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Research Article

# Prediabetes in Children: A Single Center Experience from Qatar

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## Abstract

**Background:** Prediabetes is a state of hyperglycemia before the onset of frank diabetes mellitus. The prevalence of prediabetes is on the increase due to the obesity epidemic. No previous studies have described the clinical, biochemical, and immunological features of children and adolescents with prediabetes from the State of Qatar.

**Aim:** To describe our single-center experience of children with prediabetes.

**Method:** From 2018 to 2022, we enrolled patients below 18 years of age diagnosed with prediabetes. Clinical parameters were meticulously collected, encompassing age of onset, familial history, anthropometric measurements including weight and body mass index (BMI), HbA1C levels, diabetes-associated autoantibodies (GAD65, IAA, IA2, and ZnT8), as well as Insulin and C-peptide concentrations. Prediabetes diagnosis was established using HbA1C, with a diagnostic threshold set at 5.8%

**Results**: Our study examined the prevalence of prediabetes among 1325 diabetes patients in Qatar, revealing a 1.6% prevalence rate. Among the cohort, 60% were Qatari nationals, and a significant 95% were overweight or obese (BMI 25 -40 kg/m$^2$), emphasizing the connection between prediabetes and obesity. Obesity-related complications, such as obstructive sleep apnea and non-alcoholic fatty liver disease, were common. Approximately 22.7% of patients exhibited positive antibodies, with two later developing Type 1 Diabetes. These findings stress the need for tailored interventions and monitoring for high-risk individuals to curb diabetes progression and complications.

**Conclusions:** The primary risk factors identified for the development of Prediabetes were obesity and a familial history of diabetes. The majority of patients had grandparents affected by Type 2 Diabetes Mellitus (T2DM), with fewer having affected parents. Notably, 70% of patients were categorized as obese. Promoting healthy lifestyle modifications to manage obesity emerges as a pivotal strategy to mitigate the progression of Prediabetes towards full-blown diabetes in the future.

***Keywords:*** *Prediabetes, Diabetes, Obesity, Qatar, Complications, Antibodies, Type 1 Diabetes.*

## 1. Introduction

Prediabetes is a state of intermediate hyperglycemia that does not reach the diagnostic threshold for frank diabetes mellitus. It describes multiple facets of altered glucose metabolism, including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), elevated HbA1c or combinations of them [1]. It is seen as a continuous spectrum in abnormalities of glucose metabolism. Each of these abnormalities in glucose metabolism, whether detected in childhood or adolescence, will increase the risk of later development of type 2 diabetes, chronic kidney and cardiovascular disease.

Prediabetes may comprise overlapping group of individuals with one or more abnormalities in their glucose metabolism. It is possible that presence of IFG and IGT identifies subjects with different pathological abnormalities in their glucose metabolism [2]. Approximately 25% of individuals with prediabetes will progress to overt type 2 diabetes within 3–5 years, and as many as 70% of individuals with prediabetes will develop overt diabetes within their lifetime [3]. Prediabetes may be reversible, through the implementation of lifestyle modification programmes based around the adoption of healthier diet and increased levels of physical activity [4].

The criteria for defining prediabetes are not uniform. The definitions and screening criteria for prediabetes differ between guidelines published by different organizations, resulting in estimations of prevalence that can vary widely from one another. For example The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters as following 1) IFG defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to125 mg/dL, 2) IGT defined as 2 h plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 hour oral glucose tolerance test (OGTT) [5]. However the The American Diabetes Association (ADA), has the similar threshold value for IGT (140-200 mg/dL) but has a lower threshold value for IFG (100 125mg/dl) and has additional hemoglobin A1C (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes [6].

Each of the abnormalities in glucose metabolism (IFG, IGT and raised HBA1c) is not perfect for identifying all patients with prediabetes. For example the positive predictive value of HbA1c for diagnosis of prediabetes in clinical setting is low [7] and the OGTT has poor reproducibility in obese youth, in particular for the 2-h plasma glucose [8]. The increase in the prevalence of prediabetes in children and adolescents parallels the rise in rates of childhood obesity [9] . A recent study from the United States examined the prevalence of IFG, IGT, and increased glycated hemoglobin A1c (HbA1c) levels in US adolescents (aged 12-18 years) and young adults (aged 19-34 years) without diabetes. The study found that 1 out of 5 adolescents and 1 out of 4 young adults had prediabetes with the adjusted prevalence of prediabetes being higher in male individuals and in people with obesity [10] A recent study from our center reported a high prevalence of type 2 diabetes in youth) with obesity, maternal gestational diabetes and family history of diabetes were the key risk factors for the development of type 2 diabetes. [11]. No previous studies have reported the clinical, biochemical and immunological aspects of prediabetes in youth from Qatar. Previous studies on prediabetes in adults report a prevalence between 11.9% to 32% [12, 13].

## 2. Methods

### 2.1 Ethical compliance

This study was approved by the Institutional Review Board (IRB) to protect human subjects in Sidra Medicine, Qatar (IRB reference number 1702007592). Informed consent and assent were taken from patients and legal guardians as required. All experiments were performed under relevant guidelines and regulations.

### 2.2 Patient recruitment

In this study, we recruited children and adolescents with prediabetes from 0-18yr of age who attended the outpatient clinics in Sidra Medicine from 2018-2021. Clinical details about ethnicity, age of onset of prediabetes, family history, BMI, and weight, were documented. We also collected information about the blood test done, including HBA1C, C-peptide level, diabetes autoantibodies, and OGTT.

### 2.3 Antibody assay methodology

GADA-Radioimmunoassay performed. (125) I-labeled recombinant human glutamic acid decarboxylase is incubated with the patient's diluted serum. Antihuman IgG and IgM are then added to form an immunoprecipitation. After washing the precipitated immune complexes, specific antibodies are detected by counting gamma-emission from the pellet's bound (125)I-GAD65[12]. Insulin autoantibody-Radioimmunoassay performed. (125) I-labeled recombinant human insulin is added to the test serum; if the Antibody is present, it forms a soluble complex with the labeled insulin. Subsequent addition of goat antihuman IgG and IgM precipitate the complex. The amount of radioactivity in the precipitate is proportional to the serum antibody level [13] .

IA-2 autoantibody- Radioimmunoassay performed. (125) I-labeled recombinant human IA-2 is added to the test serum. If the Antibody is present, it forms a soluble complex with the (125) I-labeled IA-2. Subsequent addition of goat antihuman IgG and IgM precipitate the complex. The amount of radioactivity in the precipitate is proportional to the level of Antibody in the serum [14].

Zinc Transporter 8 (ZnT8) autoantibody- Enzyme immunoassay. Zinc Transporter 8 (ZnT8) antibodies are principally directed against the C terminal domain of ZnT8. The ZnT8 autoantibody ELISA is based on the bridging principle that employs the ability of divalent ZnT8 autoantibodies to bind to ZnT8 coated onto the plate well with one arm, and to liquid ZnT8-biotin with the other arm. Calibrators or undiluted serum samples in duplicate are added to ZnT- coated plate wells and incubated overnight. ZnT8-biotin is added to each well and plate. After another incubation, aspiration, and wash, streptavidin-peroxidase is added to each well. Another incubation, aspiration, and wash are performed, and peroxidase substrate is added. After a final incubation, 0.5mol/L H2S04 stop solution is added to each well. Absorbance is measured at 450nm, blanked against wells containing peroxidase substrate and H2S04 only [15].

## 3. Results

A total of 22 patients with prediabetes were found in our cohort. Prediabetes diagnosis was made according to the American Diabetes Association (ADA) by having either two abnormal independent tests.

These tests included any of the following.

1) Fasting plasma glucose (FPG) between 100 and 125 mg/dl

2) HbA1c level between 5.7 and 6.4%

3) Blood glucose between 144 and 199 mg/dl after giving 75 g of glucose. In our center, the patients were diagnosed with prediabetes with HBA1C in the prediabetic range, and 22% had OGTT test impaired.

### 3.1 Clinical features

We collected data about the patient's gender, time of diagnosis of prediabetes, family history, obesity, BMI, diabetes autoantibodies, c-peptide level, and any complications associated with obesity like obstructive sleep apnea and fatty liver. Table 1 summarizes all the clinical features observed.

**Table 1:** Summarizes the clinical features observed.

| Clinical features | Most common values | Mean |
|---|---|---|
| Male: Female | 45%:55% | 11 |
| Age of onset (years) | 6-16 | 10 |
| Parents with Diabetes | 30% | - |
| Nationality Qatari: non-Qatari | 63%:37% | - |

### 3.2 Laboratory investigations

The glycated hemoglobin (HbA1c) levels across all patients ranged from 5.8% to 7.8%. Impaired oral glucose tolerance test (OGTT) results were identified in 22% of patients. Of the patients who underwent autoantibody testing, 77% exhibited positivity, with 22.7% testing positive for specific antibodies. Among these, positive results were observed for GAD antibodies in two patients, Zn antibodies in one patient, IA2 antibodies in one patient, and IAA antibodies in two patients. Notably, two individuals who tested positive for antibodies progressed to develop Type 1 diabetes. Among the six patients with positive antibodies, three were obese. Fatty liver, detected through abdominal ultrasound, was present in 27% of patients. Of the 22 patients who underwent OGTT, 10 were identified with impaired glucose tolerance (IGT), all of whom had a BMI exceeding 40 and were classified as obese.

### 3.3 Abdomen Ultrasound Findings:

We found 23% of patients with high BMI to have fatty liver. 13% of patients were found to have obstructive sleep apnea, and all of them were morbidly obese with BMI above 30kg/m$^2$. Two patients developed type 1 diabetes after a few years of being diagnosed with prediabetes and having T1 Diabetes antibodies positive.

### Figures and Charts

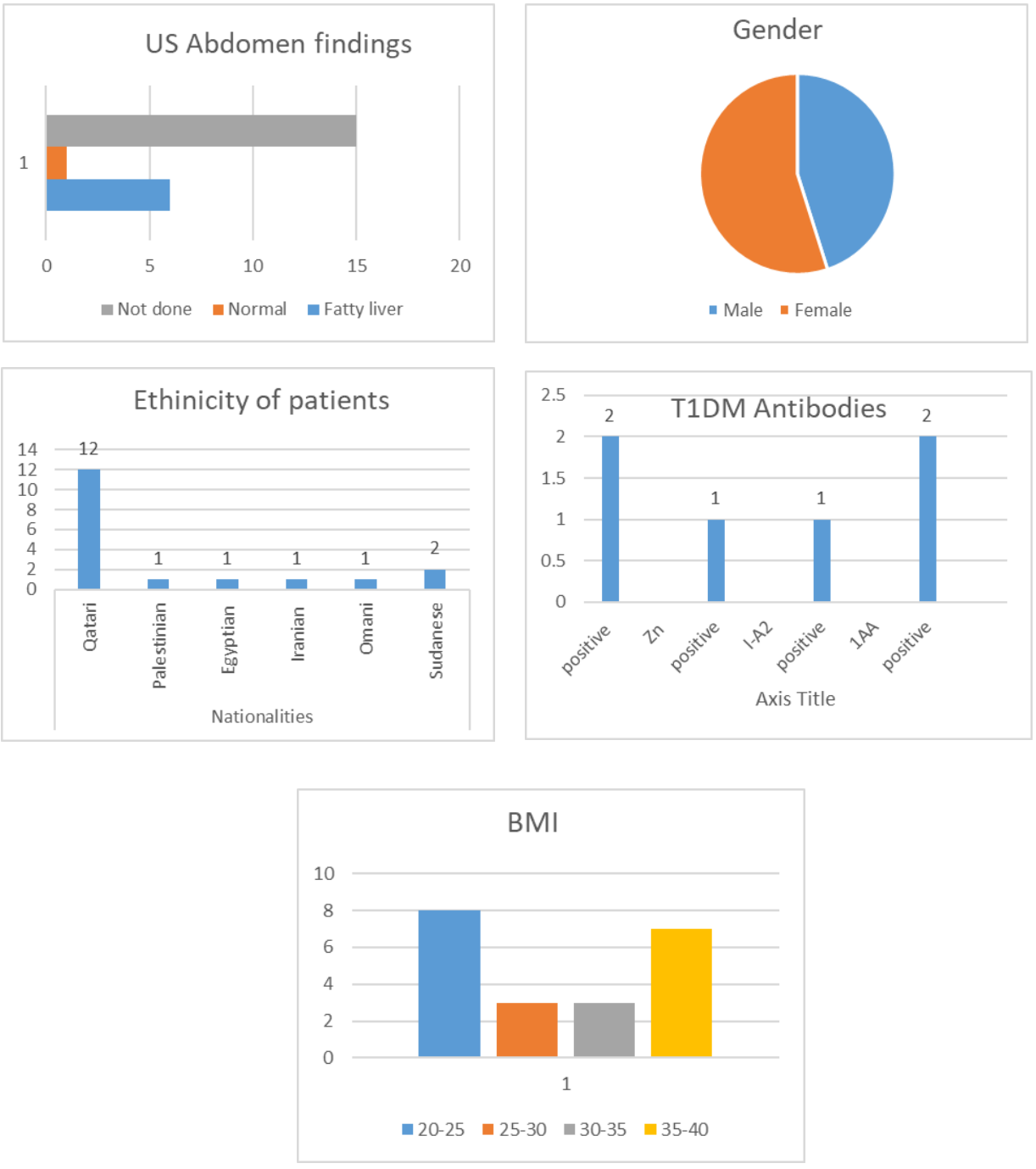


***Figure 1:*** *Represents the clinical and laboratory parameters observed.*

## 4. Discussion and Conclusion

Prevalence estimates of prediabetes reported in the literature vary significantly due to the diagnostic criteria used, the choice of test, and the populations being studied. In the Middle East region, virtually all previous studies on prediabetes have focused on adults, and the prevalence estimates vary greatly(11.9 to 47%). 22.4%[21],30.29%[22],36%[23] 44.2% [24]47.9%[25].27.6%[26]

A systematic review and meta-analysis of the global prevalence of prediabetes in children and adolescents found a pooled prevalence of 8.84% (95% CI, 6.74%-10.95%) for childhood[14]. The prevalence of prediabetes in children with diabetes in Qatar was found to be 1.6% in our study. The prevalence was higher in males than females, in older compared to younger children, in urban compared to rural areas, and higher in children with a family history of diabetes than in those without such a history. A national surveillance study from Saudi Arabia reported a prevalence of 6.12% of impaired fasting glucose tolerance for children and adolescents aged 6 to 18. It concluded that impaired fasting glucose tolerance was highly prevalent in that society[15].

We found obesity and a family history of diabetes to be the main risk factors in our cohort for developing prediabetes. The incidence of Type 2 DM is rising among the pediatric population due to rapid urbanization, sedentary lifestyle, and physical inactivity leading to obesity which is the main factor in developing type 2 diabetes. In the United States, using data from the National Health and Nutrition Examination Surveys (NHANES; 2005–2016), approximately 20% of adolescents aged 12 to 18 years have prediabetes, while other researchers have estimated the prevalence of T2DM among adolescents will quadruple by 2050 [6].

Our study showed that of children diagnosed with prediabetes, 13% had obstructive sleep apnea and were morbidly obese. Cong Wang et al. [8] did a meta-analysis review about the association between OSA and prediabetes risk by collecting data from 25 studies. They found a significant association between OSA with prediabetes. Our research also found that 13% of prediabetic children with OSA. Prediabetes pathophysiology is similar to Type 2 Diabetes, with Insulin resistance and a decline in insulin secretion mainly due to Obesity. They also mentioned in the paper the increase in insulin resistance during puberty that increases the progression of prediabetes to Type 2 Diabetes. [6].

Prediabetes is an emerging clinical priority among high-risk adolescents. In our cohort, 23% of children with prediabetes were found to have fatty liver. Numerous research studies conducted on children have indicated that increased levels of fat within the liver are linked to more significant levels of insulin resistance and impaired glucose control before the manifestation of evident diabetes. [18].

Monique et al. [7] mentioned in their paper a six years intervention randomized trial done in China to look for changes in the OGTT and impaired fasting plasma glucose between participants assigned to groups randomized to an intervention group with diet or exercise only or both and a control group. The study showed that after six years, 32% returned to normoglycemia, 21%remained IGT, and 47% progressed to Type 2 Diabetes. This study showed that most participants who went to Type 2 Diabetes were from the control group, almost 65%. This suggests that controlling diet and exercise to improve BMI is the primary factor in preventing the progression of Prediabetes to diabetes.

Although studies conducted on the pediatric demographic have not yet yielded findings regarding the potential enhancement of long-term outcomes for Type 2 Diabetes Mellitus (T2DM) through early prediabetes diagnosis, data indirectly inferred from adult research suggests that lifestyle interventions could potentially extend the onset or prevent the progression (19,20) Our study showed that most children diagnosed with Prediabetes are adolescents, and Obesity is the common finding in most of them. This finding is due to the modern Sedentary lifestyle. To avoid the Progression of Type 2 Diabetes from Prediabetes, we need to have a screening criterion implemented in the Country to diagnose these children earlier so that we can implement strategies by changing their lifestyle and healthy diet to improve Obesity which in turn will decrease the progression to Type 2 Diabetes Monique et al. [7]. mentioned in their paper that microvascular and macrovascular complications are also present during the Prediabetes stage, and by controlling the progression to Type 2 Diabetes, we can decrease the risk of these complications, reducing the future burden of disease.

Our study showed one prediabetic patient of age six years, after one year of diagnosis of Prediabetes, developed Type 1 Diabetes and started on Insulin treatment. She had GAD and Zinc Ab positive with a family history of Type 1 Diabetes in her elder sibling.

Michigan University published an article that highlighted the association between prediabetes and the development of both type 1 and type 2 diabetes. It has been known for years that prediabetes increases the risk for type 2 diabetes. However, recent studies have shown that prediabetics can end up having type 1 diabetes as they are primarily a case of late onset autoimmune diabetes [17].

## Data Availability Statement

The datasets generated during and analyzed during the current study are not publicly available to protect patient confidentiality but are available from the corresponding author upon reasonable request.

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## Author Contributions

SS Recruited the patients, collected, analyzed, and interpreted data, and drafted the manuscript. KH Designed the study, obtained funding, and reviewed and edited the manuscript. BH Collected patient information and reviewed the manuscript.

## Conflict of Interest

The authors declare they have no potential conflicts of interest to disclose.

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