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Association of parental history of diabetes with cardiovascular disease risk factors in children with type 2 diabetes

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ABSTRACT

Aims: Determine if parental diabetes (DM) is associated with unhealthier cardiovascular disease (CVD) risk profiles in youth with type 2 diabetes (T2D), and whether associations differed by race/ethnicity.
Methods: Family history was available for 382 youth with T2D from 2001 prevalent and 2002–2005 incident SEARCH for Diabetes in Youth cohorts.
Parental DM was evaluated in two ways: two-category—any parent vs. no parent DM (evaluated overall and stratified by race/ethnicity); and four-category—both parents, mother only, father only, or no parent DM (evaluated overall only). Associations with hemoglobin A1c (HbA1c), fasting lipids, blood pressure (BP), and urine albumin:creatinine ratio (ACR) were examined using regression models.
Results: Overall, sample characteristics included: 35.9% male, 19.1% non-Hispanic white (NHW), mean T2D duration 26.6 ± 22.2 months, mean HbA1c 7.9% ± 2.5% (62.6 ± 27.8 mmol/mol). Unadjusted two-category comparisons showed that youth with parental DM had higher HbA1c, higher DBP, and higher frequency of elevated ACR. Adjusted two-category comparisons showed associations remaining in non-stratified analysis for ACR [OR (95% CI) = 2.3 (1.1, 5.0)] and in NHW youth for HbA1c [6.8% ± 0.4 vs. 8.0 ± 0.4 (51.1 ± 4.8 vs. 63.9 ± 4.2 mmol/mol), $p = .015$], DBP (67.7% ± 4.5 vs. 76.9 ± 4.4 mm Hg, $p = .014$) and lnTG (4.7 ± 0.3 vs. 5.3 ± 0.3, $p = .008$). There were no significant findings in the adjusted four-category evaluation.
Conclusions: Parental history of diabetes may be associated with unhealthier CVD risk factors in youth with T2D.

1. Introduction

Cardiovascular disease (CVD) is an established macrovascular complication of type 2 diabetes (T2D), and individuals with T2D are known to be at an increased risk for early onset of CVD. Adults with any type of diabetes have death rates from CVD 1.7 times higher than adults who do not have diabetes (Centers for Disease Control and Prevention, 2014). In adults aged 65 years and older with diabetes-related causes of death, 68% of death certificates also cite heart disease and 16% also cite stroke as causes of death (Centers for Disease Control and Prevention, 2011). These problems are magnified in the population by the increasing incidence of T2D (Centers for Disease Control and Prevention, nd). Additionally, it is well-known that atherosclerosis emerges during childhood (Berenson, Wattigney, Tracy, et al., 1992; Strong, Malcom, McMahan, et al., 1999). Therefore, the estimated 5100 youth who are diagnosed with T2D each year in the United States may be at a higher risk for cardiovascular morbidity and mortality because of the early onset and longer duration of T2D as they enter adulthood (Lawrence et al., 2014). The SEARCH for Diabetes in Youth Study (SEARCH) has shown that youth with T2D have more arterial stiffness than youth with type 1 diabetes (T1D), while the TODAY study has shown that over a 3 year period, the number of youth with T2D meeting recommended thresholds for treatment with lipid-lowering medication treatment tripled (TODAY Study Group, 2013a; Wadwa, Urbina, Anderson, et al., 2010).

Familial clustering of cardiovascular disease risk factors such as T2D, hypertension, hypercholesterolemia, and hyperalbuminuria is well-known. Certainly, shared lifestyles are involved in the pathophysiology of the development of these disorders; however, family and twin studies

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also suggest underlying genetic and epigenetic influences (Bunt, Tataranni, & Salbe, 2005; Carmelli, Cardon, & Fabsitz, 1994; Hong, Pedersen, Brismar, & de Faire, 1997; Lascaux-Lefebvre, Ruidavets, Arveiler, et al., 2001; Mayer et al., 1996; Nelson, Morgenstern, & Bennett, 1998; Shear, Webber, Freedman, Srinivasan, & Berenson, 1985). Additionally, CVD risk factors have been shown to differ by ethnicity (Forouhi & Sattar, 2006). Considering the interplay of genetic background and epigenetic and lifestyle influences, it is plausible that the relationship between family history of diabetes and the risk for CVD in offspring may differ for individuals of varying racial or ethnic backgrounds.

Therefore, the goal of this study was to explore the association between parental diabetes and the CVD risk profiles of youth with T2D enrolled in the SEARCH study. The secondary goal of this study was to examine whether the association between parental history and CVD risk profile also differed by race or ethnicity. We hypothesized that unhealthier CVD risk factors [as assessed by higher levels of HbA1c, higher blood pressure (BP), higher fasting total cholesterol (TC), higher fasting low density lipoprotein (LDL), higher fasting triglycerides (TG), lower fasting high density lipoprotein (HDL), higher apolipoprotein B (apoB), and higher urine albumin to creatinine ratio (ACR)] would be most likely present in the offspring of two parents with diabetes and the most favorable profile would be seen in those without a parental history of diabetes. Among youth with T2D with at least one parent with diabetes, we hypothesized that those with a mother with diabetes would have a more adverse CVD risk profile than those with a father with diabetes due to the additional contribution of possible intrauterine exposure.

2. Subjects, materials, and methods

Data for these analyses were collected as part of the SEARCH study protocol. A detailed description of the SEARCH study methods has been published elsewhere (SEARCH Study Group, 2004). Briefly, SEARCH has been conducting population-based case ascertainment of youth <20 years old with prevalent diabetes in 2001 and 2009 and newly diagnosed (incident) diabetes starting in 2002 and continuing through the present. SEARCH recruited participants from four geographically defined populations in Ohio, Colorado, South Carolina and Washington, as well as from Indian Health Service beneficiary roles of several American Indian populations, and among enrollees in a managed health care plan in California. Participants were invited to participate in a research visit, during which fasting blood samples were obtained if metabolically stable (defined as no episode of diabetic ketoacidosis during the previous month), physical measurements were taken, and questionnaires were administered. The study was reviewed and approved by the local institutional review board(s) that had jurisdiction over the local study population and all participants provided informed consent and/or assent.

2.1. Measurements

Study visits occurred after an eight hour overnight fast. Participants did not take diabetes medications the morning of the visit. Participants on long-acting insulin took it the evening before the visit and then it was withheld. A brief physical examination was conducted including measurement of BP, weight, and height using standardized procedures. Body mass index was calculated (BMI [kg/m^2]), and age- and sex-specific BMI z-scores were calculated using growth charts with a SAS program available from the Centers for Disease Control and Prevention (2011). Waist circumference was measured using NHANES III protocol (Fernandez, Redden, Pietrobelli, & Allison, 2004). Waist z-scores were calculated by age and gender from CDC growth reference year 2000. Race and ethnicity were self-reported using 2000 United States Census questions (Ingram, Parker, Schenker, et al., 2003) and classified as Hispanic, non-Hispanic White (NHW), non-Hispanic Black (NHB), American Indian (AI), and Asian/Pacific Islander (API). For these analyses, race or ethnicity was categorized as NHB, Hispanic, NHW, and combined API/AI. API and AI were combined to create a category of comparable size to the other categories and also of sufficient size for analysis. Family history of diabetes was collected by questionnaire; however, information on type of parental diabetes was not collected. History of parental diabetes at any time point (regardless of timing with offspring's birth or diagnosis) was classified as a positive parental history in these analyses.

Fasting blood samples were used to analyze diabetes autoantibodies (DAA), HbA1c and lipids (TC, TG, HDL, LDL, and apoB). Spot urine samples were used to measure ACR. Assays were performed at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington. Glutamic acid decarboxylase-65 (GAD65) and insulinoma-associated-2 (IA-2A) autoantibodies were analyzed using a standardized protocol and a common serum calibrator developed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored standardization group (Bonifacio, Yu, Williams, et al., 2010). The cutoff values for positivity were 33 NIDDK U/ml for GAD65 and 5 NIDDK U/ml for IA-2A. HbA1c (%) was measured in whole blood with an automated nonporous ion-exchange high-performance liquid chromatography system (model G-7; Tosoh Bioscience, Montgomeryville, Pennsylvania).

2.2. Study Participants

Inclusion criteria for this report include all youth aged <20 years whose diabetes was prevalent in 2001 or newly diagnosed in 2002–2005, with T2D as diagnosed by their health care provider and who had a SEARCH study visit ($n = 581$). From the 581 individuals, we hierarchically excluded those with positive DAA ($n = 42$), time from diagnosis to initial study visit was less than 3 months to allow for some stabilization of glycemic control which could otherwise negatively impact outcome measures ($n = 26$), history of steroid use or diagnosis of other medical conditions frequently treated with steroids ($n = 9$), missing information for race or ethnicity ($n = 4$), missing information on all outcomes of interest ($n = 45$), and those for whom we were unable to determine that at least 1 parent had diabetes or both parents did not have diabetes ($n = 73$). For the four category exposure analysis, we excluded an additional 20 individuals for whom diabetes status could not be determined for both parents.

2.3. Statistical analysis

Participant characteristics were described using means (SD) or proportions (%). Comparisons across parental diabetes groups were examined using chi square or Fisher's exact test, as well as simple and multivariable logistic regression models (categorical outcomes), or simple and multivariable linear regression models (continuous outcomes). Natural log transformation was applied to the triglyceride variable before analysis due to skewed distribution.

Parental diabetes exposure groups were divided both into 2 categories [parental history of diabetes in either or both parents (parental DM) and no parental history of diabetes (no parental DM)] and 4 categories [both parents with history of diabetes (both parents DM), maternal history of diabetes only (maternal DM), paternal history of diabetes only (paternal DM), and no parental history of diabetes (no parental DM)]. The 2 category exposure definition was examined overall and stratified by the 4 race or ethnicity groups (NHB, Hispanic, NHW, and API/AI), however the 4 category exposure definition was not stratified by race or ethnicity because of sample size limitations.

Modeling was conducted using sequential models with groups of covariates added to subsequent models culminating in the maximally adjusted model. Model covariates included: gender, clinic, highest parental education, smoking status, physical activity level, BMI z-score, waist z-score, time since diagnosis, age at diagnosis, insulin use, hypertensive medication use (blood pressure and ACR outcomes