB1*0405 - 31.8% vs. 22.1%;

DQA1* 0301- 77.3% vs. 74.7%; DQB1* 0201- 95.5% vs. 75.7%, ($p=0.042$); DQB1*0302-50% vs. 64.2%.

Discussion

The marked increase in the absolute number of patients with familial T1D in Israel during the past three decades provided us with the opportunity to determine the similarities in and the differences between the parent-offspring and sib-pair groups at presentation of the disease. In this retrospective comparative clinical study we found a significant distinction in gender distribution and age at onset of diabetes between the two subgroups. Male preponderance and younger age of the offspring distinguished the parent-offspring from the sib-pairs group. To the best of our knowledge this is the first study demonstrating that the offspring present at a younger age than their affected parents.

Male preponderance in our parent-offspring group, i.e. an increased percentage of fathers as well as sons, may stem from an increased genetic susceptibility for diabetes in males within these families. A higher percentage of affected fathers with familial T1D as well as the increased percentage of males among the affected offspring are consistent with previous reports; yet, the underlying cause still needs clarification (2,14,16). A number of theories have been raised in the attempt to explain the preferential sex-specific transmission of T1D from either the father or the mother to their offspring but none have yet been validated (16).

Age at onset of diabetes may also be modified by genetic factors. Previous studies showed that HLA genes related to high disease susceptibility (HLA-DR and DQ genotypes) were associated with earlier onset of diabetes (23,24). Since the mean age at diagnosis of diabetes was significantly older in the parent-offspring group than in the sib-pairs, it is possible that the parent-offspring and sib-pair groups possess different HLA-alleles. Unfortunately, we do not have data on the HLA alleles for all of our parent-offspring population to confirm this assumption. However, subdivision of the parent-offspring group into index cases and second affected family members revealed an older age at diagnosis only in the parents. Age at presentation of diabetes in their offspring was significantly younger and was similar to that of the sib-pairs. The difference between parents and offspring may be related to the year of diagnosis; all studied offspring were diagnosed in more recent years. Their younger age at presentation most probably reflects the worldwide secular decrease in age of emerging diabetes (1,4,16). This trend may be attributable to novel environmental risk factors appearing in the last decades, inducing epigenetic changes which instigate the development of diabetes in this genetically susceptible population. Subdivision of the sib-pairs group also demonstrated a significant difference in age at presentation between probands and affected siblings. However, in contradistinction to the parent-offspring group, the index cases in the sib-pairs were significantly younger than their affected siblings. This observation is in line with previous reports, demonstrating a younger age at diagnosis among first affected siblings (12–14). As both index cases and their affected siblings were of the same generation the underlying cause for this phenomenon remains elusive.

The mode of presentation of diabetes was quite similar in the parent-offspring and the sib-pair groups. All patients exhibited the classical symptoms of diabetes (polyuria, polydipsia weight loss) over a similar mean time period before diagnosis. Subdivision of the familial patients into first- and second-affected cases showed that metabolic decompensation, (as judged by HbA1C levels and frequency of DKA) was more pronounced in the first affected member and resembled that of the sporadic cases. However, the second affected family members presented with fewer episodes of DKA and lower HbA1c levels. Their better metabolic condition at diagnosis most likely stemmed from earlier recognition of signs and symptoms of hyperglycemia by experienced parents or relatives (13). Hence, a greater

family awareness has a critical role in achieving earlier diagnosis and in preventing severe metabolic derangements. Furthermore, according to our data, parents should also be aware of the fact that age at presentation in the second affected family member may differ from that of the index case, with younger age in offspring and older age in second affected sibling. Interestingly, although a marked decrease in the percentage of DKA was found in second affected family members, some familial diabetic patients did present with DKA. This disconcerting phenomenon may be prevented by increasing parent awareness, especially in families with clustering of T1D and autoimmune diseases in the extended family.

It has been well established that familial T1D is associated with increased genetic susceptibility, attributed to a higher prevalence of both HLA and non-HLA genes among affected family members (5–9,13,15). Although we do not have a complete genetic work-up for all our familial T1D patients, the higher frequency of susceptibility alleles in the familial cases as opposed to that in the sporadic cases would seem compatible with this line of thought. Moreover, the higher incidence of T1D as well as other autoimmune diseases in second- and third-degree relatives of both paternal and maternal origin indicates an increased genetic susceptibility for autoimmune diseases in these families. This finding is in accordance with previous studies demonstrating that HLA genes associated with autoimmune diseases tend to cluster in extended family members of patients with familial T1D (25–27). Consanguineous marriages, which were more common among the familial patients, may also contribute to an increased genetic predisposition for the development of T1D since the two parents may share similar susceptibility genes that could be transmitted to their offspring. The high incidence of T1D and other autoimmune diseases in second-degree relatives of both paternal and maternal origin also indicates an increased risk for diabetes.

Pancreatic auto-antibodies at diagnosis have been found to be a surrogate marker of beta-cell autoimmune destruction (1). Similarly to previous reports (15), the number and type of positive pancreatic autoantibodies detected did not differ in the two familial groups, but the higher absolute number of autoantibodies in the familial cases as compared to those in the sporadic cases suggests a different autoimmune background, most probably associated with increased genetic susceptibility.

Our investigation of such a large cohort of patients with familial T1D seen in our tertiary care center through the period of three decades has enabled us to delineate more clearly the characteristics of familial T1D and its parent-offspring and sib-pair subgroups. A notable limitation of the study is the lack of genetic analysis for the entire cohort and not just for part of it. Furthermore, since the study was retrospective appropriately matched sporadic cases of T1D could not be found as controls for every one of the familial cases. For further clarification of the genetic susceptibility and genetic risk factors that could explain the familial clustering of T1D in Israel, prospective studies should be carried out.

In conclusion

The genetic background for T1D would appear to differ not only between familial and sporadic cases but also between parent-offspring and sib-pair subgroups. The male preponderance in the parent-offspring group indicate that each subgroup possesses distinctive susceptibility genes. The fact that in second affected family members' age at diagnosis of diabetes was younger in the offspring and older in the second affected siblings suggests the influence of both genetic and environmental factors. The less severe clinical manifestations in the second affected family member, with a lower incidence of DKA upon presentation, are attributable to awareness of diabetes symptoms rather than to genetic or environmental changes. To determine whether genetic susceptibility differs in the various types of familial cases and to assess its impact on disease pathogenesis, future genome-wide association studies should be carried out.

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Figure 1. Classification of the 92 T1D multiplex families according to the affected family members with T1D – parent (either father or mother)-offspring pairs and sib-pairs, and the number of affected family members.

Figure 2.

Prevalence of new T1D cases in the Institute for Endocrinology and Diabetes at Schneider Children's Medical Center of Israel during last 3 decades – the absolute number and the percentage of sporadic and familial (parent-offspring and sib-pairs) cases in each decade.

Table 1

Demographic and clinical characteristics at presentation of T1D - comparison between familial subgroups (parent-offspring and sib-pairs) and between familial and sporadic cases

	Familial T1D Parent- offspring	Familial T1D Sib-pairs	p	Familial T1D total	Sporadic T1D	p
Demographic characteristics						
Number	87	107		194	133	
Age (years)	11.3±6.4	9.7±4.9	0.04	10.4±5.6	9.8±4.7	NS
Male : Female n (%)	56:31 (64.4:35.6)	48:59 (44.9:55.1)	0.009	104:90 (53.6:46.4)	65:68 (48.9:51.1)	NS
Consanguinity n (%)	9/87 (10.5)	4/107 (3.7)	NS	13/194 (6.7)	0/133 (0)	0.001
Extended family						
T1D n (%)	25/75 (33.3)	23/107 (21.5)	NS	48/182 (26.4)	19/133 (14.3)	0.012
Autoimmune Diseases n (%)	20/75 (26.7)	41/107 (38.3)	NS	61/182 (33.5)	31/133 (23.3)	0.06
Clinical characteristics at diagnosis						
Duration of symptoms (days)	9.8±23.2	20 ±19.9	<0.001	21.7±21.4	22.5±20.7	NS
DKA n (%)	17/74 (23)	25/105 (23.8)	NS	42/179 (23.5)	51/133 (38.3)	0.006
HbA1c (%)	10.7±2.5	11.2 ±2.6	NS	11.1±2.6	11.8±2.7	0.025

T1D= type 1 diabetes mellitus; n=number; DKA=diabetic ketoacidosis; NS= nonsignificant; values are means ± SD

Clinical characteristics at presentation of T1D in familial cases – comparison between first affected and second affected family members in the parent-offspring and the sib-pairs

Table 2

	Parent	Offspring	p	Proband	Sibling	p
Number	39	48		53	54	
CA (yrs)	15.5±6.1	8.6±5.0	<0.001	8.3±4.4	11.0±5.0	0.03
Male:Female	26:13 (67:33)	30:18 (67:33)	NS	26:27 (49:51)	22:32 (41:59)	NS
Symptoms – duration (days)	39.0±28.6	14.6±12.1	<0.001	23.1±20.8	17.3±19	NS
Polyuria/Polydipsia n (%)	28/28 (100)	44/47 (93.6)	NS	48/50 (96)	52/54 (96.3)	NS
Weight loss n (%)	24/28 (85.7)	25/47 (53.2)	0.005	32/50 (64)	30/54 (55.6)	NS
Malaise n (%)	18/28 (64.3)	14/47 (29.8)	0.004	23/50 (46)	13/54 (24.1)	0.024
Concurrent Infection n (%)	6/28 (21.4)	6/47 (12.8)	NS	8/50 (16)	4/54 (7.4)	NS
DKA n (%)	10/28 (35.7)	7/46 (15.2)	0.05	20/50 (40)	5/54 (9.3)	<0.001
Mild (pH 7.2 – 7.3)	3/28 (10.7)	4/46 (8.7)	NS	7/50 (14)	1/54 (1.9)	0.027
Moderate (pH 7.1 – 7.2)	5/28 (17.9)	2/46 (4.3)	NS	9/50 (18)	2/54 (3.7)	0.025
Severe (pH < 7.1)	2/28 (7.1)	1/46 (2.2)	NS	4/50 (8)	2/54 (3.7)	NS
HbA1c (%)	12.6±1.4	10.1±2.5	<0.001	12.4±2.7	10.3±2.2	<0.001
BMI-SDS	-0.67±1.3	-0.12±1.39	NS	-0.78±1.15	-0.62±1.28	NS

T1D= type 1 diabetes mellitus; N=number; CA= chronological age; DKA=diabetic ketoacidosis; NS= nonsignificant; BMI-SDS= body mass index – standard deviation score; values are means ±SD