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Clinical features, biomarkers and diabetic ketoacidosis at diagnosis of type 1 diabetes among children and adolescents in Sana'a, Yemen

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ABSTRACT

Introduction There is little published information on type 1 diabetes (T1D) in children in Yemen. We aimed to identify the clinical characteristics, biomarkers and diabetic ketoacidosis (DKA) at diagnosis of T1D among children and adolescents in a diabetes centre in Sana'a, Yemen.

Methods A total of 485 children and adolescents aged ≤18 years diagnosed with T1D during the period 2010–2020 were included in the study. The variables investigated were demographic and clinical characteristics, biomarkers, subtypes of T1D, and the risk factors for severe DKA at diagnosis.

Results At diagnosis, children aged <10 years compared with those aged ≥10 years had higher mean plasma glucose (p<0.001) and mean HbA1c (p=0.026), and lower mean C-peptide (pmol/L) (p=0.019), and a higher frequency of DKA at diagnosis than older children (p<0.001). A majority of the study population (383, 79%) presented in DKA . Children aged <10 years presenting with DKA had significantly longer median appraisal interval (p=0.009) and median total diagnosis interval (p=0.025), and significantly lower mean C-peptide (p=0.001) as compared with their peers without DKA. The prevalence of autoantibody-negative 'idiopathic' T1D was 36 (32%) of the total number tested for autoantibody and familial T1D 61 (12.6%) of all the study population.

Conclusion In Yemen children aged <10 years with new-onset T1D frequently faced the challenge of a delay in diagnosis and treatment initiation, with severe hyperglycaemia and a higher risk of DKA at diagnosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Children in low-income countries with new-onset type 1 diabetes (T1D) are at a greater risk of high non-diagnosis or delayed diagnosis and treatment with subsequent higher risk of life-threatening diabetic ketoacidosis (DKA) soon after onset of T1D symptoms.
⇒ Evaluation of the pathways to diagnosis and treatment of the new-onset T1D can inform initiatives to increase early diagnosis.

WHAT THIS STUDY ADDS

⇒ This study aims to investigate the clinical characteristics, biomarkers, subtypes of T1D and risk factors for DKA at diagnosis of diabetes among children and adolescents in a recourse-limited country.
⇒ We also aimed at increasing community awareness on early symptoms of T1D in children and educating primary healthcare providers on skills of early diagnosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The T1D Index estimates that in 2023, 16 300 Yemeni are living with T1D, and that 47.8 years of healthy life are lost to T1D per person.
⇒ Leveraging these data and insights can help change the lives of young people affected with T1D in Yemen, by identifying attainable interventions, including timely diagnosis, and then improving access to at least an intermediate care level.

INTRODUCTION

Type 1 diabetes (T1D) is the most common form of diabetes in children and adolescents. It is characterised by destruction of pancreatic β-cells, leading to partial or absolute insulin deficiency and presentation with symptoms of severe hyperglycaemia, and frequently, diabetic ketoacidosis (DKA) at disease onset.[1] Early diagnosis of new-onset T1D in children and adolescents is vital to avoid DKA, which can increase the risk of mortality and long-term morbidity. Delay in diagnosis occurs if the patient was misdiagnosed on the first primary care visit and was first diagnosed at a secondary-care level.[2] The National Institute for Health and Care Excellence recommended in 2015 that children with suspected T1D and DKA should be offered immediate (same day) referral to a hospital with acute paediatric facilities to confirm diagnosis and to provide immediate care.[3]

Various subtypes of T1D have been suggested by some epidemiological studies.[4] However, only two main subtypes, autoimmune and idiopathic, have been categorised

by the current American Diabetes Association[5] and International Society of Pediatric and Adolescent Diabetes (ISPAD)[6] classification schemes. Most children and adolescents with T1D have autoimmune T1D resulting from immune-mediated destruction of pancreatic β-cells with both a genetic predisposition and autoantibodies. The minority have idiopathic T1D with no known aetiology, but with permanent insulin deficiency.[5 6] As family history of T1D can increase the risk, patients with onset of T1D before the age of 20 years have been also subclassified into those who have at least one first-degree relative with T1D (familial diabetes), and those who have no background of first-degree relative with T1D (sporadic diabetes).[7 8]

This study was conducted in a cohort of children and adolescents with new-onset T1D in Sana'a, Yemen. The aim was to determine the clinical and biochemical features of these individuals, assess their autoantibody status, evaluate the frequency and impact of a family history of T1D, understand the pattern of presenting symptoms, and to identify the occurrence and risk factors associated with DKA at the time of diagnosis.

METHODS

Consenting procedures

Informed consent was obtained from patients' families.

Study cohort and data collection

A total of 485 children and adolescents aged ≤18 years with new-onset T1D were prospectively recruited in the study, during the period 2010–2020, in a diabetes centre in the capital city Sana'a, Yemen. Their data were collected according to a standardised protocol and retrieved retrospectively. The patients' families were questioned and assessed at first encounter on the presenting symptoms and signs of polyuria, polydipsia, weight loss, abdominal pain, nausea or vomiting, fast breathing, fruity breath, and altered consciousness, and also the duration of symptoms.

Exclusion criteria included children and adolescents with a previous diagnosis of T1D, children with diabetes diagnosed before 9 months of age or with monogenic diabetes diagnosed after that age, and youth with type 2 diabetes (T2D) or secondary diabetes.[9]

Demographic data

Demographic variables such as age, gender, Tanner pubertal stage, family history of diabetes, and consanguinity were assessed and recorded. Parents provided family history information regarding physician-diagnosed T1D among immediate first-degree relatives, including parents and siblings. Accordingly, T1D was further subdivided into familial and sporadic cases.[7 8] In addition, parents were asked about the presence of T2D and parental first cousin consanguinity among the family.

Anthropometry data

Anthropometric characteristics included measuring height (cm) in children aged ≥2 years and length (cm) in very young children (aged <2 years) using a stadiometer, and body weight (kg), after full rehydration, using standard scales. Body mass index (BMI, kg/m^2), and height/length, by age and sex were expressed as z-scores (SD scores (SDS) and percentiles and the nutritional status was categorised using the WHO growth reference charts and calculator. According to the WHO paediatric reference standards for age 0–19 years, children and adolescents were classified into underweight (BMI < 5th percentile), healthy weight (BMI ≥ 5th to <85th percentiles) and overweight/obese (BMI ≥ 85th percentiles). Median BMI and height-for-age z-score values were used for comparing weight and height status between patients presenting with and without DKA among children aged <10 years and those aged ≥10 years.

Puberty was assessed by Tanner staging.[10] Of the 342 patients in pubertal ages, 58 (17%) were prepubertal (Tanner stage 1), 69 (20.2%) were at Tanner stage 2, 100 (29.2%) were at Tanner stages 3 and 4, and 115 (33.6%) had completed puberty at Tanner stage 5.

Clinical diagnosis of diabetes

Clinical characteristics included weight and height measurement, case definition, duration and severity of symptoms, pathway to diagnosis, insulin use, and history of DKA at diagnosis. Diagnosis of diabetes was validated by the availability in the records of data on age at onset of the disease, acute or rapid onset of severe clinical symptoms, very high blood glucose levels, ketonaemia, and immediate need for exogenous insulin therapy.[11]

The pathway to diagnosis of T1D was modified from the work of Usher-Smith *et al*[12] and has been divided into two components: the time interval between onset of symptoms and decision to seek medical help (the appraisal interval), and the overall time extending from onset of symptoms to confirmed diagnosis and treatment initiation (the total diagnosis interval).

Biochemical markers

Biochemical features included surrogate markers of hyperglycaemia and β-cell function. The main variables for measuring hyperglycaemia were random plasma glucose concentration ≥11.1 mmol/L just before initiation of insulin therapy, and HbA1c level >48 mmol/mol (> 6.5%) at diagnosis.[11] β- cell function was quantified from the level of random non-fasting serum C-peptide (NFSCP).

Autoimmunity

Autoimmunity was identified from the measurement of autoantibodies to islet cell antigen, glutamic acid decarboxylase-65 antibody (GADA) and tyrosine phosphatase antibody (IA-2A). Accordingly, T1D was further subdivided into autoimmune T1D (positive one or

both islet-autoantibodies) and idiopathic T1D (islet-autoantibody negative).[5 6]

Diabetic ketoacidosis

DKA occurring up until day 10 after diagnosis of diabetes was considered DKA at diagnosis.[7]

DKA was broadly defined as plasma glucose >13.9 mmol/L, venous blood pH<7.3 or serum bicarbonate <15 mmol/L in presence of ketonaemia (blood β-hydroxybutyrate ≥3.0 mmol/L) or moderate/large ketonuria (urine ketone ≥2+) ≥ 40 mg/dL. Severe DKA was defined as venous pH<7.1 and/or serum bicarbonate <5 mmol/L[13] or as a physician diagnosis of severe DKA from hospital records during admission. Mild DKA was defined as mild to moderate ketonuria (urine ketone ≤2+) without disorders in acid-base status.

Laboratory investigations

Serum bicarbonate, creatinine (µmol/L), electrolytes, venous pH, and urine or blood ketone were measured at diagnosis. GADA and IA-2A islet autoantibody titres were measured within 2–4 weeks of diagnosis. Random NFSCP was measured after restoring metabolic status within 2–4 weeks after the diagnosis of diabetes that was validated against a concurrently obtained blood glucose level ≥8.0 mmol/L and normal kidney function. A blood C-peptide (in EDTA) taken between 10:00 hours and 11:oo hours at 2 hours after a mixed meal consumption was considered stimulated. A cut-off level of 200 pmol/L was used because of its high sensitivity and specificity for detecting severe insulin deficiency.[14]

A quantitative assay of GADA and IA-2A was performed by means of ELISA kits provided by EUROIMMUN, Germany, and their titres were determined by Labsystem Multiscan RC ELISA Reader. The antibody titre level was categorised on a three-level scale: low or negative (titre <10 IU/mL), moderate (titre 10–20 IU/mL) and high (titre >20 IU/mL). Other laboratory tests were performed by Abbott Autoanalyzers (Abbott Laboratories, Abbott Park, Illinois, USA). The Abbott ARCHITECT c4000 system was used for chemistry and HbA1c, and Abbott ARCHITECT *i*1000SR system for hormones. Serum C-peptide was measured by Abbott ARCHITECT *CMIA (chemiluminescent microparticle immunoassay)*.

Statistical analysis

The normality of the data was evaluated using the Kolmogorov-Smirnov test, the graphs (histogram and normal Q-Q plot), and measures of skewness and kurtosis. The data are presented as mean (±SD), median (IQR 25%, IQR 75%), and frequencies and percentages, where appropriate. The mean (±SD) was used to describe the quantitative data and the difference was measured by t-test for two groups. The median (IQR) was used in cases where variables did not follow a Gaussian distribution, and the difference was measured by the Mann-Whitney U-test for two groups. Frequencies and percentages were used to describe qualitative data and the difference was measured by the χ^2 test and χ^2 test with Yate correction. A stepwise logistic regression (multivariate analysis) was applied using the significant variables identified in the univariate analysis to determine those variables significantly associated with severe DKA. Statistical analysis was performed using the SPSS for Windows V.26 statistical package, with statistical significance set at a value of $p<0.05$.

RESULTS

The study consisted of 485 children and adolescents aged between 10 months and 18 years, 257 boys and 228 girls, (ratio of 1.13) ($p>0.05$).

Two infant boys were excluded due to neonatal diabetes presenting with hyperglycaemia and severe DKA. The first was a 6 months of age with Wolcott-Rallison syndrome, and the second was 3 months of age with insulin gene mutation. Their diagnosis was established by genetic testing at the University of Exeter Molecular Genetics Laboratory, UK. We also excluded a 16-year-old adolescent boy whose history fits well with HNF 1A or HNF 4A Maturity-Onset Diabetes in the Young (MODY). He presented with non-insulin treated diabetes, low BMI, a 75% MODY-calculator probability, substantial C-peptide level, and negative GAD and IA2 antibodies.

General characteristics of children diagnosed with T1D at age <10 years and children ≥10 years

Patients with T1D were classified into two age groups: 201 children aged <10 years (41.4%), and 284 older children aged ≥10 years (58.6%), with no significant variation in sex distribution between both age groups (table 1).

The frequencies of both underweight (BMI for age <5th percentile) and short stature (height for age <5th percentile) were significantly higher in children ≥10 years than in younger children ($p=0.005$, $p<0.001$, respectively).

The biomarkers presented in the table indicate that children <10 years, compared with those ≥10 years had significantly higher mean values of HbA1c, and mean plasma glucose concentration, but significantly lower mean C-peptide levels.

The qualitative variables in the table indicate that the overall frequency of broadly defined DKA at diagnosis was 383 (79%) with significantly higher frequency in children <10 years (180 (89.6%)) than in older children (203 (71.5%)). Of the children tested, 77 (68%) had autoimmune T1D and 36 (32%) had idiopathic T1D. Compared with older peers, children <10 years presented with a higher prevalence of autoimmune cases, had significantly more frequent autoantibody positivity (120/169 (71%) vs 74/139 (53%), $p=0.001$), and had higher titre levels of autoantibodies to IA-2 antigen, and had greater loss of β-cell function. Idiopathic cases, on the other hand, presented with a comparable age at diagnosis but with a higher mean C-peptide concentration (221 pmol/L vs 176 pmol/L).

Table 1 General characteristics of children diagnosed with T1D at age <10 years versus.≥10 years

Variable	Total n=485	<10 years n=201	≥10 years n=284	P value
Sex, n (%)				0.780
Boy	257 (53)	105 (52.2)	152 (53.5)	
Girl	228 (47)	96 (47.8)	132 (46.5)	
BMI for age percentile (%), n (%)				
Underweight (<5th percentile)	159 (32.8)	67 (33.3)	92 (32.4)	0.828
Height-for-age percentile (%), n (%)				
Short stature (<5th percentile)	186 (38.4)	62 (30.8)	124 (43.7)	0.004
HbA1c (mmol/mol), mean (±SD)	93 (16)	94.9 (15.4)	91.7 (16.3)	0.026
Plasma glucose (mmol/L), mean (±SD)	21.6 (5.6)	23 (5.3)	20.6 (5.7)	<0.001
C-peptide (pmol/L), mean (±SD)	234.4 (134.9)	210.2 (142.1)	258 (123.8)	0.019
DKA, n (%)	383 (79.0)	180 (89.6)	203 (71.5)	<0.001
Autoantibody positivity (GADA and/or IA-2A), n (%)				
Positive one or both autoantibodies	194/308 (63)	120/169 (71)	74/139 (53)	0.001
Negative both autoantibodies	114 (37)	49 (29)	65 (47)	
Family history of T1D among parents or siblings, n (%)				
Familial T1D: Positive FH for T1D	61 (12.6)	27 (13.4)	34 (12)	0.647
Sporadic T1D: Negative FH for T1D	424 (87.4)	174 (86.6)	250 (88)	
Family history of T2D among parents, n (%)	70 (14.4)	21 (10.4)	49 (17.3)	0.033
Family history of T2D among grandparents, n (%)	255 (52.6)	144 (71.6)	111 (39.1)	<0.001
Family history of parental consanguinity; First cousins (1C/D1C), n (%)	91 (18.8)	41 (20.4)	50 (17.6)	0.437

HbA1c-mmol/mol (SI units); plasma glucose (mmol/L).
Islet autoantibodies.
The values of p indicate comparison between variables in children <10 years compared with those ≥10 years. A value of p<0.05 is statistically significant.
BMI, body mass index; 1C/D1C, first cousin/double first cousin; C-peptide, connecting peptide; DKA, diabetic ketoacidosis; GADA, glutamic acid decarboxylase-65 autoantibody; IA-2A, tyrosine phosphate autoantibody; T1D, type 1 diabetes; T2D, type 2 diabetes.

A total of 61 cases with sibling-pairs and parent-offspring familial T1D were identified representing a prevalence of 12.6% of the total study population. Of these, 58 patients had sibling-pairs familial diabetes, the majority of them came from two sib-pair families. The family history of T2D was significantly more prevalent among parents of children ≥10 years than in the younger children (p=0.033), and significantly more prevalent among grandparents of children <10 years than in the older children (p<0.001). No difference in parental consanguinity was noted between children <10 years and ≥10 years.

Clinical and biochemical features of patients presenting with and without DKA

DKA at T1D onset was very common in both age groups, with no difference in sex distribution (table 2).

The mean (SD) age of patients presenting with DKA was significantly lower than in those without DKA (5.5 (2.5) *vs* 6.7 (2.5), p=0.036 for children <10 years and 13.3 (2.4) *vs* 14.8 (2.4), p<0.001 for children ≥10 years).

Mean (SD) HbA1c (mmol/mol) of patients presenting with DKA was significantly higher than in those without DKA (97 (14.5) *vs* 77.1 (10.4), p<0.001 for children <10 years and 96.6 (15.1) *vs* 79.4 (12.6), p<0.001 for children ≥10 years). Mean (SD) plasma glucose (mmol/L) of patients presenting with DKA was significantly higher than in those without DKA (23.7 (4.8) *vs* 16.3 (5), p<0.001 for children <10 years and 22.6 (5.2) vs 15.8 (3.3), p<0.001 for children ≥10 years). Mean (SD) serum C-peptide (pmol/L) of patients presenting with DKA was significantly lower than in those without DKA in children <10 years (190.9 (133.6) *vs* 344.1 (130.8), p=0.001), and non-significant for children ≥10 years (241.6 (108.5) *vs* 314.4 (156.8), p=0.063).

Median (IQR) BMI-for-age z-score was not significantly different between patients with and without DKA in either age group. However, median (IQR) height-for-age z-score was significantly lower in children ≥10 years without DKA (−1.7 (1.4) SDS) for patients without DKA vs (−1.5 (1.2) SDS) for patients with DKA, p=0.007. Median (IQR) values for appraisal interval and total diagnosis interval were significantly longer in children <10 years with DKA than in those without DKA but not in children ≥10 years. Median was 12 (5) days versus 10 (3) days, p=0.009, for

Table 2 Clinical and biochemical features of patients presenting with and without diabetic ketoacidosis

	<10 years			≥ 10 years		
Variables	DKA	No DKA	P value	DKA	No DKA	P value
Age at diagnosis of diabetes (years), mean (±SD)	5.5 (2.5)	6.7 (2.5)	0.036	13.3 (2.4)	14.8 (2.4)	<0.001
Sex, n (%)						
Boy	92 (87.6)	13 (12.4)	0.349	104 (68.4)	48 (31.6)	0.221
Girl	88 (91.7)	8 (8.3)		99 (75.0)	33 (25)	
BMI-for-age z-score, median (IQR)	−1.1 (1.6)	−0.9 (1.5)	0.179	−1.0 (1.9)	−1.3 (1.5)	0.441
Height-for-age z-score, median (IQR)	−1.1 (1.5)	−1.1 (1.4)	0.316	−1.5 (1.2)	−1.7 (1.4)	0.007
HbA1c (mmol/mol), mean (±SD)	97 (14.5)	77.1 (10.4)	<0.001	96.6 (15.1)	79.4 (12.6)	<0.001
HbA1c %, mean (±SD)	11 (1.3)	9.2 (1)	<0.001	11 (1.4)	9.4 (1.2)	<0.001
Plasma glucose (mmol/L), mean (±SD)	23.7 (4.8)	16.3 (5)	<0.001	22.6 (5.2)	15.8 (3.3)	<0.001
C-peptide (pmol/L), mean (±SD)	190.9 (133.6)	344.1 (130.8)	0.001	241.6 (108.5)	314.4 (156.8)	0.063
Autoimmune T1D, n (%)	42 (89.4)	5 (10.6)	0.786	26 (86.7)	4 (13.3)	0.145
Appraisal interval (days), median (IQR)	12 (5.0)	10 (3.0)	0.009	14 (8.0)	14 (8.0)	0.143
Total diagnosis interval (days), median (IQR)	18 (5.0)	16 (3.0)	0.025	20 (8.0)	20 (10.0)	0.22
Polydipsia, n (%)	179 (89.5)	21 (10.5)	1.000	203 (71.5)	81 (28.5)	NA
Polyuria, n (%)	180 (89.6)	21 (10.4)	NA	203 (71.7)	80 (28.3)	0.634
Weight loss, n (%)	164 (93.7)	11 (6.3)	<0.001	174 (76.0)	55 (24.0)	0.001
Abdominal pain, n (%)	58 (96.7)	2 (3.3)	0.031	79 (97.5)	2 (2.5)	<0.001
Nausea and/or vomiting, n (%)	102 (97.1)	3 (2.9)	<0.001	103 (96.3)	4 (3.7)	<0.001
Hyperventilation (fast breathing), n (%)	69 (100)	0 (0)	<0.001	71 (97.3)	2 (2.7)	<0.001
Acetone smell, n (%)	110 (100)	0 (0)	<0.001	94 (98.9)	1 (1.1)	<0.001
Altered consciousness, n (%)	36 (97.3)	1 (2.7)	0.159	44 (100.0)	0 (0.0)	<0.001

HbA1c-mmol/mol (SI units); HbA1c % (NGSP units); plasma glucose (mmol/L).
Autoimmune T1D: autoantibody-positive diabetes; appraisal interval: time between onset of symptoms and decision to seek medical help; total diagnosis interval: time between onset of symptoms and treatment initiation; the values of p indicate comparison between patients with and without DKA in children <10 years and children ≥10 years. A value of p<0.05 is statistically significant.
BMI, body mass index; C-peptide, connecting peptide; DKA, broadly defined diabetic ketoacidosis; T1D, type 1 diabetes.

appraisal interval, and 18 (5) days versus 16 (3) days, p=0.025, for total diagnosis interval.

The presenting symptoms associated with DKA at diagnosis included weight loss, abdominal pain, nausea and/or vomiting, hyperventilation and acetone smell in breath.

Risk factors for severe DKA at diagnosis

The proportion of broadly defined DKA cases at diagnosis was 383 (79%) with a higher frequency in children <10 years than in those ≥10 years, p<0.001 (table 1). The frequency of severe DKA cases requiring hospital admission was 194 (40%) with significantly higher risk in children <10 years than in children ≥10 years (table 3).

Important variables perceived as risk factors for DKA in table 2 were included in univariate analysis and subsequently in multivariate analysis of the risk factors associated with severe DKA. The analysis revealed that age at diagnosis <10 years, female sex, severe hyperglycaemia (plasma glucose concentration ≥22.2 mmol/L and HbA1c >86 mmol/mol, 10%), and low serum C-peptide concentration (< 200 pmol/L) were potential independent risk factors for severe DKA. Children aged <10 years had over twice the risk for presenting with severe DKA compared with patients aged ≥10 years (OR 2.31, 95% CI 1.59 to 3.36, p<0.001). Other significant risk factors included being girls (OR 1.5, 95% CI 1.04 to 2.17, p=0.028), HbA1c >86 mmol/mol (OR 5.91, 95% CI 3.85 to 9.1, p<0.001), plasma glucose ≥22.2 mmol/L (OR 4.78, 95% CI 3.22 to 7.1, p<0.001) and serum C-peptide <200 pmol/L (OR 2.14, 95% CI 1.15 to 4.0, p=0.016). Other variables assessed in the univariate analysis were not found to be significant risk factors.

A stepwise multivariate logistic regression analysis was conducted to identify independent associated variables. The analysis confirmed that age at diagnosis <10 years (OR 2.5, 95% CI 1.24 to 5.06, p=0.01), HbA1c level >86 mmol/mol (OR 2.79, 95% CI 1.26 to 6.17, p=0.012) and plasma glucose concentration ≥22.2 mmol/L (OR 2.18, 95% CI 1.01 to 4.69, p=0.047) were independent risk factors for severe DKA at presentation.

Table 3 Risk factors for severe diabetic ketoacidosis (DKA) at diagnosis of T1D

	Severe DKA		Mild/no DKA		Univariate			Multivariate		
Variables	n	%	n	%	OR	95% CI	P value	OR	95% CI	P value
Age at diagnosis (years.)					2.31	1.59 to 3.36	<0.001	2.50	1.24 to 5.06	0.010
<10	104	51.7	97	48.3						
≥10	90	31.7	194	68.3						
Sex					1.50	1.04 to 2.17	0.028	1.52	0.77 to 3.00	0.226
Girl	103	45.2	125	54.8						
Boy	91	35.4	166	64.6						
HbA1c (mmol/mol %)					5.91	3.85 to 9.09	<0.001	2.79	1.26 to 6.17	0.012
> 86 (>10%)	158	56	124	44						
≤ 86 (≤10%)	36	17.7	167	82.3						
Plasma glucose (mmol/L)					4.78	3.22 to 7.09	<0.001	2.18	1.01 to 4.69	0.047
≥ 22.2	138	58.2	99	41.8						
< 22.2	56	22.6	192	77.4						
C-peptide (pmol/L)					2.14	1.15 to 4.00	0.016	1.27	0.63 to 2.59	0.503
<200	36	46.2	42	53.8						
≥200	28	28.6	70	71.4						
Autoimmune T1D, n (%)					1.45	0.62 to 3.47	0.387			
Positive	30	39.0	47	61.0						
Negative	11	30.6	25	69.4						
Appraisal interval (days)					1.13	0.79 to 1.63	0.504			
>12	106	41.4	150	58.6						
≤12	88	38.4	141	61.6						
Total diagnosis interval (days)					1.00	0.70 to 1.44	1.000			
>18	104	40	156	60						
≤18	90	40	135	60						
Family history of T1D					0.97	0.54 to 1.73	0.911			
Positive (familial T1D)	24	39.3	37	60.7						
Negative (sporadic T1D)	170	40.1	254	59.9						

HbA1c (mmol/mol, SI units); plasma glucose (mmol/L).
Severe DKA: DKA with confirmed severe acidosis or from hospital records during admission; autoimmune T1D: autoantibody-positive diabetes; appraisal interval: time between onset of symptoms and decision to seek medical help; total diagnosis interval: time between onset of symptoms and treatment initiation; OR (95% CI): OR with 95% CI of independent risk factors for severe DKA and the values of p indicate the significance of risk association. A value of p<0.05 is statistically significant.
C-peptide, connecting peptide; T1D, type 1 diabetes.

DISCUSSION

Young people with T1D in less-resourced countries face the challenge of misdiagnosis, non-diagnosis, high risk of complications and premature mortality. The main findings achieved in this study were lack of timely diagnosis of diabetes, severe hyperglycaemia at presentation and high frequency of DKA at diagnosis. Delayed diagnosis or difficulty in recognising diabetes in younger age groups has been reported to be associated with rapid β-cell destruction that speeds up the progression to more severe DKA at diagnosis.[15]

Autoimmune T1D presented with positive islet autoimmunity and low C-peptide concentration. The higher titre levels of autoantibodies to islet antigen, IA-2 that we found in our children <10 years appears to be associated with more severe disease in this age group. High IA-2A islet autoantibody titre level is believed to be associated with younger age at diagnosis and to provide additional information over positivity in T1D at diagnosis and predict disease severity and progression.[16]

Idiopathic T1D presented as a clinically distinct type of diabetes with negative autiantibodies at disease onset and unclear pathogenesis. It has similar clinical features, a similar or later age at onset, and same risk for DKA at diagnosis. The prevalence of idiopathic T1D was 32% in our study, 30% in India[17] and 5.5% in Qatar.[18]

The overall prevalence of familial T1D in our study was 12.6%, the majority being full sib-pair children. This figure is higher than that identified from the DPV registry in Germany[7] (6.6%) and that identified from Qatar[19] (3.64%). All three cohorts demonstrated that familial compared with sporadic cases, had a lower age at

onset of T1D, less aggressive course at presentation, and less frequent DKA events at disease onset likely related to higher diabetes symptoms awareness in affected families. A recent study from Sweden[20] demonstrated that childhood-onset T1D in full siblings tended to have a stronger family history and higher heritability than adult-onset T1D in full siblings.

Our data on the family history of T2D are similar in part to other studies suggesting that the occurrence of T2D in parents[21] and grandparents[22] tended to delay the onset of T1D in their children to an older age.

DKA has a fatal outcome without treatment. Variation between countries in the frequency of DKA at first presentation of T1D in children has been found to be inversely associated with gross domestic product, latitude and background incidence of T1D,[23 24] with low-income and middle-income countries having the highest rate of DKA at diagnosis and associated premature death,[25] as the case in Yemen.[26] The overall incidence of broadly defined DKA at diagnosis of T1D in our study was 79% with a significantly higher frequency in children <10 years than in older children. Lower incidence rates have been reported from other countries in the region including Kuwait (37.7%),[27] Jordan (31.7%)[28] and Egypt (53.5%).[29]

In a systematic review, Usher-Smith *et al* demonstrated that the occurrence of DKA at diagnosis of T1D in children and adolescents was associated with individual, family, disease and epidemiological factors.[30] Important variables identified as risk factors for DKA in the current study were younger age at diagnosis, girls, severe hyperglycaemia and low serum C-peptide. A delay in diagnosis of diabetes was associated with a higher risk for DKA at diagnosis in our young children only. Age at onset of T1D <10 years, high HbA1c and severe hyperglycaemia were the independent risk factors for severe DKA at presentation. Our results are consistent with other studies showing that children with T1D who presented with DKA tended to be younger than those without DKA at diagnosis, and that girls face an increased risk of developing DKA than boys.[31] The younger children in this study presented with shorter duration of hyperglycaemic symptoms and rapid progression to DKA than did the older peers. This difference could be attributed to delayed treatment initiation defined as time interval more than 1 day between diagnosis and treatment initiation[32] in younger children who usually have poor residual β-cell function, lower C-peptide levels and more severe hyperglycaemia[33] compared with the older adolescents who have higher β-cell mass and insulin secretion leading to higher C-peptide levels and less severe hyperglycaemia.[34]

The global burden of T1D among children aged <20 years is currently large and is predicted to increase rapidly, especially in resource-limited countries.[35] With the high non-diagnosed incidence in these countries, the number of young people suffering from life-threatening DKA soon after onset of T1D symptoms is devastating. The T1D Index project published by the JDRF, Life for a Child, ISPAD and the International Diabetes Federation launched in October 2022, was designed to produce just such an understanding by providing estimates of T1D prevalence and mortality in all countries, both now and into the future.[36] The T1D Index estimates that in 2023, 16 300 Yemenis are living with T1D, 20 400 have died early due to T1D, 47.8 years of healthy life years are lost to T1D per person, and that an estimate of one in four of young people with T1D die without a diagnosis.[37] Leveraging these data and insights can help change the lives of young people affected with T1D by identifying attainable country-by-country interventions including timely diagnosis, accessible care and funding decisions for T1D.[35–37]

The unique feature of this study is the comprehensive presentation of clinical and biochemical features of new-onset T1D among children and adolescents living in Yemen, as well as the different subtypes of T1D occurring, and the risk factors for severe DKA at diagnosis.

The study has the limitation of missing data on islet autoantibody and C-peptide among a substantial number of patients due to lack of laboratory facilities during earlier years of the study. A second limitation is the unavailability of reliable data on the number of patients who had cerebral oedema and or mortality with DKA.

In conclusion, this study provides information on T1D at diagnosis in this poorly studied population. The most alarming conclusion was the high frequency of delay in diagnosis and treatment of the disease among younger children in particular and the subsequent high incidence of DKA at diagnosis. We recommend establishing interventions to reduce adverse outcomes from misdiagnosis and improving access to at least an 'intermediate care' level[38] to reduce projected life years lost to T1D in Yemen.

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