ORIGINAL ARTICLE

The epidemiology, clinical, biochemical, immunological and radiological features of youth onset type 2 diabetes mellitus in the state of Qatar

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Abstract

Objectives To describe the epidemiology, clinical, biochemical, immunological and radiological aspects of youth with type 2 diabetes.

Methods Patients under 18 year of age with type 2 diabetes were recruited from 2018 to 2020, clinical data collected, autoantibodies (GAD65, IAA, IA2 and ZnT8), insulin, ALT and c-peptide were measured. Hepatic ultrasound was performed for assessment of non-alcoholic fatty liver disease (NAFLD).

Results 104 patients were identified. The incidence in 2020 and prevalence per 100,000 was 2.51 and 23.7, respectively. The age of onset was between 8.5 and 18 years with 74% of the patients being of Qatari nationality. Males were more affected than females (1.5/1). Overweight/obesity was present in 98% of all the patients, a positive family history (either both parents or a single parent) in 71% and maternal gestational diabetes mellitus (GDM) in 60% of patients. More than 90% of the patients had acanthosis nigricans. 5 patients had 1 autoantibody positivity and hepatic ultrasound detected evidence of NAFLD in majority of patients.

Conclusion Obesity, maternal GDM and family history of diabetes were the key risk factors for the development of type 2 diabetes. Autoantibody positivity may be present in youth type 2 diabetes. As youth type 2 diabetes is associated with early onset microvascular and macrovascular complications, these findings have important social and health budget implications for Qatar. Tackling the burden of maternal GDM and childhood obesity and building programmes for early detection and intervention, are therefore, essential to reduce the risk of future complications.

Keywords Type 2 diabetes · Paediatric diabetes · Epidemiology · Obesity

Abbreviations

GAD65	Glutamic acid decarboxylase 65
IAA	Insulin autoantibody
IA2	Islet antigen-2 auto antibody
ZnT8	Zinc transporter 8
NAFLD	Non-alcoholic fatty liver disease
GDM	Gestational diabetes mellitus
CI	Confidence interval
TG	Triglyceride

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Introduction

Type 1 diabetes is the most common form of diabetes in the childhood period. However, over the last 2 decades type 2 diabetes in children has been increasing at an alarming rate. The prevalence of type 2 diabetes in children and adolescents in the USA between 2001 and 2009 increased by 30.5% [1], thus illustrating the magnitude of the problem. Type 2 diabetes is a complex, chronic metabolic disease,

with a heterogeneous aetiology, with social, behavioural, environmental risk factors as well as genetic risk susceptibility [2]. In the childhood period type 2 diabetes is associated with certain risk factors including obesity, sedentary lifestyle, family history of type 2 diabetes, maternal gestational diabetes mellitus (GDM), low birth weight and ethnicity [3].

Biochemically type 2 diabetes is characterised by hyperglycemia and insulin resistance but also relative impairment in insulin secretion [4]. The presence of insulin resistance explains the strong clinical association of type 2 diabetes with obesity and other insulin-resistant states. Impaired insulin secretion has been demonstrated in a variety of studies that show that both adolescents and adults usually have lost approximately 80% of their pancreatic beta-cell function before the diagnosis of type 2 diabetes [4]. In most cases, the pancreatic beta-cell dysfunction does not appear to be mediated by antibodies against the pancreatic islet cells.

Childhood obesity is the primary cause of type 2 diabetes at a young age. The increased prevalence of obesity in the Arab world over the last two decades has increased the number of children and adolescents who have type 2 diabetes [5]. In the Arab world, it is estimated that the number of people with diabetes is projected to increase by 96.2% by 2035 mostly driven by the increase in type 2 diabetes [6]. Genetic risk factors may play a crucial role in this uncontrolled rise in the prevalence of type 2 diabetes in children in the Middle Eastern region. Genome wide association studies undertaken on mostly European and Asian cohort of adult patients have identified > 80 common variants for type 2 diabetes with small effect sizes (risk of type 2 diabetes increased by 5–40%) [7]. Interestingly a recent study has shown that SNPs associated with type 2 diabetes in Europeans and Asians do not contribute significantly to the high prevalence of type 2 diabetes in the Qatari population, suggesting that the genetic risks for type 2 diabetes are likely different in Qataris compared to other populations [8].

In the Arab region, factors such as obesity, rapid urbanisation and lack of exercise are other key determinants of this rapid increase in the rate of type 2 diabetes in children (especially those less than 18 years of age). The number of studies that focus primarily on type 2 diabetes in children from the Middle East is limited with most reporting only on prevalence and incidence rates [9–18]. Qatar is a small peninsula located in the Arabian Gulf region which has undergone rapid urbanisation and development over the last 10 years. As in other parts of the world, type 2 diabetes in adults in Qatar has become a major health concern [19]. A previous study assessing the incidence and prevalence of type 1 and type 2 diabetes in children in Qatar noted that there were no cases of childhood type 2 diabetes noted before 2008 [15]. However, in subsequent years the same study reported that the incidence increased from 1.82 per 100,000 in 2012 to 2.7 per 100,000 in 2016, with an incidence of type 2 diabetes equal to 2.9 per 100,000 per year [15]. No previous prospective studies on youth onset type 2 diabetes have been conducted in Qatar describing the detailed epidemiology, clinical, immunological, biochemical and radiological features of a large cohort of patients.

Research design and methods

Patient recruitment

In this prospective study every child with diabetes (aged 0–18 years), attending the diabetes clinics, or admitted as an inpatient in Sidra Medicine (which is the only paediatric diabetes centre in Qatar) were recruited. Clinical details about the birth history, gestational age, ethnicity, age of onset of type 2 diabetes, family history (gestational diabetes and obesity), BMI, weight, signs of insulin resistance (acanthosis nigricans) and other system involvement were collected and documented.

Peripheral blood samples were collected for complete antibody profiling—all 4 autoantibodies namely Glutamic Acid Decarboxylase 65 (GAD65), Insulin Autoantibody (IAA), Islet Antigen-2 Auto Antibody (IA-2A) and Zinc Transporter 8 (ZnT8A) were measured and titers recorded. Fasting blood glucose, serum insulin and c-peptide were measured and standard oral glucose tolerance tests were performed in some patients. Liver function tests, lipid profile and liver ultrasound investigations were conducted. The diagnosis of type 2 diabetes was made in subjects with hyperglycemia according to the ADA guidelines, with detectable c-peptide levels, signs of insulin resistance and type 1 diabetes autoantibody negativity. Patients with prediabetes range blood glucose levels and with associated obesity syndromes were excluded from the cohort.

Annual incidence for the year 2020 and prevalence of type 2 diabetes was calculated in patients aged 0–18 years. The population statistics in 2020 for children living in Qatar was obtained from the Planning and Statistics Authority in Qatar. For each age group, the prevalence per 100,000 is estimated with a 95% confidence interval. The method for confidence interval estimation is Clopper-Pearson Exact as it has good coverage guarantees. The epidemiology analysis is performed using epiR package (version 2.0.19) from R Statistics software (version 3.6.3).

Antibody assay methodology

Complete antibody profiling of every child with type 2 diabetes was performed. The tests were done at Mayo Clinic laboratories using standard methodology [20, 21].

Criteria for diagnosis of fatty liver and hepatomegaly on ultrasound

In our subjects fatty liver was diagnosed on ultrasound based on the increased echogenicity of liver parenchyma when compared to adjacent kidney, loss of appreciation of the intrahepatic vasculature and loss of appreciation of the deeper aspects of the liver. Hepatomegaly was diagnosed when liver span was greater than normal for age of the subject.

Results

The total cohort of patients (aged between 0 and 18 years) attending the diabetes clinic was 1325 of which 104 patients with type 2 diabetes were identified. The incidence of type 2 diabetes in 2020 was 2.51 (CI 1.25–4.49) per 100,000 and the prevalence was 23.7 (CI 19.36–28.71).

Clinical features

The clinical history of every patient was obtained. Table 1 summarises some of the clinical features observed. Most of the patients were products of term gestation (90%) with average birth weight (72%), large for gestational age (12%) and small for gestational age (6%). Evidence of clinical insulin resistance was observed in the form of acanthosis nigricans in 90% of the patients.

Laboratory investigations

Glycated hemoglobin (HbA1C) was in the pre-diabetes range (5.8–6.4%) in 8.4% of the patients at the time of diagnosis and before starting treatment, 22.9% of patients had

HbA1C > 12% while the majority of patients had HbA1C in between 9 and 11%. Table 2 summarises the laboratory investigations conducted on youth with type 2 diabetes. Liver enzymes were measured at diagnosis, ALT was within the normal range in 65% of patients, within 3 times the upper limit in 30% and more than 3 times upper limit in 5% of patients. 5 patients had positive type 1 diabetes autoantibodies.

Radiology

Figure 1 shows the liver ultrasonography findings observed in the cohort.

Conclusions

This is the first comprehensive prospective study of type 2 diabetes in children and adolescents from the Middle East region. In children and adolescents, obesity is the main risk factor for developing type 2 diabetes and this is now replicated in our study where we found that virtually all patients in our cohort were either overweight or obese with a large

Table 2 Summarises the laboratory investigations conducted on youth with type 2 diabetes

Parameter	Value (most common)	Mean/median
Hba1C at diagnosis	9–11%	Mean = 10.07 (± 2.35 SD)
Insulin at diagnosis (pmol/L)	100–500	Median = 202 (44, 360)
ALT (IU/L)	< 39	Median = 30 (18.5, 41.85)
Triglycerides (mmol/L)	< 1.7	Mean = 1.69 (± 1.54 SD)
GAD autoantibody positive	4.8%	–
C-peptide (ng/ml)	0.5–5.5	Mean = 3.73 (± 3.43 SD)

Table 1 Summarises the clinical features observed

| Parameter	Value (most common)	Mean
Age of onset (years)	13–15	13.87 (± 2.6 SD)
Male:female ratio	56:44	–
Gestational age (weeks)	37–40	39 (± 0.98 SD)
Birth weight (kg)	2.5–4	3.17 (± 0.55 SD)
Maternal GDM present	60%	–
Mode of delivery—vaginal birth: caesarian section	53:47	–
Parents with diabetes	71%	–
Siblings with diabetes	28%	–
Body mass index SD	> +2SD	+2.43 (± 0.56 SD)
Nationality—Qatari:non-Qatari	74:30	–
Acanthosis Nigricans	90%	–
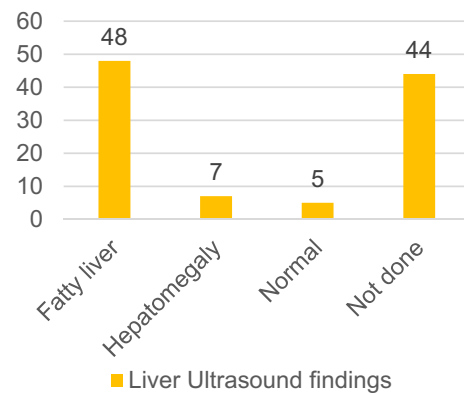
Fig. 1 Shows the liver ultrasonography findings observed in the cohort

proportion being morbidly obese. Similar degrees of obesity in youth type 2 diabetes have been reported in other populations, for example in a young Pima Indian cohort with diabetes, 85% of the patients were found to be obese [22]. Obesity is strongly associated with insulin resistance and acanthosis nigricans is an established clinical marker of insulin resistance which is more prevalent in some ethnic groups (such as African–Americans and Mexican–Americans) than others (Japanese patients) More than 90% of our patient cohort had clinical evidence of clinical insulin resistance in the form of acanthosis nigricans suggesting that this is also an important clinical marker in our Arab population of youth with type 2 diabetes. The majority of patients also had biochemical evidence of insulin resistance as reflected in the high plasma insulin levels.

Family history is another important risk factor for the development of youth onset type 2 diabetes. Among affected youth 45–80% have at least one parent with diabetes and 74–100% have a first or second-degree relative with type 2 diabetes [23, 24]. Among Pima Indians, the cumulative incidence of type 2 diabetes was highest in offspring if both parents had diabetes [25]. In our study, the risk of developing type 2 diabetes was highest in those patients where both parents also had type 2 diabetes thus confirming the previous observations in other populations. Maternal history of type 2 diabetes was associated with twice the risk of developing diabetes as compared to a paternal history of diabetes. Studies on Pima Indian women and youth have shown that maternal GDM increases the risk of obesity and type 2 diabetes in youth [26, 27]. In our patient cohort, a history of maternal GDM significantly increased the risk of developing type 2 diabetes in the youth thus confirming that in some patients in-utero exposure to maternal glycaemia programmes the individual to obesity and type 2 diabetes later in life.

Type 2 diabetes in children and adolescents typically develops around the pubertal growth spurt but there have been reports of type 2 diabetes developing in children as young as 5 and 8 years [28, 29]. Most of our patients developed type 2 diabetes between the ages of 13–15 years of age but some of our patients are young as 8.5 years of age. Some previous studies [30] have reported that females are more likely to develop types 2 diabetes (ratio of 1.7/1) but in our study, we found that males were affected more than females. The reason for this different finding is unclear at the present.

In adults with type 2 diabetes ethnicity has been recognised as an important risk factor. There is evidence that the influence of ethnicity is even stronger for type 2 diabetes in youth as compared to adults [31]. Higher prevalences have been seen in Asians, Hispanics, indigenous people (USA, Canada, Australia), and African–Americans, with some of the highest rates in the world being observed among Pima Indians [23]. When we compared the ethnicity of our patients 74% were of Qatari nationality suggesting that type 2 diabetes is much more common in the obese Qatari youth compared to youth from other ethnic groups. These figures are similar to the prevalence of type 2 diabetes in the Pima Indian population.

The presence of beta-cell autoantibodies has been documented in a subset of youth with type 2 diabetes including anti-GAD, anti-IA-2, and anti-ICA [32–36]. One of these studies [33] did not find any difference between antibody positivity and negativity in relation to age, gender, weight status, lipids, blood pressure, C-peptide, glucose, and HbA1c at presentation of the patients. However another study [34] found that antibody positivity was significantly associated with race with positive subjects more likely to be white and male and BMI, C-peptide, HBA1c, triglycerides, HDL cholesterol, and blood pressure were significantly different by antibody status. In all these studies the degree of antibody positivity in all the studies varied from 10.8 to 70%. None of the previous studies measured ZnT8 autoantibody. In our study, 5 patients had GAD65 autoantibody positivity.

Nonalcoholic fatty liver disease (NAFLD) is commonly found in adults but adolescents with type 2 diabetes (T2DM) and NAFLD have also been reported [37]. In one study, nearly 30% of children with NAFLD also had type 2 diabetes or prediabetes [38]. The cause and effect relationship between insulin resistance, type 2 diabetes and NAFLD is unclear with each condition driving the other. Due to the low cost, safety profile and availability heptic ultrasound is the study of choice for detecting NAFLD [39]. In our study, the hepatic ultrasound showed evidence of a fatty liver in 55 patients but the hepatic ALT was only elevated in 35 patients. It is known that hepatic enzymes are not a sensitive marker of established NAFLD and in patients with type 2 diabetes and NAFLD abnormal hepatic enzymes may be seen in less than 20% of patients [40]. A limitation of our study is that 44 subjects did not agree to undergo a liver ultrasound who could, although unlikely, have normal findings.

In this study, we have summarised the epidemiological, clinical, biochemical, immunological and radiological aspects of a large well-defined group of Arab youth with type 2 diabetes. Youth of Qatari ethnicity are more severely affected than other ethnic groups and virtually all patients with type 2 diabetes are either overweight or obese. Interestingly males were more affected than females and the reasons for this are unclear and maternal GDM was a key association with type 2 diabetes in our patients. Some of the type 2 patients had antibody positivity and in our findings, a large proportion of the patients has a fatty liver on ultrasound.

As type 2 diabetes in the youth is associated with early onset microvascular and macrovascular complications, [41] these findings have important social and health budget implications for Qatar and possibly for the rest of the Middle East region. Tackling the burden of maternal GDM and childhood

obesity and building programmes for early detection and intervention are therefore essential to reduce the risk of future complications.

Data availability Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Declarations

Conflict of interest All authors have no conflicts of interest to declare.

Human and animal rights This study was approved by the Institutional Review Board (IRB) for the protection of human subjects in Sidra Medicine, Qatar. Approval number 1702007592, approved on 03–10-2017. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and/or with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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