Journal of Adolescent Health xxx (2014) 1–6

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Diagnosing Dysglycemia in Adolescents With Polycystic Ovary Syndrome

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Article history: Received July 12, 2013; Accepted December 18, 2013
Keywords: Adolescent; Polycystic ovarian syndrome; Screening; Diabetes

A B S T R A C T

Purpose: Screening for impaired glucose tolerance (IGT) is recommended for adolescents with polycystic ovary syndrome (PCOS) with oral glucose tolerance test (OGTT). Whether glycated hemoglobin (HbA1c) can be used for screening in this patient population is unknown. We sought to determine the utility of HbA1c and 2-hour OGTT for diagnosing dysglycemia in adolescents with PCOS.

Methods: This was a retrospective cohort study of 68 adolescents with PCOS seen in the Boston Children's Hospital Division of Adolescent Medicine between 2008 and 2011 and not known to have diabetes. Prevalence of dysglycemia (impaired fasting glucose, IGT, increased risk for diabetes, or diabetes mellitus as diagnosed by fasting plasma glucose, 2-hour OGTT, and/or HbA1c) and sensitivity and specificity of HbA1c for diagnosing dysglycemia compared with OGTT were assessed.

Results: Twenty-four participants had abnormal glucose testing, including one participant (1.5%) who met criteria for diabetes mellitus and 23 participants (34%) who met criteria for impaired fasting glucose/IGT/prediabetes. More patients were identified as having dysglycemia by HbA1c than OGTT. Compared with OGTT, HbA1c had a sensitivity of 60% and a specificity of 69% for diagnosing dysglycemia.

Conclusions: In adolescents with PCOS, HbA1c had moderate sensitivity and specificity for detecting dysglycemia compared with OGTT. Clinicians should be aware that both tests have benefits and limitations, and the optimal test for follow-up requires further study.

IMPLICATIONS AND CONTRIBUTION

Our study demonstrates that both glycated hemoglobin (HbA1c) and oral glucose tolerance test (OGTT) are useful for identifying adolescents with polycystic ovary syndrome (PCOS) with dysglycemia and may identify different populations of girls at risk for long-term cardiometabolic consequences. Future studies are necessary to determine which test best predicts future dysglycemia or progression to diabetes in longitudinal follow-up.

PCOS affects 5%–10% of reproductive-age women and often presents during adolescence [1]. Many patients with PCOS are insulin resistant even if they are not overweight or obese [2], placing them at increased risk for developing impaired glucose tolerance (IGT) and progression to diabetes mellitus (DM) [3–5]. Because IGT can present as early as adolescence in patients with PCOS [6,7], health care providers are tasked with initiating the evaluation for IGT and DM in these young women. The Androgen Excess Society recommends IGT screening for adolescent and adult women with PCOS who are obese, over 40 years of age, or have a personal history of gestational diabetes or a family history of type 2 diabetes [8] with a 2-hour OGTT, as fasting plasma glucose (FPG) alone is less sensitive in this population [3]. The American Diabetes Association (ADA) and American Academy of Pediatrics recommend screening obese youth with two or more risk factors for diabetes (one of which can be PCOS) with FPG [9].

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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http://dx.doi.org/10.1016/j.jadohealth.2013.12.020

Given that 70% of adolescents with PCOS are obese, the majority will qualify for screening [10]. Despite these recommendations, pediatric adolescent and gynecology providers report evaluating only 25%–60% of adolescents diagnosed with PCOS for IGT/DM [11].

In 2010, the ADA endorsed the use of HbA1c for the diagnosis of diabetes in adults [12]. HbA1c is a reflection of the average blood glucose levels over the life of a red blood cell (approximately 90 days) and is closely associated with microvascular disease in diabetes [13]. HbA1c is less subject to intraindividual variation and does not require that the patient be fasting. This latter advantage may be particularly relevant for adolescent patients, for whom there may be barriers to access to care and who may be less likely to return for follow-up [14]. However, the Androgen Excess Society concluded in their 2010 position paper that there were insufficient data on the use of HbA1c testing in PCOS to recommend its use at that time [8].

Several recent studies have compared screening for dysglycemia by HbA1c with either FPG or OGTT in adult [15–21] and pediatric [22,23] groups, including adult women with PCOS [24,25]. Most of these studies have found only fair agreement among HbA1c, FPG, and OGTT. The role of HbA1c as a screening tool in adolescents with PCOS has not been clarified and may differ from its use in adults due to the lower prevalence of dysglycemia in adolescents. We thus sought to examine the prevalence of dysglycemia as diagnosed by HbA1c and OGTT in adolescents with PCOS to help clinicians identify strategies for clinical practice.

Methods

Participants

We used *International Classification of Diseases* (*ICD-9*) billing codes to identify patients seen in our Adolescent and Young Adult Medicine Clinic from 2008 to 2011 who were diagnosed with PCOS by their treating clinician and underwent both a 2-hour OGTT and HbA1c testing within 90 days (N = 68, 45 of whom had both tests on the same day), as well as N = 125 individuals with PCOS who did not have both OGTT and HbA1c testing for a comparison sample. If multiple OGTT or HbA1c results were recorded within the study period, those closest to the initial evaluation were used for analysis. Data on demographic characteristics, social and family history, physical examination findings, laboratory studies, pelvic ultrasound results, and treatment were collected through a standardized chart abstraction tool and entered into the RedCap database [26]. All participants met 1990 National Institutes of Health (NIH) Consensus Criteria for PCOS and thus had irregular menses and either clinical or biochemical hyperandrogenism [27]. Participants were excluded if they had a prior diagnosis of type I or type II diabetes or IGT or if they were taking medications known to affect the results of an OGTT or HbA1c (such as metformin). This study was approved by the Boston Children's Hospital (BCH) Committee on Clinical Investigations.

Demographic information

Age (in months/years) was defined by subtracting the date of chart extraction from the participant's date of birth. Race/ethnicity was obtained from self-reported data from the electronic patient registration system. Family history was recorded by the treating clinician.

Measures

Body mass index (BMI) was calculated using the formula: weight (kg)/height^2 (m). Sexual maturity rating of pubertal development for both breast and pubic hair was recorded by the treating clinician. Blood pressure was obtained by GE Dinamap DPC100X-US, measured in the right arm resting at heart level with both feet on the ground per standard clinic policy.

Laboratory assays

An OGTT was performed in the morning on a random day of the menstrual cycle in 68 fasting individuals who were instructed to consume a normal amount of carbohydrates for the 3 days preceding the test in either the BCH clinical laboratory or another certified laboratory (n = 4). Blood glucose was measured at baseline (FPG) and at 120 minutes (BG 120) after a 75 g oral glucose load. ADA criteria [12] were used to classify participants as having normal fasting glucose or glucose tolerance (FPG < 100 mg/dl or BG 120 < 140 mg/dl), impaired fasting glucose (IFG) or IGT (FPG, 100–125 mg/dl or BG, 120 140–199 mg/dl), or diabetes (FPG ≥ 126 mg/dl or BG 120 ≥ 200 mg/dl) based on their OGTT results. For HbA1c results (turbidimetric inhibition immunoassay, BCH clinical laboratory), we classified subjects as "normal" if HbA1c < 5.7%, "increased risk for diabetes" if HbA1c 5.7%–6.4%, or "diabetic" if HbA1c ≥ 6.5% based on ADA criteria.

Additional laboratory values (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides, alanine aminotransferase, total and free testosterone levels, dehydroepiandrosterone sulfate, and sex hormone binding globulin) were obtained using standard assays in either the BCH clinical laboratory or another certified laboratory. Elevation in testosterone levels was defined as values greater than the normative range in that laboratory for a given patient's sexual maturity rating.

Statistical analysis

Descriptive statistics are presented as mean (SD) or frequency (%). Median (interquartile range) are presented in lieu of mean (SD) for continuous factors with non-normal distributions upon visual inspection. Demographic and clinical factors at initial visit were compared by HbA1c categories. All tests were performed at an alpha level of .05 using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). Independent two-tailed *t* tests were used to assess differences between participants classified as "normal" and "abnormal" by HbA1c on continuous factors. Wilcoxon rank-sum nonparametric test was used to assess differences between HbA1c categories on continuous factors with a non-normal distribution where indicated in results and tables. Chi-square or Fisher's exact test (where appropriate) was used to assess differences between the HbA1c categories on categorical factors.

Diagnostic characteristics of FPG and HbA1c were compared using OGTT in terms of the predictive ability of these tests to classify participants as having "normal" or "abnormal" glucose findings. Measures of the diagnostic ability calculated were sensitivity, specificity, positive and negative likelihood ratios, and the kappa statistic as a measure of overall agreement between the test and the gold standard. Empirically derived cut points that maximize sensitivity and specificity were also generated from the data. Receiver operating characteristic (ROC) curves were constructed using the binary OGTT result classification of "normal"