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Type 2 Diabetes in Youth: New Lessons from the SEARCH Study

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Abstract

Purpose of Review—The purpose of this review is to provide an update on the recent body of evidence emerging for type2 diabetes as identified through the SEARCH for Diabetes in Youth study.

Recent Findings—This body of evidence illustrates that type 2 diabetes continues to increase in incidence, although this increase may be partially attributable to increased surveillance. Disease management is influenced by the transition from adolescent to adult care and psychosocial factors may also contribute. This evidence also describes a high prevalence of disease-associated complications and comorbidities. Risk factors for cardiovascular disease are also highly prevalent.

Summary—The SEARCH for Diabetes in Youth study continues to inform our understanding of the descriptive epidemiology and natural history of type 2 diabetes in youth. As the cohort matures, new opportunities emerge for building on our understanding of how youth-onset type 2 diabetes impacts future health.

Keywords

Incidence; Prevalence; Risk factors; Complications and comorbidities

Introduction

Type 2 diabetes contributes to a high burden of disease-associated complications and comorbidities. Disease pathogenesis is driven by both environmental and genetic factors, with elevated hepatic glucose production, impaired insulin secretion, and insulin resistance acting as key drivers in the development of disease [1]. Altered glucose-insulin homeostasis

Compliance with Ethical Standards

Conflict of Interest Elizabeth T. Jensen and Dana Dabelea have no conflicts of interest to report.

Human and Animal Rights and Informed Consent Local IRBs at each of the five clinical sites and at the SEARCH for Diabetes Coordinating Center provided Human Subjects approval for study implementation. The SEARCH for Diabetes in Youth study obtains written informed consent from participants > 18 years of age or their parents of legal guardians if < 18 years of age. Assent is obtained in accordance with local IRB requirements.

is typically associated with obesity and most, although not all [2], of those with type 2 diabetes are obese at disease onset. While disease onset is primarily in adults, the increase in prevalence of obesity among youth has resulted in an increasing incidence of onset of type 2 diabetes in youth [3•].

The SEARCH for Diabetes in Youth (SEARCH) study is one of only a few studies established to address gaps in knowledge regarding type 2 diabetes in youth. Supported by the Centers of Disease Control and the National Institute of Diabetes and Digestive and Kidney Diseases, SEARCH is currently conducted at five sites across the United States (U.S.) and represents a diverse, representative sample of youth with diabetes in the U.S. The study has been on-going since 2000 and includes an active surveillance component and a longitudinal follow-up of registered, incident cases. The study design provides opportunity to not only characterize the descriptive epidemiology of diabetes in youth in the U.S., including incidence, prevalence, and patterns of disease over time, but also to describe and evaluate risk factors for disease-associated complications and comorbidities [4•]. Below, we summarize recent evidence provided through the SEARCH study on the descriptive epidemiology of youth-onset (< 20 years of age) type 2 diabetes, possible etiologic factors for disease development, factors contributing to disease management, and disease-associated complications and comorbidities.

Descriptive Epidemiology

Characterizing the descriptive epidemiology of youth-onset diabetes is a primary aim of the SEARCH registry study. Incidence and prevalence in SEARCH are estimated using physician-diagnosed diabetes at each of the five SEARCH study sites, including Washington, South Carolina, Ohio, Colorado, and California. Washington, South Carolina, Ohio, and Colorado are geographically based and collectively span 31 counties. California is based on membership in the Kaiser Permanente Southern California health system, which includes members from a geographic area of 7 counties. Colorado is also conducting ascertainment of cases from surrounding American Indian tribes. All SEARCH sites use active surveillance and a two-mode ascertainment, and capture-recapture approach is used to evaluate completeness of case-ascertainment within the four geographically based sites. Additional details of the SEARCH registry have been described previously [5•, 6].

Prevalence

The most recent prevalence estimates of type 2 diabetes in youth, as reported by SEARCH, indicate that youth-onset type 2 diabetes is more prevalent among minority racial and ethnicity groups. Among youth with diabetes, the proportion of type 2 diabetes among non-Hispanic whites is 5.5%, while the proportion of type 2 diabetes among non-Hispanic blacks is 37.6%. For American Indian/Alaskan Natives, the proportion of type 2 diabetes is 80.0%. The proportion of type 2 diabetes in Asian or Pacific Islander and Hispanic youth is 34.2 and 35.2%, respectively [5•]. Additionally, among youth < 20 years of age, prevalence increases with age. Overall, based on standardization of SEARCH estimates to the U.S. census population, there were an estimated 20,262 youth with type 2 diabetes in 2009 (Table 1) and a prevalence of 0.24 case subjects/1000 (95% CI: 0.23, 0.26) [5•].

Incidence

Recent (2012) estimates of youth-onset type 2 diabetes incidence from SEARCH indicate that American Indians and non-Hispanic blacks experience the highest incidence of type 2 diabetes (46.5/100,000/year in American Indians and 32.6/100,000/year in non-Hispanic blacks), relative to non-Hispanic whites (3.9/100,000/year), Hispanics (18.2/100,000/year), and Asian or Pacific Islanders (12.2/100,000/year). Incidence in girls is substantially higher than in boys (16.2/100,000/year in girls versus 9.0/100,000/year in boys) (Table 2) [7••].

Temporal Trends

Of concern, the incidence of type 2 diabetes has increased considerably over the previous decade, with racial and ethnic minorities driving this increase. SEARCH data indicate an overall 4.8% (95% CI: 3.2, 6.4) annual increase (adjusted for age and sex)in incidence. Annual increases were estimated to be highest among non-Hispanic blacks (6.3%; 95% CI: 4.0, 8.8), Asian/Pacific Islanders (8.5%; 95% CI: 2.0, 15.4), and American Indians (8.9%; 95% CI: 5.0, 13.1) in contrast to an annual increase of just 0.6% (95% CI: − 2.0, 3.4) among non-Hispanic whites and 3.1% (95% CI: 0.8, 5.4%) among Hispanics. The annual increase in incidence among girls was estimated to be nearly twice that of boys (6.2% [95% CI: 4.2, 8.2] versus 3.7% [95% CI: 1.6, 5.8]) [7••].

It has been suggested that the increase in incidence is due to increased surveillance of disease. In a recently conducted study in SEARCH of self-reported modes of case presentation, 65% of youth reported diagnosis as a result of symptoms and 30% reported diagnosis during a routine check-up. The proportion of those reporting diagnosis due to symptoms has decreased overtime, from 72.1% in 2002–2004 to 59.1% in 2008–2010 [8]. This suggests that some proportion of increased disease incidence may be a result of increased disease surveillance, although this is unlikely the main explanation for the increase.

Projections

SEARCH projections on type 2 diabetes in youth indicate an increasing and high burden of disease [9•]. By 2050, at current incidence rates, the number of youth with type 2 diabetes may double, primarily due to shifts in the population distribution of racial minorities. Of concern, if the incidence of type 2 diabetes continues to increase, as suggested by SEARCH data, the number of youth with type 2 diabetes may increase more than fourfold [9•].

Etiologic Factors

Several ancillary studies have been conducted in SEARCH, including a case-control study conducted at two SEARCH sites (South Carolina and Colorado), and the inclusion of controls in this study has provided an opportunity to evaluate possible etiologic factors contributing to increased risk of type 2 diabetes in youth. Methods of the SEARCH case-control study have been previously described, but in brief, controls were recruited from primary care health-care provider offices, thus mitigating possible selection bias resulting from controls that may not be representative of exposure distribution of the source population giving rise to cases [10•].

Contextual Factors in Disease Risk

While it has been well-documented that obesity is a significant determinant for the development of type 2 diabetes, less is known as to the factors that may contribute to the obesogenic environment that ultimately leads to type 2 diabetes in youth. Ina recent sub-study from the SEARCH case-control ancillary study, type 2 diabetes cases ($n = 91$) and non-diabetic controls ($n = 293$) from the same catchment areas as the identified cases were compared to evaluate the contribution of neighborhood-level factors. Adjusted for age, sex, race/ethnicity, study site, breastfeeding, maternal diabetes, parental education, and parental income, this study indicated an increased risk of type 2 diabetes in less densely populated residential areas (< 500 residents/sq. mile) versus densely populated areas (1000+ residents/sq. mile) (aOR 3.22, 95% CI: 1.40, 7.41). Small and large towns, as opposed to urban areas, were similarly associated with increased risk (aOR 3.04; 95% CI: 1.25, 7.41). No other associations were observed with adjustment across factors, including housing values, food desert status, proportion of households receiving social security, median household income, and proportion of residents with at least a high school education [11].

Arsenic

Studies conducted in adult populations have suggested that inorganic arsenic (iAs) exposure may increase risk for developing type 2 diabetes [12, 13]. Exposure to arsenic is believed to be increasing, due to increased consumption of rice-based diets that confer increased risk for exposure [14]. In a case-control sub-study, plasma levels of arsenic were evaluated in relation to both type 1 and type 2 diabetes. While associations were observed for type 1 diabetes, no association was observed for type 2 diabetes [15]. One challenge in estimating the effect of arsenic on disease development is estimating exposure, and chronic sources of exposure may be more relevant than recent, high levels of exposure. Additional investigations are needed to establish the relationship, if any, between arsenic and type 2 diabetes [16, 17].

Fetal Overnutrition

Several reports (recently summarized in Dabelea D. et al., Diabetes in America) have convincingly shown that exposure to maternal diabetes in utero is a significant risk factor for obesity, impaired glucose tolerance, and type 2 diabetes later in life [18•]. Of note, work by the SEARCH case-control study provided novel evidence that intrauterine exposure to maternal diabetes and obesity are each important determinants of type 2 diabetes in 10–19-year-old multi/ethnic youth. In this study, exposure to maternal gestational diabetes mellitus (OR 5.7; 95% CI: 2.4, 13.4) and exposure to maternal pre-pregnancy obesity (OR 2.8; 95% CI: 1.5, 5.2) were independently associated with type 2 diabetes in the offspring. Combined exposure to maternal diabetes and obesity in utero accounted for 47% of the type 2 diabetes risk in this population [19].

Breastfeeding

In observational studies, breastfeeding is protective against later development of obesity and type 2 diabetes [18•]. In the SEARCH case-control study, the prevalence of breastfeeding (any duration) was lower among youth with type 2 diabetes than among controls and, thus,

breastfeeding was associated with significantly lower odds of type 2 diabetes (OR 0.26; 95% CI: 0.15, 0.46) [10•]. Thus, for offspring of pregnancies that carry a high risk for future obesity, early infant diet may represent an opportunity to mitigate risk.

Disease Management

Pediatric to Adult Transition

A challenge in many chronic diseases with youth onset is the continuation of disease management through the transition from pediatric to adult care providers [20]. Indicators of disease management through this transition, as evidenced by glycemic control (HbA1c ≥ 75 mmol/mol [9.0%]), were examined in SEARCH in 182 young adults with type 2 diabetes who were initially receiving care through a pediatric provider, who reached age 18–25 while enrolled in SEARCH, and who had at least one follow-up in SEARCH after reaching age 18. In the participants included in analyses, 57% reported transferring to an adult care provider, 15% reported no care, and 28% reported still receiving care from their pediatric provider. Lack of insurance was associated with having no designated health-care provider. Adjusting for disease duration, age at diagnosis, sex, race/ethnicity, and HbA1c at baseline, provider type at follow-up was strongly associated with poor glycemic control, with transition to an adult care provider associated with a 350% increase in odds of poor glycemic control at the follow-up study visit as compared to having continued care with a pediatric care provider (aOR 4.5; 95% CI: 1.8, 11.2). Similarly, no care was associated with increased risk of poor glycemic control (aOR 4.6; 95% CI: 1.4, 14.6) [21].

Psychosocial Factors

Psychosocial factors are well-known to be associated with increased risk of poor disease management in type 1 diabetes, but less is known about type 2 diabetes [22]. Symptoms of depression and health-related quality of life markers are collected at SEARCH study visits using the Center for Epidemiologic Studies Depression (CES-D) scale [23] and the Pediatric Quality of Life Inventory (PedsQL) generic and diabetes modules [24]. Using data collected from these assessments and routinely collected data on glycemic control, SEARCH evaluated the association between psychosocial factors early in disease development in relation to glycemic control over time. This study identified lower quality of life scores and more indications of depressive symptoms across time points in participants with type 2 diabetes, as compared to those with type 1 diabetes, and an association between declining diabetes-specific quality of life scores and HbA1c [25]. A recent study of risk factors for health-related quality of life suggested a positive association between female gender and BMI and lower health-related quality of life in type 2 diabetes [26].

Complications and Comorbidities

The longitudinal cohort component of the SEARCH study is particularly well-suited for study of diabetes-associated complications and comorbidities. Participants are invited to participate in on-line questionnaires, but also in-person visits from which detailed assessments are conducted to ascertain the presence of clinical and subclinical indicators of disease. In-person visit assessments include evaluation for early signs of disease-associated

complications (diabetic retinopathy, peripheral neuropathy, cardiac autonomic neuropathy, and diabetic nephropathy) and comorbidities (arterial stiffness, hypertension). Blood samples are collected and biobanked for future use [4•].

The presence of complications and comorbidities in diabetes has been well-described in adult populations, and through SEARCH it is being demonstrated that these complications and comorbidities may initiate early in the disease process. Risk of complications and comorbidities may be particularly high for youth diagnosed with type 2 diabetes. In a SEARCH study comparing the prevalence of early complications and comorbidities in type 2 diabetes and type 1 diabetes at age 21, type 2 diabetes was associated with a significantly higher prevalence of diabetic nephropathy, retinopathy, peripheral neuropathy, arterial stiffness, and hypertension. Overall prevalence of cardiac autonomic neuropathy was not different between type 1 and type 2 diabetes; although among non-Hispanic whites, a difference was observed [27••]. A summary of the prevalence of comorbidities and complications at age 21 for type 2 diabetes is described in Fig. 1 ($n = 272$). In addition, this study also examined longitudinally measured risk factors for comorbidities and complications: HbA1c, BMI, waist-height ratio, and mean arterial pressure (MAP). This increased risk of microvascular complications persisted despite adjustment for HbA1c, BMI, waist-height ratio, and MAP. For arterial stiffness and hypertension, obesity-related risk factors accounted for the differences observed by diabetes type [27••].

Diabetic Ketoacidosis at Diagnosis

At the time that cases are registered in the SEARCH registry, core data elements are abstracted from each registered case's medical record, including presence of diabetic ketoacidosis (DKA) at diagnosis. DKA is indicated when, in the presence of hypoglycemia, blood bicarbonate levels are < 15 mmol/L, and/or pH is < 7.25 (venous) or < 7.30 (capillary), and/or DKA is indicated in the medical record [28]. Among those with type 2 diabetes, there was a decrease in the proportion of participants with DKA at diagnosis from 11.7% (95% CI: 8.2, 15.2%) in 2002–2003 to 5.7% (95% CI: 4.1, 7.4%) in 2008–2010. DKA at diagnosis was more prevalent among younger age groups, males, and in minority race/ethnicity groups [29].

Other Disease-Associated Markers for Risk

Albuminuria—Albuminuria in long-standing diabetes is a biomarker for increased risk of developing diabetic kidney disease [30]. Albuminuria occurs more commonly in type 2 diabetes, as compared to type 1, and this difference has been suggested to be independent of differences in body mass index and hypertension [31]. One possible factor contributing to this observed difference could be severity of insulin resistance. In a recently published study, SEARCH examined insulin resistance in relation to urinary albumin to creatinine ratio (UACR) in both type 1 and type 2 diabetes. This study indicated that there was an inverse association between insulin resistance and UACR in type 2 diabetes only and that below an insulin sensitivity index of 4.7, the relationship was stronger, suggesting a possible threshold effect [32].

Cardiovascular Disease Risk Factors—Adults with type 2 diabetes are at increased risk for developing cardiovascular disease as a macrovascular complication of disease. Youth-onset development of type 2 diabetes portends longer duration of disease and thus, increased potential for disease-associated complications. Assessment of the presence of cardiovascular disease risk factors provides an opportunity to identify opportunities for mitigation of risk. Familial clustering of risk factors for cardiovascular disease is well-established. While this may be partially explained by shared environmental factors, underlying genetic factors also likely contribute. SEARCH investigated the association between parental diabetes mellitus and the presence of cardiovascular disease risk factors in participants with type 2 diabetes (n = 382 in primary analyses). This study suggested higher levels of cardiovascular disease risk factors, particularly among non-Hispanic whites. Specifically non-Hispanic white SEARCH participants with parent diabetes mellitus, compared to those without parental diabetes, exhibited a higher adjusted mean HbA1c, diastolic blood pressure, and triglyceride level (log transformed). Overall, for all racial and ethnic groups combined, higher UACR levels were observed for participants with parental history of diabetes mellitus [33].

Television watching and computer use is associated with a more sedentary lifestyle and may increase risk of developing cardiovascular disease risk factors in individuals already at risk of developing these risk factors. Longitudinal patterns of self-reported television watching and computer use were evaluated in association with HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (log transformed) and increased television watching over time was associated with higher increases in HbA1c in participants with type 2 diabetes [34].

Future Directions

Much works lies ahead in understanding risk factors for complications and comorbidities. This work is essential to identifying opportunities for mitigating risk. On-going studies in SEARCH are working towards unraveling genetic and epigenetic factors in disease complications risk. We have only begun to understand the role of environmental exposures and increased risk, but several studies are on-going and will add to our understanding of how these factors may contribute. As the SEARCH cohort continues to age, SEARCH is also well-positioned to begin addressing questions regarding reproductive health, pregnancy in the setting of diabetes, and impact of diabetes on future offspring.

Conclusions

Through the SEARCH study, we have begun to address many of the salient questions regarding type 2 diabetes in youth, including understanding of disease incidence, prevalence, and temporal patterns in incidence over time. We have also begun to appreciate the high prevalence of complications and comorbidities experienced in youth-onset type 2 diabetes. As the study population continues to mature, new opportunities emerge for building our understanding of this highly complex disease. This knowledge will guide strategies for disease prevention and mitigation, including resource allocation, programmatic and policy decision-making, and interventional approaches.

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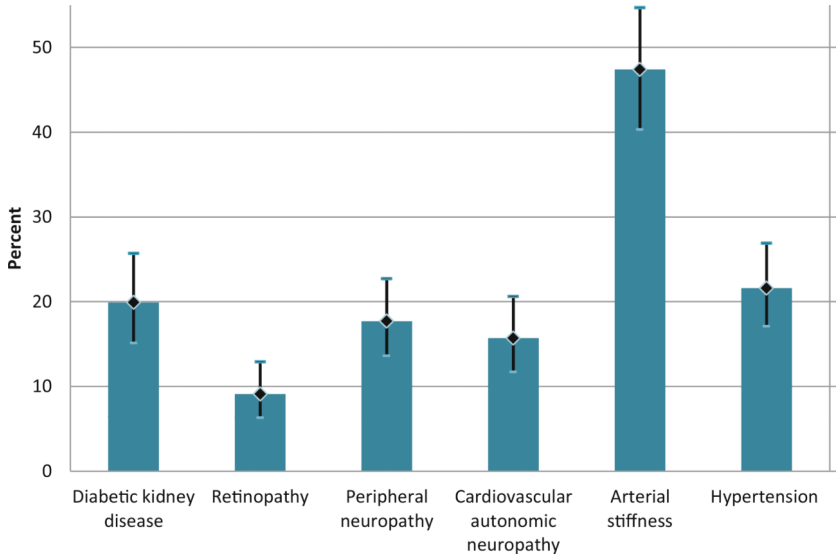

Fig. 1.

Estimated prevalence of complications and comorbidities in type 2 diabetes at age 21 in SEARCH

Table 1

Estimated cases of type 2 diabetes by age and race/ethnicity in the U.S. in 2009

Age(years)	Non-Hispanic White(*n*)	Black(*n*)	Hispanic(*n*)	Asian/Pacific Islander (*n*)	American Indian(*n*)
0–4	0	0	0	0	0
5–9	85	232	125	49	1
10–14	1152	1542	1733	205	97
15–19	3187	5585	5289	506	438
Total	4364	7152	7427	779	540

Table 2

Estimated cases and incidence of type 2 diabetes by age, sex, and race/ethnicity in the U.S. in 2012

Demographic feature	Cases (*n*)*	Incidence(cases/100,000/year)
Age at diagnosis (years)		
10–14	154.0	12.1
15–19	167.5	12.9
Sex		
Girls	203.5	16.2
Boys	118.0	9.0
Race or ethnic group		
Non-Hispanic White	56.1	3.9
Non-Hispanic Black	118.8	32.6
Hispanic	98.6	18.2
Asian/Pacific Islander	19.1	12.2
American Indian	28.8	46.5

*Counts represent a 2-year moving average of the number of cases for 2011–2012