A Clinic-based Approach to Diagnosis and Management of Prediabetes in High-risk Children and Adolescents

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Background: Type 2 diabetes (T2D) in youth is increasing in prevalence. Diabetes screening is recommended for at-risk youth but best-practice strategies for management of pediatric prediabetes are unknown. This study leverages a pediatric prediabetes clinic to assess identification of high-risk patients, the rate of clinic follow-up and progression to T2D in youth over time.

Methods: Retrospective chart review of children referred to a single center for evaluation of prediabetes over a 3-year period. Measurements included hemoglobin A1c (HbA1C) and oral glucose tolerance testing. Patients were classified as normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or T2D based on 2019 American Diabetes Association criteria. Patients classified as IGT/T2D were prescribed metformin.

Results: Of the 254 patients included; 25.6% had IGT and 6.7% had T2D. The IGT/T2D groups were older and more obese than the NGT group. There was a moderate correlation between HbA1C and fasting glucose ($r = 0.59$, $P < 0.001$); HbA1C and 2-hour glucose ($r = 0.63$, $P < 0.001$). Over the 3-year study, 52 of 82 patients with IGT/T2D (63%) returned for follow-up. Four patients regained NGT; 3 of those had isolated impaired fasting glucose (100 to 102 mg/dL). Three patients (4.6%) progressed from IGT to T2D over an average of 13 ± 6.2 months. In those patients, body mass index had increased 1.7 ± 2.3 kg/m^2 from baseline.

Conclusions: A pediatric prediabetes clinic may allow for identification of high-risk youth but lost to follow-up rates are high. Continued weight gain is a risk factor for progression to T2D and effective weight management programs are needed.

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; HbA1C, hemoglobin A1C; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; T2D, type 2 diabetes.

Type 2 diabetes (T2D) in youth is a recent epidemic with increasing prevalence over the past 3 decades. The diagnosis may be made based on fasting plasma glucose, 2-hour plasma glucose during a 75-g oral glucose tolerance test (OGTT), or hemoglobin A1C (HbA1C) [1]. Patients with elevated glucose or HbA1C levels who do not meet T2D criteria are categorized as having prediabetes [1]. The newest guidelines from the American Diabetes Association (ADA) recommend considering metformin therapy for prevention of T2D in younger, obese patients with prediabetes [2]. Although diagnostic criteria are derived from long-term outcomes in adults, it is recognized that mortality risk is inversely correlated with the age at diagnosis [3]. Real-world strategies are needed to identify the highest risk pediatric patients for intensification of lifestyle management and possibly addition of pharmacotherapies.

The Vanderbilt Pediatric Prediabetes Clinic was founded in 2015 with the goal of better triaging patients referred to pediatric endocrinology with concern for prediabetes or T2D. Patients with abnormal glucose tolerance or T2D were prescribed metformin and asked to return for follow-up, whereas those with normal glucose tolerance (NGT) were prescribed lifestyle modification and returned to their primary care physician for ongoing care. We conducted a chart review of patients evaluated in this clinic over a 3-year period to assess the ability to identify high-risk patients, the rate of clinic follow-up, and the risk for progression to T2D in youth over time.

1. Materials and Methods

A. Study Groups

The study protocol was approved by the Vanderbilt Institutional Review Board. The study population included children ≤18 years of age who were seen at the Vanderbilt Pediatric Prediabetes Clinic from May 17, 2015, through July 17, 2018. Children subsequently diagnosed with type 1 diabetes or maturity onset diabetes of the young were excluded from analysis. Patients were assigned to 1 of 3 groups for analysis: NGT, impaired glucose tolerance (IGT), or T2D. Group assignments were based on the 2019 ADA criteria [1]. Briefly, the 2019 ADA criteria for T2D are symptoms of diabetes plus 1 laboratory criteria (glucose ≥ 200 mg/dL, fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%), or 2 laboratory criteria. Children were classified as IGT if they had a fasting glucose of 100 to 125 mg/dL or a 2-hour glucose of 140 to 199 mg/dL [1].

B. Clinic Protocol

Patients seen at the Vanderbilt Pediatric Prediabetes Clinic were referred from their primary pediatrician with concern for prediabetes/T2D and an HbA1C ≥ 5.7%, fasting glucose ≥ 100 mg/dL, or random glucose ≥ 150 mg/dL. All patients were scheduled for a first morning visit. At the beginning of the visit patients underwent a 2-hour 75-g OGTT and fasting laboratory measurements including insulin (by chemiluminescent microparticle immunoassay), lipid panel, 25-OH vitamin D level, and complete metabolic panel by standard commercial assays in the Vanderbilt Medical Center CLIA-certified clinical laboratory. HbA1C was measured on a single point-of-care machine. Per clinic protocol, all patients were also required to have a concomitant laboratory HbA1C (by HLPC) to screen for hemoglobin variants if a previous Vanderbilt University Medical Center HbA1C by HLPC was unavailable. Height was measured without shoes using a wall-mounted stadiometer. Weight was measured using a digital scale. Patients were seen by a pediatric endocrinologist for evaluation of diabetes risk and other obesity comorbidities, followed by guidance on lifestyle modification by a pediatrician or pediatric nurse practitioner trained in motivational interviewing. At the end of the visit, the patients attended a group class on the plate method with a registered dietitian. In the plate method, patients are taught to fill one-half of the plate with nonstarchy vegetables, one-quarter with carbohydrates, and one-quarter with lean protein. Patients with an abnormal OGTT were started on metformin (typically

metformin XR 750 mg by mouth daily, titrating up to 1500 mg once tolerating) and scheduled for follow-up with a diabetes nurse practitioner and registered dietitian in 3 months.

C. Data Collection

Data were collected via retrospective chart review of the electronic medical record and stored in a deidentified REDCap database [4]. Demographic information collected included gender, race, insurance type, and travel distance to clinic. Clinical data were extracted from each clinic visit including referral HbA1C, body mass index (BMI), weight, blood pressure, symptoms of diabetes, presence of acanthosis, family history of T2D, and laboratory studies. This study was approved by the Vanderbilt University Medical Center Institutional Review Board.

D. Data Analysis

Homeostasis model assessment calculator, version 2, was used to estimate steady-state insulin resistance (HOMA-IR), beta cell function, and insulin sensitivity [5]. All glucose and insulin measurements used for this calculation were performed in the same Vanderbilt University Medical Center CLIA-certified clinical laboratory. The laboratory did not change assays during the study period. Parametric statistical analyses were performed using SPSS, version 25, software. All data are presented as mean $\pm$ SD. Continuous variables were analyzed by 1-way ANOVA. Categorical variables were analyzed by χ^2 tests. Pearson correlation was used to assess the relationship between diabetes laboratory markers. $P < 0.05$ was considered statistically significant.

2. Results

A. Study Population

A total of 276 charts were reviewed for study inclusion. Eight patients were excluded for diagnosis of type 1 diabetes, 2 patients were excluded for monogenic diabetes, and 12 patients were excluded because they were taking metformin at the time of the first clinic visit. Of the 254 patients included in the study, 65 (25.6%) were classified as IGT and 17 (6.7%) as T2D. Demographic characteristics are shown in Table 1. The NGT group was younger than the IGT group (11.9 ± 2.9 vs. 13.0 ± 2.3 years, $P < 0.01$) and the T2D group (11.9 ± 2.9 vs. 12.9 ± 2.9 years, $P = 0.15$). There were no significant differences between gender, race, ethnicity, insurance type, or travel distance to clinic.

B. Clinical Data

Baseline visit data are reported in Table 1. The NGT group had a lower BMI compared with IGT (32.7 ± 8.4 vs. $0.36.1 \pm 7.4$ kg/m^2, $P < 0.01$) and T2D groups (32.7 ± 8.4 vs. $0.38.9 \pm 10.6$ kg/m^2, $P < 0.01$). Almost all patients (98%) had a family history of T2D but patients with IGT or T2D were more likely to have an affected first-degree relative ($P = 0.014$). Vitamin D deficiency, defined as lower than 20 ng/mL, was present in 40.4% of patients [6].

C. Diabetes Laboratory Markers

The diabetes laboratory findings are reported in Table 1. HbA1C significantly increased with worsening dysglycemia. Insulin sensitivity and beta cell function decreased with progression from NGT to T2D, though the change in beta cell function was not significant. In the IGT group, there are 3 distinct patterns: patients with impaired fasting glucose alone, patients with an elevated 2-hour glucose, and patients with both (Fig. 1A). In contrast, the T2D group tended to have both abnormal fasting (118 ± 24 mg/dL, range 89 to 179 mg/dL) and 2-hour glucose levels (223 ± 62 mg/dL, range 91 to 330 mg/dL). One notable exception was a 15-year-old male with 2 HbA1C

Table 1. Baseline Characteristics and Laboratory Findings

	Normal Glucose Tolerance (n = 172)	Impaired Glucose Tolerance (n = 65)	Type 2 Diabetes (n = 17)
Age (years)[a]	11.9 ± 2.9	13.0 ± 2.3	12.9 ± 2.9
Female (%)	51.2	60	70.6
Race (%)			
White	55.2	52.3	29.4
Black	29.1	30.8	52.9
Unknown	15.7	16.9	17.6
Ethnicity (%)			
Hispanic	15.7	9.2	6.7
Non-Hispanic	72.7	80	82.4
Unknown	11.6	10.8	11.8
Insurance (%)			
Public	75.6	72.3	76.5
Private	22.3	27.7	23.5
Military	0.6	0	0
Travel distance (%)			
<25 miles	30.8	29.2	47.1
25–50 miles	26.2	24.6	17.6
>50 miles	43	46.2	35.3
Weight (kg)[a]	83.7 ± 29.8	94.9 ± 24.3	104.7 ± 36.7
BMI (kg/m^2)[a]	32.7 ± 8.4	36.1 ± 7.4	38.9 ± 10.6
SBP (mm Hg)[a]	126.8 ± 14.4	133.4 ± 11.7	133.4 ± 13.1
DBP (mm Hg)	72.1 ± 8.0	73.0 ± 6.7	72.9 ± 9.5
Symptoms (%)			
None	65.7	58.5	58.8
Polyuria/polydipsia	34.3	41.5	41.2
Acanthosis	76.6	75.4	88.2
Family history of T2D (%)			
First degree[b]	30.2	47.6	47.1
Any	97.7	98.5	100
Vitamin D (ng/mL)	22.9 ± 7.6	22.1 ± 10.5	18.6 ± 7.2
Liver function			
Elevated ALT (%)	43.3	50	68.8
Elevated AST (%)	14	14.3	25
Referral HbA1C (%)[c]	5.9 ± 0.3	6.0 ± 0.3	6.6 ± 0.5
HbA1C (%)[c]	5.5 ± 0.3	5.7 ± 0.4	6.7 ± 0.8
Fasting C-peptide (ng/mL)[b]	3.2 ± 1.7	4.6 ± 2.6	6.0 ± 3.2
Fasting glucose (mg/dL)[c]	88.0 ± 5.6	97.2 ± 9.8	118 ± 24.3
2-hour glucose (mg/dL)[c]	102.7 ± 17.6	148.0 ± 29.6	223.6 ± 62.4
HOMA beta cell function (%)	175.6 ± 61.6	180.2 ± 73.6	157.3 ± 68.5
HOMA insulin sensitivity (%)[a]	57.7 ± 37.1	43.6 ± 39.7	29.3 ± 11.2
HOMA insulin resistance[c]	2.3 ± 1.2	3.0 ± 1.2	3.8 ± 1.2

Results presented as mean ± SD or percent. Number of subjects for laboratory results (normal glucose tolerance group, impaired glucose tolerance group, type 2 diabetes group): vitamin D (n = 146, 60, 17), liver function (n = 157, 62, 16), referral HbA1c (n = 167, 60, 16), HbA1c (n = 169, 63, 16), fasting c-peptide (n = 141, 55, 13), fasting glucose (n = 161, 65, 16), 2-hour glucose (n = 159, 65, 14), all HOMA calculations (n = 138, 52, 11).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HOMA, homeostasis model assessment; SBP, systolic blood pressure; T2D, type 2 diabetes.

[a]$P \leq 0.01$ by 1-way ANOVA.

[b]$P < 0.05$ by χ^2.

[c]$P < 0.001$ by 1-way ANOVA.

measurements ≥ 6.5% but a fasting glucose 98 mg/dL and 2h glucose 91 mg/dL. No hemoglobinopathy was detected. There was a moderate correlation between HbA1C and fasting glucose ($r = 0.59$, $P < 0.001$, Fig. 1B) and HbA1C and 2-hour glucose ($r = 0.63$, $P < 0.001$, Fig. 1C). Clinic HbA1C ≥ 5.7% had 70% sensitivity and 66.9% specificity for diagnosing IGT/T2D.
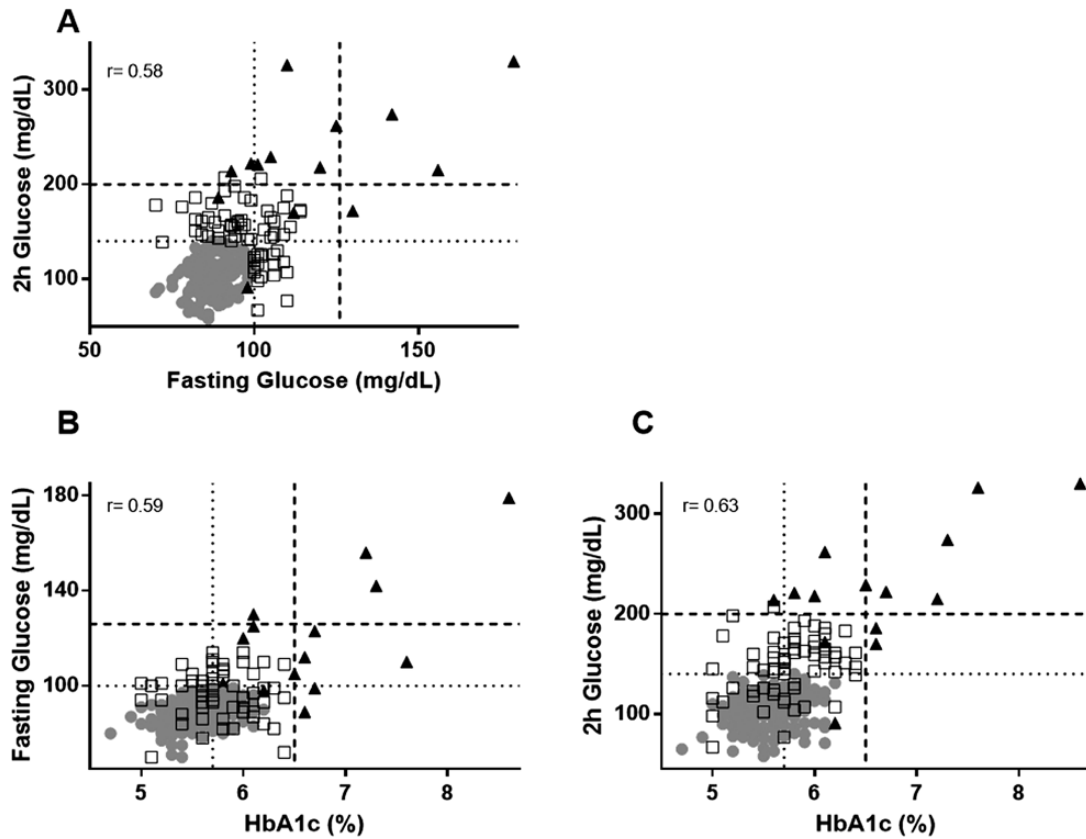
Figure 1. Results from the baseline 75-g oral glucose tolerance test. Patients were divided into 3 groups—normal glucose tolerance (gray circles), impaired glucose tolerance (open squares), and type 2 diabetes (black triangles). Dotted lines mark the threshold for prediabetes—HbA1C 5.7%, fasting glucose 100 mg/dL and 2-hour glucose 140 mg/dL. Dashed lines mark the threshold for prediabetes—HbA1C 6.5%, fasting glucose 126 mg/dL, and 2-hour glucose 200 mg/dL. Pearson correlations (*r*) were all significant with $P < 0.001$. HbA1C, hemoglobin A1C.

D. Progression and Follow-Up Visits

All patients with IGT or T2D were scheduled for follow-up visits. All patients were prescribed metformin (typically 1500 to 2000 mg daily) but no additional weight loss or diabetes medications were prescribed. Over the 3-year study period, 52 of 82 patients (63%) returned for at least 1 follow-up visit. Of those who returned to the clinic, 4 patients regained NGT over 6.8 ± 5.7 months (Fig. 2). All patients were off metformin for > 1 month at the time of repeat testing. Three of those patients had presented with mild impaired fasting glucose (100 to 102 mg/dL). The fourth patient had more significant glucose intolerance with a fasting glucose 110 mg/dL and 2-hour glucose 188 mg/dL. Three patients (4.6%) progressed from IGT to T2D over an average of 13 ± 6.2 months (Fig. 2). One patient with NGT was re-referred after 6 months for progression to T2D. Compared with baseline, BMI increased (1.7 ± 2.3 kg/m^2) and HbA1C increased ($0.7 \pm 0.3\%$) in patients who progressed to T2D. Patients that reverted to NGT had decreasing BMI (-0.5 ± 2.5 kg/m^2) and HbA1C ($-0.1 \pm 0.3\%$). The 34 patients with persistent IGT had stable BMI (0.1 ± 2.4 kg/m^2) and HbA1c ($0.1 \pm 0.3\%$). The 12 patients with persistent T2D all had controlled diabetes at last follow up (HbA1C $5.9 \pm 0.5\%$, range 5.0% to 6.7%) on metformin monotherapy.

3. Discussion

Pediatricians are increasingly tasked with the challenge of managing health risks associated with obesity. The 2015–2016 National Health and Nutrition Examination Survey reported
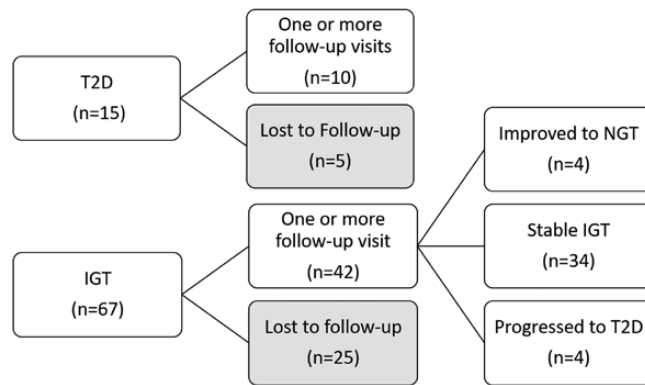
Figure 2. Trends over time in patients who presented with impaired glucose tolerance (IGT) or type 2 diabetes (T2D). NGT, normal glucose tolerance.

a national obesity rate of 18.5% for youth 2 to 19 years old [7]. T2D in youth is increasing in prevalence and expected to quadruple from 2010 to 2050 [8]. The ADA recommends risk-based screening for T2D and prediabetes in children who are ≥ 10 years old or pubertal with overweight/obesity plus 1 or more additional risk factor [1]. Our data support these recommendations as we found increased risk for IGT or T2D in older adolescents, those with greater obesity and a strong family history of T2D. In our referral area (primarily Tennessee, Alabama, and Kentucky), pediatricians are increasingly screening for prediabetes but may struggle with how to proceed when results are abnormal. Therefore, we established the Vanderbilt Prediabetes Clinic with the goal of identifying and treating those patients at highest risk for progression to T2D while providing basic lifestyle modification education for all families. Patients with NGT (67.7%) return to their pediatrician for continued efforts in lifestyle modification because most patients in our area do not have access to a formal pediatric weight management program. The clinic has been well received by community physicians.

The Drugs and Therapeutics Committee of the Pediatric Endocrine Society recommends using clinical judgment when diabetes screening test results do not correlate with each other, as is seen in our patient population [9]. We have chosen to treat and follow patients with 2 or more results in the prediabetes range—fasting glucose ≥ 100 mg/dL or 2-hour glucose ≥ 150 mg/dL, in addition to HbA1C ≥ 5.7%. Along with lifestyle changes, our clinic's choice for first-line pharmacotherapy is metformin. There is emerging evidence that metformin may prevent progression to T2D in adults; in the Diabetes Prevention Program cohort, obese patients 25 to 45 years of age with IGT were less likely to develop T2D over 15 years of follow-up when taking metformin vs. placebo (hazard ratio 0.73) [10]. It is not clear, however, that metformin is similar effective in adolescent prediabetes. A systemic review of metformin use in obese children was unable to provide conclusions on insulin resistance or glucose tolerance because of the wide variety of outcome measures [11]. It is evident that youth with T2D are less responsive to metformin than adults, likely because of more rapid progression of beta cell failure [12, 13]. In June 2019, after completion of this study, the glucagon-like peptide-1 receptor agonist liraglutide was approved for use in children and adolescents 10 to 17 years old with T2D. Glucagon-like peptide-1 receptor agonists may improve pancreatic beta cell mass and function [14–16] and could be a more effective therapy treatment of prediabetes and early T2D in adolescents. Further research is needed to determine if any pharmacotherapy is effective at preventing progression to T2D in adolescents.

There is concern about potential for overtreatment of adolescents because many adolescents will transiently meet criteria for prediabetes because of insulin resistance of puberty, but without the subsequent risk of progression to T2D. In a study of middle-school aged children (10 to 14 years old), only 1% of children with HbA1C > 5.7% or impaired fasting glucose progressed to T2D over a 2-year follow-up period [17]. It is not clear how to best identify children and adolescents at highest risk for progression to T2D. Prediabetes and T2D cutoffs

are the same in children and adults though the justification for these cutoffs comes from the adult literature. The ADA criteria for diabetes was chosen based on the glycemic threshold predicting retinopathy [18] and similar outcome data are not yet available for youth. The diagnostic cutoffs for HbA1C, 2-hour glucose, and fasting glucose have not been validated in a pediatric population and none can be referenced as a gold standard [1, 9].

The longitudinal data that we collected are greatly limited by the high rate of lost to follow-up. All patients in the T2D and IGT groups were requested to return to the clinic, but 37% never returned and 60% were lost to follow-up during the 3-year study period. This is consistent with nationwide data on lost to follow-up in pediatric T2D clinics [19]. Our preliminary analysis of patients with multiple clinic visits and longitudinal data are not statistically significant but support previous conclusions that progression to T2D is associated with continued weight gain. This highlights the importance of obesity treatment in the management of pediatric prediabetes and T2D. We also do not have follow-up data on the NGT group members because they returned to their primary care physician for follow-up and did not return to our clinic unless there was clinical concern for worsening HbA1C or hyperglycemia. It is possible that some patients in the NGT group could have progressed to IGT or T2D without our knowledge.

An interesting finding of this study was the observance of distinct patterns of early pediatric dysglycemia. Within the IGT group, some patients had isolated impaired fasting glucose, whereas others had an abnormal 2-hour glucose. Three patients with mild, isolated impaired fasting glucose had NGT on repeat testing. It is possible that these patients may not have been compliant with fasting at the initial visit. This could reflect differing pathogenesis of prediabetes with some children exhibiting greater baseline insulin resistance with higher fasting glucose versus an impaired insulin response to glucose with elevated 2-hour glucose. Perhaps the isolated elevated fasting glucose simply reflects expected relative insulin resistance during puberty, though obese adolescents may not recover insulin sensitivity in adulthood [20]. A previous study showed that HbA1C and 2-hour glucose measures correlate better with continuous glucose monitor outcomes in obese adolescents when compared with fasting glucose [21]. Further studies are needed to see if these differing patterns of IGT are predictive of progression to T2D so that interventions can better target those high-risk patients.

In conclusion, a pediatric prediabetes clinic may allow for identification of high-risk youth, but high lost to follow-up rates remain a challenge. Correlation between common markers of prediabetes (HbA1C, fasting, and 2-hour glucose) are moderate and none are established as a gold standard. Continued weight gain is a risk factor for progression to T2D and effective weight management programs are needed.

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Additional Information

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