Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Glycemic control and variability in association with body mass index and body composition over 18 months in youth with type 1 diabetes

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ARTICLE INFO

Article history:
Received 11 February 2016
Received in revised form
28 July 2016
Accepted 31 July 2016
Available online 6 August 2016

Keywords:
Body mass index
Body composition
Diabetes mellitus, type 1
Adolescent
Hemoglobin A glycosylated
1,5-Anhydroglucitol

ABSTRACT

Aims: The impact of adiposity on glycemic control in type 1 diabetes patients has important implications for preventing complications. This study examined associations of glycemic outcomes with body mass index (BMI, kg/m^2) and body composition in youth with type 1 diabetes.

Methods: This is a secondary analysis of an 18-month randomized controlled dietary intervention trial (N = 136, baseline age = 12.3 ± 2.5 y, HbA1c = 8.1 ± 1.0% (65 ± 11 mmol/mol)). Measured height and weight every 3 months were abstracted from medical records. Body composition was assessed by dual energy X-ray absorptiometry (DXA) at baseline, 12 and 18 months. Glycated hemoglobin (HbA1c) and glycemic variability assessed by masked 3-day continuous blood glucose monitoring (CGM) were obtained every 3 months. 1,5-Anhydroglucitol (1,5-AG) was assessed every 6 months. Adjusted random effects models for repeated measures estimated associations of time-varying BMI and body composition with time-varying glycemic outcomes.

Results: There was no treatment effect on glycemic outcomes. HbA1c was not associated with BMI or body composition indicators. 1,5-AG was inversely associated with BMI and adiposity indicators (%fat, trunk fat mass and trunk %fat), adjusting for developmental covariates. Adiposity indicators were positively associated with %glucose >180 mg/dL and >126 mg/dL when adjusting for developmental covariates, and %glucose >126 mg/dL when additionally adjusting for diabetes-related covariates. Fewer consistent relationships were observed for 3-day mean glucose and %glucose <70.2 mg/dL. BMI and body composition variables were not associated with standard deviation of glycemic values or mean amplitude of glycemic excursions.

Conclusions: The role of greater BMI and adiposity in diabetes management in youth with type 1 diabetes may relate specifically to increased hyperglycemic excursions.

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Abbreviations: HbA1c, glycated hemoglobin; BMI, body mass index; 1,5-AG, 1,5-anydroglucitol; DXA, dual energy X-ray absorptiometry; CGM, continuous glucose monitoring; MAGE, mean amplitude of glycemic excursions; IIT, intensive insulin therapy

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http://dx.doi.org/10.1016/j.diabres.2016.07.028
0168-8227/Published by Elsevier Ireland Ltd.

1. Introduction

The overall impact of body weight and adiposity on glycemic control in patients with type 1 diabetes is unclear. Despite the macro- and micro-vascular benefits of glycemic control achieved through intensive insulin treatment in patients with type 1 diabetes [1], numerous studies have shown increased risk of weight gain [2,3], which in turn may have adverse cardiovascular effects [4,5]. Increased adiposity in this population has been associated with increased insulin resistance [6–8], which may adversely impact glycemic control [9]. Reported associations of glycated hemoglobin (HbA1c) with body mass index (BMI, kg/m^2) are inconsistent with regards to direction, magnitude and significance [10–13]. While findings from a recent prospective study of U.S. youth suggest that modest weight gain is associated with concomitant improvement in glycemic control [14], other studies have reported both positive [10,15] and null associations [12,16]. Differences in study design, analytic methods, and advancements in treatment regimen likely contribute to discrepancies in the findings.

Research on the association of glycemic control with body weight in type 1 diabetes patients has relied almost exclusively on BMI as a measure of adiposity. While BMI is strongly correlated with body fat, it is an indirect measure, and does not reflect body fat distribution [17], which may be differentially associated with glycemic control. Similarly, while HbA1c is the clinical benchmark for assessing chronic glycemic control, the measure does not reflect short-term glucose excursions shown to predict diabetes complications [18]. Complementary measures of overall glycemic control include 1,5-anhydroglucitol (1,5-AG), which is sensitive to recent glucose excursions in moderately well-controlled type 1 diabetes [19–22], and continuous glucose monitoring, which can be used to assess glycemic variability. To our knowledge, the associations of BMI and body composition with 1,5-AG and glycemic variability have not been evaluated. Examination of these relationships may reveal important mechanistic linkages between weight status, glycemic control, and diabetes complications.

The purpose of this study is to estimate the longitudinal associations of BMI and body composition with multiple indicators of glycemic control and variability in youth with type 1 diabetes participating in a randomized controlled dietary intervention trial.

2. Methods

2.1. Design, setting and recruitment

This is a secondary analysis of data from a randomized controlled trial of an intervention conducted from Aug 2010 to May 2013 at an outpatient, free-standing, multidisciplinary tertiary diabetes center in the northeast United States. Details regarding recruitment and randomization are described in detail elsewhere [23]. Eligibility criteria included age 8.0–16.9 years, diagnosis of type 1 diabetes $\geqslant$1 year, daily insulin dose $\geqslant$0.5 units per kilogram, most recent HbA1c $\geqslant$6.5% (48 mmol/mol) and $\leqslant$10.0% (86 mmol/mol), with either an insulin regimen of $\geqslant$3 injections daily or insulin pump, at least one clinic visit in the past year, and ability to communicate in English. Exclusion criteria included daily use of premixed insulin, transition to insulin pump therapy in the last three months, real-time continuous glucose monitoring use in the last three months, participation in another intervention study in the last six months, and presence of gastrointestinal disease such as celiac disease, multiple food allergies, use of medications that interfere significantly with glucose metabolism, or significant mental illness.

Families were enrolled in the study for 18 months, and attended study visits in the clinic. Those in the intervention condition received six "core" sessions during the first seven months of the study period and three "booster" sessions during the next five months. Session content was designed to increase intake of whole plant foods (fruit, vegetables, whole grains, legumes, nuts and seeds); sessions focused on healthful eating but did not address weight management. Participants in the control condition received equal frequency of contacts with research staff. Further details regarding the intervention and control conditions have been previously reported [23]. At enrollment, all youth provided assent, and parents provided written informed consent; youth turning 18 years of age during the trial additionally provided written informed consent. Study procedures were approved by the institutional review boards of the participating institutions. Of 622 eligible families invited to participate, 148 (24%) enrolled in the study, 139 (22%) completed baseline assessments, and 136 were randomized to intervention or control group after excluding 1 sibling each from 3 sibling pairs. The primary reason for declining to participate was lack of time.

2.2. Measures

2.2.1. Body mass index (BMI) and body composition

Measured height and weight at clinic visits at baseline and at 3 months, 6 months, 9 months, 12 months and 18 months were abstracted from the medical records and used to calculate BMI (kg/m^2). Body composition was assessed by dual energy X-ray absorptiometry (DXA; Hologic Inc.) at baseline, 12 and 18 months. Body composition variables for these analyses included total fat mass (g), total lean mass (g), percent of total fat mass (%fat), trunk fat mass (g), trunk lean mass (g) and percent of trunk fat mass (trunk %fat).

2.2.2. Glycemic control

Glycated hemoglobin (HbA1c) was assessed at baseline and at 3 months, 6 months, 9 months, 12 months and 18 months during routine clinical care and processed on-site using a laboratory assay standardized to the Diabetes Control and Complications Trial (reference range, 4–6%, [20–42 mmol/mol]). Initial HbA1c assays were performed with the Tosoh (Tosoh Medics, South San Francisco, CA, USA); subsequent assays were performed by the Roche Cobas Integra (Indianapolis, IN), and Tosoh values were standardized to the Roche assay. Samples were kept at room temperature for 20–30 min following collection, then centrifuged for 15 min at ~3000 RPM at temperature of 4 °C, aliquoted and frozen at −80 °C for later assay. 1,5-Anhydroglucitol (1,5-AG) was