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Epidemiology, genetic landscape and classification of childhood diabetes mellitus in the State of Qatar

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ABSTRACT

Aims/Introduction: To study the epidemiology, genetic landscape and causes of childhood diabetes mellitus in the State of Qatar.

Materials and methods: All patients (aged 0–18 years) with diabetes mellitus underwent biochemical, immunological and genetic testing. American Diabetes Association guidelines were used to classify types of diabetes mellitus. The incidence and prevalence of all the different types of diabetes mellitus were calculated.

Results: Total number of children with diabetes mellitus was 1,325 (type 1 n = 1,096, ≥1 antibody; type 2 n = 104, type 1B n = 53; maturity onset diabetes of the young n = 20; monogenic autoimmune n = 4; neonatal diabetes mellitus n = 10;, syndromic diabetes mellitus n = 23; and double diabetes mellitus n = 15). The incidence and prevalence of type 1 diabetes were 38.05 and 249.73 per 100,000, respectively, and for type 2 were 2.51 and 23.7 per 100,000, respectively. The incidence of neonatal diabetes mellitus was 34.4 per 1,000,000 live births, and in indigenous Qataris the incidence was 43.6 per 1,000,000 live births. The prevalence of type 1 diabetes and type 2 diabetes in Qatari children was double compared with other nationalities. The prevalence of maturity onset diabetes of the young in Qatar was 4.56 per 100,000.

Conclusions: This is the first prospective and comprehensive study to document the epidemiology and genetic landscape of childhood diabetes mellitus in this region. Qatar has the fourth highest incidence of type 1 diabetes mellitus, with the incidence and prevalence being higher in Qatari compared with non-Qatari. The prevalence of type 2 diabetes mellitus is also higher in Qatar than in Western countries. The incidence of neonatal diabetes mellitus is the second highest in the world. *GCK* is the most common form of maturity onset diabetes of the young, and a large number of patients have type 1B diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a chronic metabolic condition with hyperglycemia resulting from inadequate production of insulin or resistance to insulin action. The chronic hyperglycemia leads to macro- and microvascular complications[1]. The global burden of diabetes mellitus is rapidly increasing, with an estimated average increase of 3–4% in prevalence every year[2,3]. The age of onset of newly diagnosed children with diabetes is also progressively becoming lower, especially in the developed parts of the world, such as Europe, Australia and USA[3]. The highest incidence of type 1 diabetes is reported in Finland and Sweden, whereas the lowest rates are reported in South America and East Asia[3]. According to the International Diabetes Federation

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Diabetes Atlas 9th edition, there are 1.1 million children and adolescents (aged <20 years) with type 1 diabetes, which is much higher than the previous edition reports[4].

The causes of childhood onset diabetes mellitus are varied, and classified into different types based on pathogenesis. These include type 1 diabetes, type 2 diabetes, neonatal diabetes mellitus (NDM), maturity onset diabetes of the young (MODY), syndromic forms of diabetes mellitus and some as yet unclassified forms of diabetes mellitus[5]. Type 1 diabetes is a chronic disease caused by an autoimmune-mediated destruction of pancreatic β-cells leading to a deficiency in insulin production[6]. It is multifactorial in etiology, with genetic mechanisms playing an important role[6]. Type 1 diabetes is the most common cause of diabetes in children worldwide, but it can occur at any age[7]. The underlying defect in type 2 diabetes is insulin resistance leading to hyperglycemia and progressive failure of β-cells[8]. Type 2 diabetes is relatively rare in the pediatric population, but its incidence is on the rise globally[9]. MODY is due to monogenic mutations in genes important for β-cell development and function, resulting in hyperglycemia, and so far, mutations have been reported in at least 14 different genes[10]. NDM occurs in the first 6 months of life, and can either be transient or permanent[11]. Diabetes mellitus might also occur as part of an underlying syndrome, such as Wolcott–Rallison syndrome, Wolfram syndrome, Down syndrome and Woodhouse–Sakati syndrome among others[12]. There are also monogenic autoimmune forms of diabetes mellitus where there is multi-organ autoimmunity, and these include defects in the autoimmune regulator gene (*AIRE*), *FOXP3*, *STAT3* and lipopolysaccharide-responsive beige-like anchor protein (*LRBA*) among others[13]. Double (hybrid) diabetes is a form of diabetes with features of insulin resistance and type 2 diabetes in combination with type 1 diabetes autoantibody positivity. They often have a positive family history of type 2 diabetes[14].

The Middle East North Africa (MENA) region has one of the highest prevalence of childhood diabetes mellitus in the world[15]. The number of children with type 1 diabetes in the MENA region is estimated to be 60,700, with 10,200 newly diagnosed patients every year[16]. The incidence rate in Oman was 2.7 per 100,000 people, and 44.5 per 100,000 people in Kuwait. Saudi Arabia reported an incidence rate of 33.5 per 100,000 children per year in 2017[17]. However, childhood diabetes mellitus research in the Middle East has focused mainly on reporting retrospective reviews, case reports with very few prospective studies and some questionnaire-based studies. There is no national data on the epidemiology, genetic and molecular mechanisms of diabetes mellitus in all children in any particular country in this region[17].

Diabetes mellitus is a major public health concern in Qatar, a small peninsula located in the Arabian Gulf region, due to the rapidly increasing incidence and the effect on the quality of life. There have been some previous studies reporting on the incidence of diabetes mellitus in children in Qatar; however, they were all retrospective examinations of medical records, and do not reflect on the true prevalence of diabetes mellitus in Qatar[18].

MATERIALS AND METHODS

In the present prospective study, every patient (0–18 years) with diabetes mellitus attending the diabetes clinics or admitted as an in-patient to Sidra Medicine, Doha, Qatar, were recruited over a period of 3 years from 2018–2020. Sidra Medicine is the only childhood diabetes center in the State of Qatar, and all children with diabetes mellitus are referred there, thus allowing us to capture all children diagnosed with diabetes mellitus for the present study. Clinical details about the birth history, gestational age, ethnicity, age of onset of diabetes mellitus, family history, body mass index, weight, signs of insulin resistance (acanthosis nigricans), and other system involvement were collected and documented. Ethnicity was defined as the country the patient originally descended from, and information was obtained from a patient interview as well as hospital records. Peripheral blood samples were collected for complete antibody profiling. All four autoantibodies, namely, glutamic acid decarboxylase 65, insulin auto antibody, islet antigen-2 autoantibody and zinc transporter 8 were measured and titers recorded. C-peptide, celiac and thyroid peroxidase antibodies are also measured. Blood samples were collected for extraction and storage of serum, plasma, deoxyribonucleic acid and ribonucleic acid for further studies. Patients suspected of type 2 diabetes clinically underwent oral glucose tolerance testing, blood insulin and C-peptide level measurements, liver function tests, and abdomen ultrasound to look for signs of fatty liver. Genetic testing was undertaken as indicated. Autoantibody testing was also carried out in 100 control patients.

The protocol for this research project was approved by the institutional review board for the protection of human subjects in Sidra Medicine, Qatar, and it conforms to the provisions of the Declaration of Helsinki (Approval No. 1702007592 on 3-10-2017). All informed consent was obtained from the participant(s) and/or guardian(s).

Autoantibody testing methodology

Type 1 diabetes autoantibody testing was carried out as per the standard methodology from Mayo Clinic laboratories[19,20].

The diagnosis of diabetes mellitus was made as per the American Diabetes Association Guidelines and was further classified into different types of diabetes with the help of clinical history and examination, as well as antibody assays, biochemical tests and genetic testing. Children with at least one autoantibody positivity were classified as type 1 diabetes, patients with antibody negativity and detectable insulin level (and/or C-peptide), along with other clinical features, such as age of onset, weight (>90th centile), body mass index and acanthosis nigricans, were classified as type 2 diabetes. In children presenting with diabetes at 0–6 months-of-life, genetic testing for NDM was carried out in-house. Cases suspected of MODY clinically with negative antibody assays were also subjected to genetic

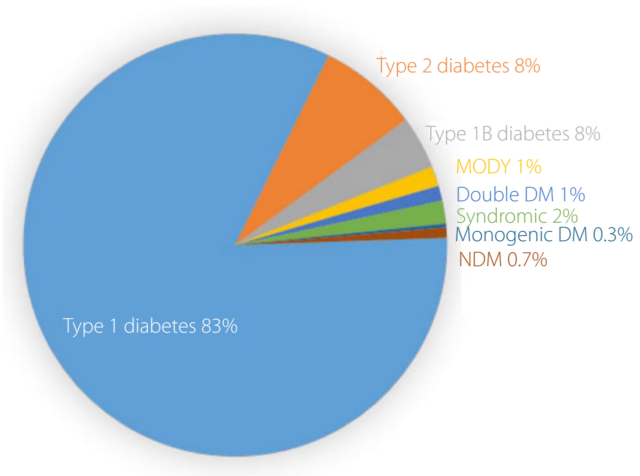

Figure 1 | Classification of different types of diabetes mellitus in children. DM, diabetes mellitus; MODY, maturity onset diabetes of the young; NDM, neonatal diabetes mellitus.

testing for the genetic causes of MODY. All children with syndromes that developed diabetes were recruited and underwent genetic testing to confirm the underlying syndrome. Children with features of type 2 diabetes with autoantibody positivity were classified as double diabetes.

The annual incidence for the year 2020 and overall prevalence of different types of diabetes mellitus was calculated for 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 was estimated with a 95% confidence interval (CI). The method for CI estimation was the Clopper–Pearson exact method, as it has good coverage guarantees[21]. The epidemiology analysis was carried out using the epiR package (version 2.0.19) from R Statistics software (version 3.6.3; The R Foundation of Statistical Computing, Vienna, Austria), which was used for the prevalence calculations.

RESULTS

All patients (neonatal to 18 years-of-age) diagnosed with diabetes mellitus were identified. The total number of children with diabetes mellitus was 1,325, and each of them was further classified into different subgroups. Figure 1 shows the classification of different types of diabetes mellitus. The incidence of diabetes mellitus (all types included) in Qatar for 2020 per 100,000 children was 39.19 with a 95% CI of 33.55–45.51, and prevalence was 301.91 with a 95% CI of 285.90–318.59. Figure 2 shows the different ethnicities of all children with diabetes mellitus in Qatar.

The prevalence of diabetes mellitus in children of Qatari ethnicity was 478.82 (95% CI 443.90–515.74) per 100,000, and the incidence was 60.80 (95% CI 48.77–74.91) in the year 2020. Tables 1 and 2 show the incidence and prevalence estimates for pediatric diabetes mellitus in Qatar. Table 3 shows the prevalence of diabetes mellitus in children of Qatari ethnicity in different age groups.

Type 1 diabetes

All children with at least one antibody positivity were classified into this subtype. The total number of children with type 1 diabetes was 1,096. The incidence of type 1 diabetes was 38.05 (95% CI 32.5–44.28). The prevalence of type 1 diabetes was 249.73 (95% CI 24.18–264.95) with a prevalence of 386.23 (95% CI 354.93–419.55) in Qataris, and 182.57 (95% CI 167.46–198.67) in non-Qataris. Autoantibody testing in 100 control patients was positive for glutamic acid decarboxylase 65 in 16 children and zinc transporter 8 in one child.

Type 2 diabetes

Children were identified based on the clinical picture of diabetes with insulin resistance, age of onset, weight, antibody negativity, detectable C-peptide levels and or insulin levels. The total number of children with type 2 diabetes was 104. The incidence of type 2 diabetes was 2.51 (95% CI 1.25–4.49). The prevalence of type 2 diabetes was 23.7 (95% CI 19.36–28.71), with a prevalence of 53.20 (95% CI 41.98–66.49) in Qataris and 9.18 (95% CI 6.05–13.36) in non-Qataris.

Type 1B diabetes

Children with all four antibodies negative and who tested negative for the known MODY genes were classified into this group. The total number of cases identified was 53.

NDM

All children who developed diabetes mellitus in the first 6 months of life were classified as NDM. A total of 10 children with NDM were identified, and whole genome sequencing was carried out in-house to identify the cause of diabetes. Each child was further classified based on their genetic mechanism, the most common cause being *PTF1A* and *INS* gene mutations[22]. The incidence of NDM (from the year 2000) was 34 per 1,000,000 live births, whereas it was 43.1 per 1,000,000 live births in the indigenous Qatari population, which is the second highest in the world[22].

MODY

Whole exome sequencing was carried out for all children with antibody negativity to identify any known MODY gene mutations. The total number of children with MODY was 20, with *GCK*, *PDX1* and *KLF11* mutations being the most common cause. The prevalence of MODY in Qatar per 100,000 children was 4.56 (CI 2.78–7.04). Table 4 shows all the MODY gene mutations found in our cohort of patients with diabetes mellitus.

Syndromic diabetes mellitus

The total number of children with genetically confirmed syndromic diabetes mellitus in the Qatari population was 23,

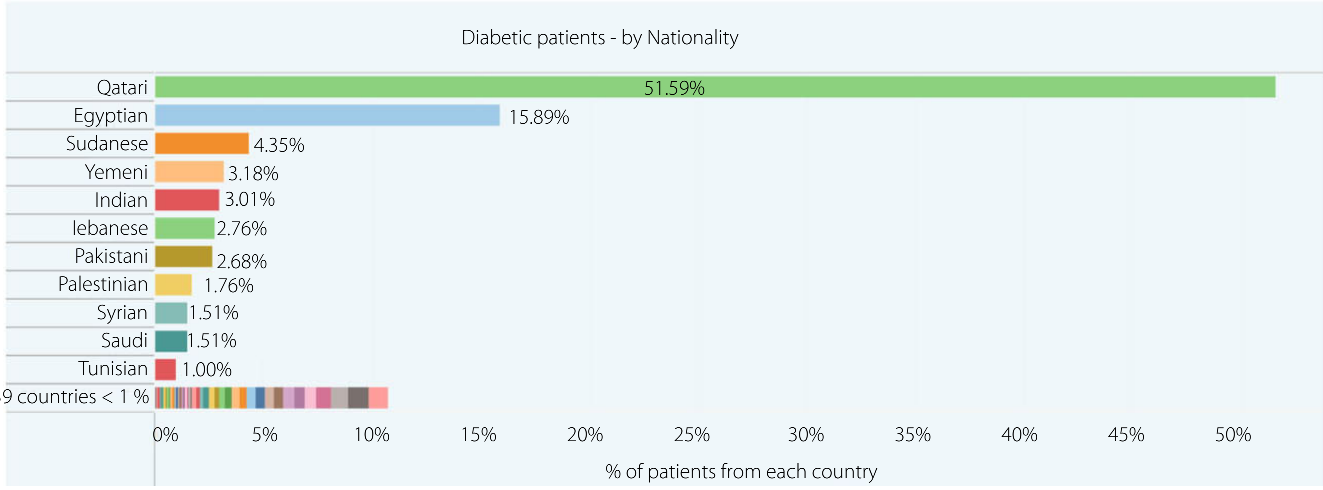

Figure 2 | Ethnicity of each patient with diabetes mellitus in Qatar.

Table 1 | Prevalence of diabetes mellitus in children

All cases	Qataris	Prevalence in Qataris	Non-Qataris	Prevalence in non-Qataris	Total children	Total prevalence
Children <19 years in 2020	144,732		294,135		438,867	
Pediatric diabetes	693	478.82 (443.91–515.74)	632	214.88 (198.46–232.27)	1,325	301.91 (285.89–318.59)
Type 1 diabetes	559	386.23 (354.93–419.55)	537	182.57 (167.47–198.67)	1,096	249.73 (235.18–264.95)
Type 2 diabetes	77	53.21 (41.98–66.49)	27	9.18 (6.05–13.36)	104	23.7 (19.36–28.71)

Table 2 | Incidence of diabetes mellitus in 2020 in children

New cases in 2020	Qataris	Incidence in Qataris	Non-Qataris	Incidence in non-Qataris	Total	Total incidence
Pediatric diabetes	88	60.80 (48.77–74.91)	84	28.56 (33.55–45.51)	172	39.19 (33.55–45.51)
Type 1 diabetes	82	54.58 (43.21–68.03)	79	24.48 (19.15–30.83)	161	38.05 (32.49–44.28)
Type 2 diabetes	6	4.15 (1.52–9.02)	5	1.36 (0.37–3.48)	11	2.51 (1.25–4.49)

Table 3 | Prevalence of diabetes per 100,000 in Qatari children by age groups

Age group	Prevalence	95% confidence interval
0–4 years	104.16	78.10–138.89
5–9 years	345.42	291.75–408.93
10–14 years	721.29	639.62–813.31
15–18 years	810.37	706.88–928.88
0–14 years	371.37	338.45–407.48
0–18 years	478.82	443.9–515.74

whereas 17 children were also identified with syndromes associated with diabetes, but they had not yet developed diabetes. The most common syndromes identified in the Qatar cohort was Woodhouse–Sakati syndrome. Table 5 shows all the syndromes found in our cohort of patients.

Monogenic autoimmune diabetes mellitus

Four patients with monogenic autoimmune diabetes mellitus were identified and genetic testing was carried out. Two children with *AIRE* mutation, one child with immunodysregulation polyendocrinopathy enteropathy X-linked syndrome and one child with *LRBA* mutation causing diabetes were identified.

Double (hybrid) diabetes mellitus

Children with features common to both type 1 diabetes (autoimmunity with decreased insulin secretion) and type 2 diabetes with a clinical picture of insulin resistance were included. Most of these children also had a positive family history of type 2 diabetes. The total number of children with double diabetes mellitus was 15.

DISCUSSION

There is an increase in the incidence of diabetes mellitus noted worldwide in adults, as well as the pediatric population, with

Table 4 | Maturity onset diabetes of the young gene mutations found in patients with diabetes

MODY gene identified	Type of MODY	Variant	Novel/reported variant	No. patients
GCK	MODY 2	c. 75G>A (p. Ala259Thr)	Reported	4
GCK	MODY 2	c.678_679+2delGGGT (splice site variant)	Reported	1
PDX1	MODY 4	c.97C>A (p. Pro33Ser)	Reported	4
HNF1A	MODY 3	c.157G>A (p. Gly53Ser)	Novel	1
HNF1A	MODY 3	c.1541 A > G (p. His514Arg)	Novel	1
HNF4A	MODY 1	c.1387A>G (p. Ile463Val)	Reported	2
INS	MODY 10	c.-331C>G (promoter variant)	Reported	1
PAX4	MODY 9	c.92 G > T (p. Arg31Leu) (functional significance uncertain)	Reported	1
BLK	MODY 11	c.1013 T > C (p. Ile338Thr)	Reported	1
KLF11	MODY 7	c.1468 G > A (p. Gly490Ser) (functional significance uncertain)	Novel	1
KLF11	MODY 7	c.1382 G > A (p. Arg461Gln) (functional significance uncertain)	Reported	1
KLF11	MODY 7	c.1298 A > G (p. Lys433Arg) (functional significance uncertain)	Reported	2

MODY, maturity onset diabetes of the young.

Table 5 | Different syndromic diabetes patients identified

Syndromic DM identified	No. patients	Genetic mutation
Woodhouse–Sakati syndrome	5	Homozygous mutation c.436del (p. Ala147fs) in *DCAF17*
Fanconi–Bickel syndrome	3	Novel variants – functional work ongoing
Down syndrome (all antibody-negative)	3	Trisomy 21
Wolcott–Rallison syndrome	1	Homozygous mutation c.1570_1573delGAAA (p. Glu524fs) mutation in exon 9 of *EIF2AK3*
Wolfram syndrome	3	Homozygous mutation c.1433 G > A (p. Trp 478*) in *WFS1* Homozygous conservative inframe deletion c.1243_1245delGTC (p. Val415del) in *WFS1*
William syndrome	1	Microdeletion at q11.23 of chromosome 7
Prader–Willi syndrome	2	Loss of paternal allele at 15q11-q13
Velocardiofacial syndrome	1	Interstitial deletion extending from cytogenetic band 22q11.1-22q11.2
H syndrome	1	Homozygous mutation c.1228 C > T (p. Gln410Ter) in *SLC29A3*
Joubert syndrome	1	Homozygous deletion c.*19_22 del GTTT (3′ variant) in *CEP290*
Johanson–Blizzard syndrome	1	Homozygous mutation in UBR1
Diabetes associated with nephrotic syndrome (not related to steroid use)	1	

the overall annual increase to be estimated as 3%[23]. However, a more stabilizing trend in the incidence of diabetes mellitus was also reported by a recent review[24]. Type 1 diabetes is the most common type of diabetes mellitus in children, with annual worldwide newly diagnosed cases estimated to be 98,200 children aged <15 years[23]. Finland has the highest incidence of childhood type 1 diabetes cases, followed by Sweden, with recent studies showing an increasing trend in the Arabian Gulf countries[25]. Type 2 diabetes, which was thought to be uncommon in children, is also increasing, and with the concurrent increase in the prevalence of obesity in children, the clinical differentiation of different types of diabetes is becoming more difficult[26].

This is the first prospective study to comprehensively recruit all patients (aged 0–18 years) with diabetes mellitus in the State of Qatar, and classify the causes of diabetes mellitus systematically. Each patient was accurately classified based on American Diabetes Association guidelines. A complement of four antibodies was tested and, hence, each case was accurately classified into different subtypes based on their mechanism; no similar nationwide study has been previously carried out in Qatar or the MENA region.

The first accurate national prevalence and incidence rates were calculated prospectively. From the present study, we were able to establish that the incidence of type 1 diabetes was higher than previously reported, placing Qatar in the top five countries in terms of the incidence of type 1 diabetes in children. The estimated type 1 diabetes incidence rate in children (aged 0–14 years) in Europe was 25.1 per 1,000 children, in the MENA region, it was 14.4 per 1,000 children, and in the African continent, it was 4.3 per 1,000 children[23]. Finland and Sweden have the highest number of cases of type 1 diabetes among children, with incidence values of 57.6 and 43.1 per 100,000 children respectively[27]. In the MENA region, Saudi Arabia reported an incidence of 31.4 per 100,000, whereas Kuwait reported an incidence of 22.3 per 100,000[2,28]. The present study shows an incidence rate of 38.05 in the pediatric population in Qatar, identifying Qatar as the country with the highest incidence of type 1 diabetes in the MENA region. This value is also comparable with the estimates from European countries, such as Norway and Sweden.

We were also able to establish the prevalence rates of type 1 diabetes in the Qatari population, which is comparable with the highest prevalence values reported in the world. The number of children aged <15 years with type 1 diabetes worldwide is estimated to be 600,900, whereas the number increases to 1,110,100 individuals aged <20 years with type 1 diabetes worldwide[29]. The SEARCH for Diabetes in Youth study among USA youth reported a prevalence of 220 per 100,000 in 2009, and that the prevalence of type 1 diabetes increased by 21.1% between 2001 and 2009[30] We identified 1,325 children aged <18 years currently in Qatar, with a prevalence of 301.91 per 100,000 population. Nationwide studies on the prevalence of pediatric diabetes are scarce; however, a countrywide study in Saudi Arabia from 2001 to 2007 reported a prevalence of 109 per 100,000 population[31]. As per the Finnish diabetes association, there are currently 4,000 children with type 1 diabetes living in Finland[32].

From the present study, we were also able to identify all pediatric cases of type 2 diabetes in Qatar, with most of them being obese with antibody negativity; however, a few cases of antibody-positive type 2 diabetes were also identified, which expands the clinical spectrum of type 2 diabetes worldwide. The prevalence of type 2 diabetes was found to be 23.7 per 100,000 children. Sweden reported the incidence of type 2 diabetes as 3.1 per 100,000 per year in the pediatric age group[33]. A study carried out in Kuwait reports a prevalence of 34.9 per 100,000 in children[34]. This further validates the stand that the MENA countries, especially Kuwait, Saudi Arabia and Qatar, have a higher prevalence of type 2 diabetes than their Western counterparts. This could be attributed to the increasing epidemic of obesity in these regions, sedentary lifestyle and unique genetic etiology. As this is a clinic- and hospital-based study, it will underestimate the incidence and prevalence of type 2 diabetes in this population.

On further analysis of the study group, the prevalence of both type 1 diabetes and type 2 diabetes in children of Qatari ethnicity was found to be considerably higher than that of non-Qatari children living in Qatar. This suggests the etiopathology of these children might be more genetic in nature than environmental. This could be attributed in part to the high level of consanguinity observed in the Qatari cohort of families and positive family history of diabetes mellitus, as well as their diet. Further studies to discern the genetics and human leukocyte antigen status of these children has been undertaken for a better understanding of the disease.

Qatar has previously reported the second highest incidence of NDM in the world[22]. However, one new case has been diagnosed later on. The most common genetic causes being insulin gene mutation and *PTF1A* mutation. A study in northwest Saudi Arabia reported the incidence of NDM as 1:21,196[35]. Other MENA countries also reported a similar incidence of NDM[36].

Studies on MODY in children are scarce in the MENA region, mainly due to misdiagnosis as type 1 or type2 diabetes. A study in Saudi Arabia reported MODY 1 in five members of a family; however, the overall prevalence of MODY in Saudi Arabia is unknown[37]. Another study from Iran studied 12 families with a history of diabetes and reported *HNF4A* mutations causing MODY1 in 26.6% of the patients, which is considered significant[38]. Another study from Iran also reported *HNF1A* mutations causing MODY 3 in their cohort of patients[39]. The present study found *GCK*, *PDX1* and *KLF11* to be the most common genetic cause of MODY in Qatar.

A study from Saudi Arabia reported type 1B diabetes in 28 patients, and double diabetes mellitus in 97 patients in their cohort[40]. There are no other studies reporting type 1B diabetes and double diabetes mellitus in the MENA region. In the present cohort, we accurately classified all the cases of type 1B diabetes.

Double diabetes includes patients with type 1 diabetes with features of insulin resistance, but there are no clear criteria to define this group. However, antibody-positive diabetes with metabolic syndrome and family history are reliable markers[41]. A study in Germany found 25.5% of patients with type 1 diabetes had associated metabolic syndrome. In Saudi Arabia, approximately one-third of pediatric diabetes patients are estimated to have atypical forms of diabetes mellitus, such as double diabetes mellitus[42]. The present study was able to identify 15 patients with double diabetes mellitus in Qatar.

We were unable to accurately classify the type of diabetes for one patient in the present cohort. This patient had antibody-negative diabetes mellitus associated with kidney failure. However, genetic testing did not show any mutation, copy number variations or deletions in the *HNF1B* gene, which is usually responsible for a similar phenotype causing MODY5. Mutations in all the known MODY genes and syndromic diabetes mellitus genes did not yield a positive finding. Hence, more detailed analysis is ongoing to understand the mechanism of diabetes mellitus in this patient.

The present study is the first of its kind in the MENA region to systematically recruit every child with diabetes mellitus from birth to 18 years, and accurately classify the underlying biochemical and genetic causes in each child. The study has highlighted the high incidence and prevalence of both type 1 diabetes and type 2 diabetes, and the data collected will form the basis for establishing the national diabetes registry for children in Qatar. It will provide a platform for undertaking further studies that will aim at understanding why type 1 diabetes is so common, and help to develop strategies for the management of all types of childhood diabetes mellitus in Qatar. In addition, understanding the underlying biochemical, immunological and molecular mechanisms of diabetes will guide therapy, and allow the implementation of present and future therapies for all different forms of childhood diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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