

Type 1 Diabetes in Immigrant and Nonimmigrant Black Youth

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Abstract

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Type 1 diabetes (T1D) affects nearly 500,000 children globally and the incidence for T1D has been rising steadily at a rate of 3% a year for the last few decades. While the causes of T1D are thought to include both genetic and environmental factors, the exact mechanisms remain elusive. Differences in both prevalence rates and health outcomes related to T1D have been reported between populations from different races and groups of mixed immigrants and native populations. However, it is not known whether T1D-related differences exist between two populations within the same race classification. This dissertation explores whether T1D-related differences exist between East African immigrant and nonimmigrant Black youth in the Seattle area through three separate papers.

The first paper explores genetic and autoimmune biomarkers involved in diabetes affecting pediatric populations. Specifically, this paper examines the role of

autoimmune biomarkers in the diagnosis of T1D. A search of PubMed identified reviews that were published from 2008-2011 and included the topics of etiology, epidemiology, genetics, epigenetics, pathogenesis and/or immunology related to diabetes in youth. A total of 19 reviews were included in this clinical update.

The second paper summarizes a retrospective descriptive study that compares demographic and clinical characteristics of immigrant and nonimmigrant youth at the time of T1D diagnosis. All Black youth diagnosed with T1D and treated at Seattle Children's Hospital (SCH) from 1/1/2000 to 7/31/2011 were identified using primary and secondary ICD-9 codes. Demographic and clinical data were obtained from existing electronic medical records. Additional data were obtained from the United States Census Bureau for use in estimating T1D prevalence rates. Results from the study revealed that T1D prevalence rates in King County, Washington were nearly 4 times higher for immigrant Black youth than nonimmigrant Black youth (6.76/1,000 vs. 1.74/1,000). Immigrant youth had a slightly lower mean age of T1D onset diagnosis (7.63, *SD* 4.42 vs. 8.29, *SD* 3.50), were more likely to have subsidized health insurance (75.0% vs. 58.5%), and almost twice as likely to have a family history of T1D (13.3% vs. 7.5%) compared to nonimmigrant Black youth. Immigrant Black youth also tested positive less frequently for T1D-related autoimmune biomarkers and if diabetic ketoacidosis (DKA) was present at diagnosis, immigrant youth were more likely to be in severe DKA. Both groups were approximately 60%

female, in contrast to much of the literature which suggests that T1D affects both genders equally.

The third paper compared glycemic control (measured by hemoglobin A1c [HbA1c]) at 12, 24, and 36 months after T1D diagnosis in immigrant and nonimmigrant Black youth. Case ascertainment and data collection utilized existing electronic medical records as described in the second paper. HbA1c levels were obtained from the clinic visit most closely corresponding to each time point. Immigrant youth had lower mean HbA1c s at each time point. Analyses of variance indicated that the effect of ethnicity (immigrant vs. nonimmigrant) on glycemic control approached statistical significance at the 36 month time point and when comparing the extreme time points (12 and 36 months).

Results from these papers suggest that there are several clinically significant differences between two pediatric populations diagnosed with T1D within the same race classification and in particular, East African immigrants may be at greater risk for developing T1D. Nurses and other diabetes care providers should be aware that T1D affects populations differently and use this knowledge to educate and advocate for diabetes patients and their families.

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I also wish to thank my many friends who are our family. Their ability to help me find humor in the mundane, share in the painful, and delight in the beautiful keep me fulfilled. My gratitude for their support of my daughter and my wife during this challenging period of life cannot be overstated.

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DEDICATION

This dissertation is dedicated in loving memory of
my mom, Maria Calette Willoughby, and to my beautiful daughter Elle Avery
Cooper-O'Connor, who missed each other in this world by three months during this
work.

CHAPTER ONE

INTRODUCTION

Miles upon miles of shantytowns. Forty percent unemployment and a seventy percent illiteracy rate. No running water or health care and little food. This is what I saw upon my arrival in South Africa in 1999. I was immediately overwhelmed and felt paralyzed by the enormity of the situation. Then one day, through meeting people and becoming involved with the local community, I realized that the people of South Africa are survivors, not the victims we might imagine them to be. I tell this story because it was at this point in my life that I realized how I wanted to spend my career—working with vulnerable populations. I initially sought a path towards providing clinical care to pediatric patients and their families, and while I was exceptionally passionate about this work, there was something missing. Shortly after I began working at Seattle Children’s Hospital, I came to realize that generating new knowledge through clinical research with vulnerable populations was the right fit for both my personality and goals.

In January of 2008, I started in my role as a diabetes research nurse coordinator and almost immediately noticed that there was a significant number of East African immigrant youth being treated for the autoimmune disease type 1 diabetes (T1D). I thought this was highly unusual given my understanding that T1D largely affects non-Hispanic White youth in northern climates. I discussed this observation with several diabetes care providers who were aware of this population, but had not considered

examining this phenomenon further. This was a serendipitous moment in my life because as a result of my time spent in South African 14 years ago, I was perfectly poised to enter a new clinical setting and make this observation almost immediately. My desire to explore whether T1D was affecting East African immigrant youth differently than other pediatric populations led to my pursuit of a PhD in Nursing Science.

T1D presents a significant burden on the health of those it affects and the number of youth affected by the disease is growing. Globally, nearly 500,000 children are affected with T1D and incidence rates have been increasing at 3% per year in countries with both high and low T1D prevalence (International Diabetes Federation (IDF), 2012). Diabetes causes significant medical complications and life-long health-related costs. By age 20, 40-60% of people with diabetes have some evidence of retinopathy and life expectancy may be reduced by up to 27 years (Centers for Disease Control and Prevention (CDC), 2010); Mayer-Davis, et al., 2009). Children are even more sensitive than adults to a lack of insulin and face greater challenges for optimal insulin replacement, which can lead to poor growth, neurological impairment, and excess mortality from diabetic ketoacidosis (DKA) (Juvenile Diabetes Research Foundation, (JDRF), 2012).

The etiology of T1D is widely accepted to include both genetic and environmental factors, but the exact mechanisms remain elusive and much variation exists in T1D incidence rates between and even within countries and by race (Karvonen, Viik-Kajander, Moltchanova, Libman, LaPorte, & Tuomilehto, 2000;

Onkamo, Vaananen, Karvonen, & Tuomilehto, 1999). In the United States (U.S.), the incidence rates of T1D are higher in non-Hispanic White youth than in African-American youth (Bell, et al., 2009; Mayer-Davis, et al., 2009). Furthermore, differences in glycemic control, diabetes complications, and mortality based on race have been reported (Delamater, et al., 1999; Lipman, et al., 2006). Mean hemoglobin A1c levels (HbA1c), the gold standard for measurement of glycemic control and a crucial indicator of risk for diabetes-related complications, differed between African-American youth and non-Hispanic white youth with T1D ($9.1\% \pm 0.1$ versus $8.3\% \pm 0.1$, $p < 0.001$; normal levels are $< 6.5\%$) (Kamps, Hempe, & Chalew, 2010). African-American youth aged 0-9 years diagnosed with T1D have been reported to have higher rates of DKA at diagnosis compared to non-Hispanic white youth (30.8% vs. 23.4%) (Bell, et al., 2009; Mayer-Davis, et al., 2009).

While differences in T1D rates and outcomes between races have been described, less is known about differences among two ethnic groups within a single race classification such as 'black/African-American'. U.S. -based organizations receiving federal funds must define race according to census groupings and ethnicity as Hispanic/Latino or not Hispanic/Latino (Institute of Medicine (IOM), 2009). An Institute of Medicine (IOM) report states that current race and ethnicity classifications are insufficient to identify health disparities (IOM, 2009).

Pilot data obtained in the first year of my doctoral studies revealed that differences may also exist based on additional ethnic characteristics, such as immigrant status and/or country of origin (O'Connor, et al., 2010). The data, which

compared East African immigrant and matched non-Hispanic white youth with T1D, suggest that East African immigrant youth in Seattle, Washington have two and a half times the prevalence rate of type 1 diabetes T1D as would be expected, East African females are disproportionately affected by the disease, and differences in diabetes autoantibodies (DAAs) detected at diagnosis also exist (O'Connor, et al., 2010).

Given that in 2011 the US had one of the highest incidence rates of T1D in youth 0-14 years (23.7/100,000) and countries in Africa had some of the lowest rates (0.3/100,000 in Ethiopia), this trend should be explored further to better understand T1D in this vulnerable population (IDF, 2012). The aim of this dissertation research was to explore whether T1D-related differences exist based on ethnic categories such as immigrant status and country of origin.

The first paper explores the role of genetic and autoimmune biomarkers involved in pediatric diabetes. The second paper considers T1D in two different populations within the same race classification (immigrant and nonimmigrant black youth) by (a) describing and comparing demographic and clinical characteristics of U.S. immigrant and nonimmigrant Black youth with T1D at time of diagnosis, (b) estimating the prevalence of T1D among these two populations in King County, Washington. Finally, the third paper compares glycemic control as measured by HbA1c levels at 12, 24 and 36 months after T1D diagnosis.

CHAPTER TWO
CLINICAL UPDATE ON GENETIC AND AUTOIMMUNE BIOMARKERS IN
PEDIATRIC DIABETES

Abstract

Purpose: The purpose of this clinical update is to review the etiology of diabetes types affecting youth under 20 and describe diabetes-related genetic and autoimmune biomarkers based on the most recent literature. This information will support diabetes care providers' efforts to better explain the complex topic to patients and families.

Methods: A PubMed search identified 396 reviews published from 2008-2011 that included the topics of etiology, epidemiology, genetics/epigenetics, pathogenesis or immunology related to diabetes in youth. Nineteen reviews were included in the current clinical update.

Results: The majority of youth under 20 years with diabetes have type 1 diabetes. Other forms of the disease affecting this population include type 2, monogenic, and secondary diabetes. Genetic and autoimmune biomarkers can help determine the risk and diagnosis of both type 1 and monogenic diabetes. An accurate diagnosis of diabetes type, allows for determination of optimal treatment options.

Conclusion: The complexity of determining etiology, risk, diagnosis and treatment, is increasing with the rate of genetic and immunologic advances related to diabetes in youth. Diabetes care providers must be able to explain to patients and families the complex genetic and autoimmune biomarkers used in determining the risk of diabetes, diagnosis of the disease and identification of treatment options.

Background

More than 150,000 youth in the United States below the age of 20 have been diagnosed with diabetes which may reduce their life expectancy by up to 27 years (Liese, et al., 2006; Mayer-Davis, et al., 2009). While the vast majority of youth (85%) have type 1 diabetes (T1D), several other forms of diabetes occur in this population, including type 2 (T2D), monogenic, and secondary diabetes (Liese, et al., 2006). Due to the variable etiology of secondary diabetes, which is specific to either the primary disease process (endocrinopathies involved in cystic fibrosis, Down's syndrome, etc.) or treatment-related (drug-induced glucose intolerance from glucocorticoids, certain chemotherapy agents, etc.), an in-depth discussion of these forms of diabetes it is beyond the scope of this clinical update (Margulies, Ergun-Longmire, Ten, & Maclaren, 2010).

An accurate diagnosis of diabetes type in youth is critical to determine the best course of treatment; however, determining diagnosis (as well as establishing the risk of developing each type) can be complex. Biomarkers are used to determine disease risk, diagnose diabetes type and ultimately the appropriate treatment for youth with

diabetes. For example, single gene mutations can identify monogenic diabetes or help determine the risk of developing T1D through identification of specific genetic alleles (or different versions of a single gene) that put individuals at risk for or protect them from T1D (Bonifacio & Ziegler, 2010; Owen, Skupien, & Malecki, 2009). Similarly, autoimmune biomarkers play a role in diagnosing and determining the risk for developing T1D. If T1D-related auto-antibodies (markers of autoimmune activity) are present in serum tests, a confirmation of T1D can be made (American Diabetes Association [ADA], 1997; DeFronzo & Reasner, 2010). The presence of T1D auto-antibodies in the serum of individuals without the disease also indicates an increased risk for developing T1D (Bingley, 2010).

The purpose of this clinical update is to review the etiology of diabetes types affecting youth under 20 and describe diabetes-related genetic/genomic and autoimmune biomarkers based on the most recent literature. This information will support nurses, educators and other diabetes care providers' efforts to better explain the complex topic to patients and families. As our knowledge of rarer forms of diabetes that affect children and adolescents grows, so does the complexity involved in determining the risk of developing, diagnosing and treating the disease. By synthesizing and summarizing that latest information in the literature, this article seeks to provide clear and concise knowledge of diabetes-related biomarkers and provide resources to find additional information for those providing care to patients with diabetes and their families.

Methods

A search of PubMed incorporated reviews published from 2008-2011 that included the topics of etiology, epidemiology, genetics, epigenetics, pathogenesis and/or immunology related to diabetes in youth. Keywords used in the search included diabetes, type 1 diabetes, youth, genetics, immunology, and biomarkers and results were limited to reviews, human studies and English language. Reviews were excluded if the article did not have diabetes as a major focus, included case-studies, or were not related to diabetes risk, diagnosis, treatment or outcomes (i.e. discussion of specific single nucleotide polymorphisms (SNPs)). A total of 396 reviews were initially identified and 19 reviews meeting inclusion criteria were included in this clinical update.

Results

Overview of Diabetes Typology Affecting Youth

Diabetes etiology affecting youth can be divided into two broad categories: 1) Polygenic disease that results in a T1D or T2D phenotype, or 2) Monogenic disease that can result in either permanent or transient neonatal diabetes (PNDM/TNDM) or maturity onset diabetes of youth (MODY) that includes six subtypes (see Table 2.1) (Rubio-Cabezas & Argente, 2008). In the United States, T1D comprises 85% of diabetes cases in youth under 20 years of age, T2D accounts for approximately 12% of cases, and monogenic diabetes accounts for 1-3% of cases (Hattersley, Bruining, Shield, Njolstad, & Donaghue, 2009; Liese, et al., 2006). Reviewing the etiology of

each type with patients and families can help clarify differences in diabetes typology and various treatment options available for each type.

Type 1 Diabetes Etiology

The incidence rate of T1D in youth has been consistently increasing by nearly 3% per year globally over the last 20 years (Whittmore, Jaser, Guo & Grey, 2010). Genomic factors involved in the development of T1D are well established, but this relatively rapid increase in disease incidence also points to environmental components of disease etiology. The etiology of T1D is a complex process involving chronic, progressive T-cell mediated autoimmune destruction of β cells in the pancreas over months or years prior to diagnosis (Bluestone, Herold, & Eisenbarth, 2010; Taplin & Barker, 2008).

The disease model for T1D suggests that a susceptible individual has a genetic predisposition for developing the disease, which is compounded by an environmental trigger or modifier (Atkinson & Eisenbarth, 2001). This trigger then initiates an autoimmune response in the pancreas and ultimately leads to symptomatology and diagnosis of T1D (Atkinson & Eisenbarth, 2001). Autoimmune activity prior to the onset of T1D diagnosis begins with the infiltration of insulin-producing β cells in the pancreas by macrophages, dendritic cells and T cells (CD4 & CD8) (Taplin & Barker, 2008). Specific environmental triggers or modifiers remain elusive, but potential candidates include viral infections (i.e. coxsackie B4 or B5), vitamin D deficiency, a reduction of exposure to microbes in developed nations (the 'hygiene hypothesis') or early introduction of dietary components such as bovine milk protein (Bluestone, et

Table 2.1
Overview of Diabetes in Youth

	T1D	T2D	Monogenic
Frequency of cases in children & adolescents	85%	12%	1-3%
Age of onset	6 months-early adulthood	Pubertal/post-pubertal (age of onset is slowly decreasing)	<u>PNDM</u> 0-6 months <u>TNDM</u> : 0-7 days; <u>MODY</u> : 0-post-pubertal
Type of onset	Acute	Varies from insidious to acute	Varies from insidious to acute
Genetic etiology	Polygenic	Polygenic	Monogenic
Parent with diabetes	2-4%	80%	90%
Auto-immune mediated	Yes	No	No
Ketosis prone	Frequent	Rare	<u>MODY</u> : rare <u>PNDM/TNDM</u> : present
Obesity present	Varies	Yes	Varies
Acanthosis nigricans present	No	Yes	No
Treatment regimen	Insulin	ODM +/- insulin	<u>PNDM</u> due to KCNJ11/ABCC8 mutation: ODM <u>PNDM</u> due to INS mutation: insulin <u>TNDM</u> -initially insulin, then no tx until relapse (ODM +/- insulin) <u>MODY1/3</u> : ODM <u>MODY2</u> : no tx-ODM (+/- insulin during pregnancy) <u>MODY 4/6</u> : no tx-ODM <u>MODY 5</u> : usually insulin

Note. T1D = type 1 diabetes; T2D = type 2 diabetes; MODY = maturity-onset diabetes of youth; TNDM = transient neonatal diabetes mellitus; PNDM = permanent neonatal diabetes mellitus; ODM = other diabetes medications (all except insulin); tx = treatment. Adapted from “Current Insights Into the Genetic Basis of Diabetes Mellitus in Children and Adolescents,” by Rubio-Cabezas, O., & Argente, J., 2008, *Journal of Pediatric Endocrinology and Metabolism*, 21(10), p. 944. Copyright 2008 by Freund Publishing House Ltd.

al., 2010; Eizirik, Collie, & Ortis, 2009; Maahs, West, Lawrence, & Mayer-Davis, 2010; Margulies et al., 2010). Exposure to such triggers is thought to speed the autoimmune activity and lead to complete and irreversible β cell destruction over time (Atkinson & Eisenbarth, 2001). Symptoms of T1D emerge when $>80\%$ of the β cell function is irreversibly lost (Margulies et al., 2010). As a result of this destruction, patients with T1D must rely on exogenous insulin for blood glucose management for the rest of their life.

Type 2 Diabetes Etiology

T2D etiology is also understood to be a combination of genomic and environmental factors that result in both insulin resistance and inadequate insulin secretion (DeFronzo & Reasner, 2010). Over time, T2D may progress to complete β cell dysfunction and ultimately insulin deficiency. Environmental factors contributing to the development of T2D include a high-calorie diet, lack of sufficient exercise and obesity (Khardori, Bessen, Buehler, Schraga, & Torkamani, n.d.). There is also strong evidence to suggest genomic involvement in the development of T2D, as evidenced by a higher prevalence of T2D in certain minority groups (Hispanic, Native American, African American, Asian American, Hawaiian/Pacific Islander) and correlation with a family history of T2D (Khardori et al., n.d.) . However, the specific mechanisms involved in the genomic predisposition related to the development of T2D remain unclear (Lyssenko & Groop, 2009). T2D may be treated with a combination of behavior modifications to diet and exercise, medications such as insulin

secretagogues, meglinitides, biguanides, PPAR- γ agonists and α -glucosidase inhibitors, or may ultimately require exogenous insulin therapy (Ergun-Longmire, Margulies, Ten, & Maclaren, 2010). While autoimmune and genomic biomarkers associated with T1D and monogenic diabetes are widely used in research and clinical care, this is not the case with T2D as this is an ongoing area of study. Due to the limited knowledge in this area, T2D-related biomarkers will not be considered further.

Monogenic Diabetes Etiology

Monogenic diabetes etiology is a result of a single gene mutation at different allelic loci and does not involve an environmental component in disease formation as seen in polygenic forms. Monogenic subtypes are relatively rare and include neonatal diabetes that is either permanent or transient (PNDM/TNDM) and MODY (Rubio-Cabezas & Argente, 2008). It is crucial to correctly identify this type of diabetes because treatment regimens, along with age of onset and clinical characteristics, vary depending on the specific type of genetic mutation involved (Hattersley, et al., 2009; Malecki & Mlynarski, 2008).

The above definitions of diabetes affecting youth are based on the unique etiology of each type. Highlighting the distinction between each disease process sets the stage for clinicians to understand the role of biomarkers in determining the risk, diagnosis and treatment of diabetes in youth.

Genetic/Genomic Biomarkers in Diabetes Affecting Youth

Biomarkers are naturally occurring molecules (i.e. blood glucose, genes) or other biological characteristics (i.e. blood pressure) that can be objectively measured and are associated with either normal physiologic processes, pathological or disease processes, or responses to treatment interventions ("Biomarkers and surrogate endpoints: preferred definitions and conceptual framework," 2001). T1D associated biomarkers include both genomic and autoimmune markers, while known biomarkers associated with monogenic diabetes are solely genetic. The genomic biomarkers implicated in the development of T1D include multiple genes, with nearly 50% of disease risk linked to the human leukocyte antigen (HLA) genes (see Table 2.2) (Morran, Omenn, & Pietropaolo, 2008) Ninety percent of patients diagnosed with T1D have high-risk alleles of the *HLA-DR* and *HLA-DQ* genes located in the Major Histocompatibility Complex (MHC) on chromosome 6p21.3 (see Figure 2.1) (Concannon, Rich, & Nepom, 2009).

The MHC is a highly variable, large genetic region that plays a major role in autoimmune processes, infections, inflammatory diseases and response to transplantation (Fernando, et al., 2008; Ounissi-Benkalha & Polychronakos, 2008). MHC has 3 subregions: 1. HLA class I (subtypes A, B, and C) genes encode for molecules located on the surface of all nucleated cells and their role is to present intracellular antigens to CD8 T cells; 2. HLA class II (subtypes DP, DR, and DQ) genes encode for molecules found on the surface of all antigen-presenting cells

Table 2.2
Major Genes That Confer Risk for Diabetes in Youth

Gene Symbol	Full Gene Name	Gene Location	Diabetes Association	Proposed/Known Diabetes-Related Mechanism of Action
ABCC8 (aka SUR1)	ATP-binding cassette, subfamily C (CFTR/MRP), member 8	11p15.1	PNDM, TNDM, T2D	Modulator of potassium channels & insulin release
FOXP3	Forkhead box P3	Xp11.23	PNDM	Regulator of transcription (forkhead/winged family)
GCK (aka MODY2)	Glucokinase	7p15.3-15.1	MODY2, PNDM	Produces glucose-6-phosphate (usually 1 st step in glucose metabolism pathway)
GLIS3	GLIS family zinc finger 3	9p24.2	PNDM	Activator and repressor of transcription; involved in development of pancreatic β cells
HLA-DQB1 (aka HLA-DQ8)	Major histocompatibility complex, class II, DQ beta 1	6p21.3	T1D	Determines extracellular peptide binding specificities on antigen-presenting cells
HLA-DRB3 (aka HLA-DR3)	Major histocompatibility complex, class II, DR beta 3	6p21.3	T1D	Determines extracellular peptide binding specificities on antigen-presenting cells
HLA-DRB4	Major histocompatibility complex, class II, DR beta 4	6p21.3	T1D	Determines extracellular peptide binding specificities on antigen-presenting cells
HNF1A (aka MODY3)	HNF1 homeobox A	12q24.2	MODY3	Transcription factor involved in liver-specific gene expression
HNF1B (aka MODY5)	HNF1 homeobox B	17cen-q21.3	MODY5	Regulates development of embryonic pancreas
HNF4A (aka MODY1)	Hepatocyte nuclear factor 4	20q13.12	MODY1	Controls gene expression in liver; may play a role in liver development
HYMAI	Hydatidiform mole associated and imprinted	6q24.3	TNDM	Non-protein coding, causative of TNDM; expressed only from paternal allele
IL2RA	Interleukin 2 receptor, alpha	10p15-p14	T1D	Encodes IL2 membrane protein; expression essential in T-cell suppression
INS	Insulin	11p15.5	PNDM, T1D	Binds to insulin receptor to stimulate uptake of glucose
KCNJ11 (aka Kir6.2)	Potassium inwardly-rectifying channel, subfamily J, member 11	11p15.1	PNDM, TNDM, T2D	Regulates potassium flow into cells; associated with the sulfonylurea receptor (SUR)
NEUROD1 (aka MODY6)	Neurogenic differentiation 1	2q32	MODY6, T2D	Regulates expression of INS gene
PDX1 (aka IPF1, MODY4)	Pancreatic and duodenal homeobox 1	13q12.1	MODY4, PNDM	Activates INS, GCK genes; involved in pancreatic development; involved in glucose-dependent regulation of INS gene

PLAGL1 (aka ZAC)	Pleiomorphic adenoma gene-like 1	6q24	TNDM	Encodes C2H2 zinc finger protein involved in transactivation and DNA- binding; over expression in fetal development leads to TNDM; preferential expression of paternal allele
PTPN22	Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	1p13.2	T1D	May be involved in regulating protein (CBL) function in T-cell receptor pathway
TCF7L2	Transcription factor 7-like 2	10q25.3	T2D	Involved in blood glucose homeostasis

Note. PNDM = permanent neonatal diabetes mellitus; TNDM = transient neonatal diabetes mellitus; T2D = type 2 diabetes; MODY = maturity-onset diabetes of youth; T1D = type 1 diabetes (Morran, Omenn, & Pietropaolo, 2008; National Center for Biotechnology Information, 2011; Ounissi-Benkalha, & Polychronakos, 2008).

(dendritic cells, macrophages and T cells) and their role is to present extracellular antigens to CD4 T cells; 3. HLA class III encodes for various immune-related molecules (cytochrome 450 enzymes CYP21P and CYP21, cytokines such as TNF α and TNF β , and complement factors C4A, C4B, factor B and C2) (Morran, et al., 2008; Ounissi-Benkalha & Polychronakos, 2008). Within the MCH, the HLA class II haplotypes *DR3/4*, *DQ8* carry the highest genetic risk associated with the development of T1D (with an odds ratio of up to 49.2) (Ounissi-Benkalha & Polychronakos, 2008). Haplotype variants (closely related genetic alleles) on the same chromosome are generally inherited together; therefore, many individuals at risk for T1D inherit both the mutations in the HLA *DR3/4* and the *DQ8* alleles in the MCH region of chromosome 6 (King, Stansfield, & Mulligan, 2007). A recent meta-analysis of genome-wide association studies (GWAS) confirmed the strong association between the HLA region and T1D, and identified other non-HLA genes also thought to confer disease risk (Concannon, et al., 2009).

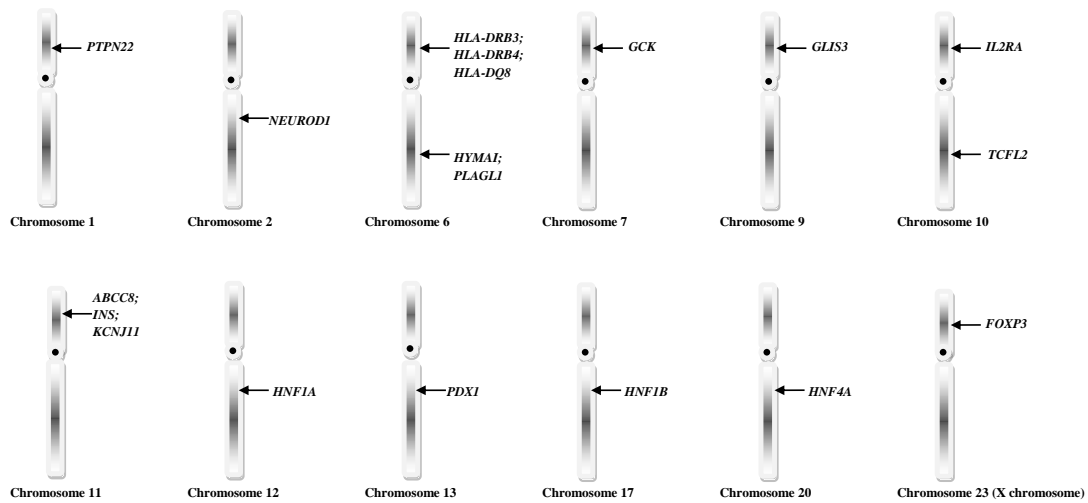


Figure 2.1. Diabetes-related gene locations (National Center for Biotechnology Information, 2011).

Current biomarkers associated with monogenic diabetes are the result of a variety of single gene mutations. PNDM is caused by single gene mutations in either the potassium channel regulators of β cells that affects the release of insulin (*KCNJ11* or *ABCC8* genes), a mutation in the *INS* gene itself that creates ineffective insulin molecules, or may rarely involve other genes (*GCK*, *PDX1*, *GLIS3* or *FOXP3*) (see Table 2.2 for additional information) (Greeley, et al., 2010; National Center for Biotechnology Information [NCBI], 2011; Rubio-Cabezas & Argente, 2008). TNDM involves different single mutations of either the *KCNJ11* or *ABCC8* gene resulting in abnormalities in the potassium channels of β cells or imprinting errors in the *PLAGL1* and *HYMAI* genes (Hattersley, et al., 2009). Up to 70% of TNDM results from imprinted *PLAGL1* and *HYMAI* genes in which only the paternal allele of the gene is expressed in offspring (Mitchell & Pollin, 2010). MODY subtypes are also caused by single gene mutations resulting in β cell transcription factor errors and are classified

according to the gene affected: MODY1 (*HNF4A* gene), MODY 2 (*GCK* gene), MODY 3 (*HNF1A* gene), MODY 4 (*PDX1* gene), MODY 5 (*HNF1B* gene) and MODY 6 (*NEURODI* gene) (Margulies et al., 2010; NCBI, 2011).

Many ethical issues arise when providing genetic results to youth and their families. While beyond the scope of this article, familiarization with the ethical considerations of providing genetic results is crucial for diabetes care providers. A general discussion of ethical issues related to genetic testing in children is provided by Ross and Moon (2000) and Gustafsson Stolt, Ludvigsson, Liss and Svensson (2003) address specific issues related to parents, children and T1D genetic testing.

Autoimmune Biomarkers in Diabetes Affecting Youth

Autoimmune biomarkers associated with the development of T1D are referred to as diabetes auto-antibodies (DAAs). DAAs are markers of autoimmune activity targeted against various parts of β cells or at insulin directly. Currently they are thought to be byproducts of autoimmune processes in the pancreas rather than a causative factor (Taplin & Barker, 2008). The first DAA identified was the islet cell antibody (ICA) in 1974 and while its specific target still remains unclear, it appears to be a variety of cytoplasmic and/or surface cell antigens (Taplin & Barker, 2008). Four other DAAs play a major role in T1D: glutamic acid decarboxylase 65 (GAD65), protein tyrosine phosphatase insulinoma antigen 2 antibody (IA-2, also called ICA512), insulin antibody (IAA), and zinc transporter 8 antibody (ZnT8) (see Table 2.3) (Bingley, 2010; Wenzlau, et al., 2007). Levels of DAAs fluctuate and their

presence can change over time (Bingley, 2010; Bonifacio & Ziegler, 2010). DAAs can be present by 12-24 months after birth, but progression to the diagnosis of T1D may take up to 25 years (Bingley, 2010; Bonifacio & Ziegler, 2010).

Table 2.3
Diabetes Auto-antibodies in Type 1 Diabetes

Diabetes Auto-Antibody	Sensitivity (%)	Comments
Insulin Autoantibody (IAA)	Up to 92%	Levels decrease with age
Glutamic Acid Decarboxylase (GAD)	84%	Higher sensitivity in adult onset T1D
Insulinoma antigen 2 (IA-2; aka ICA 512)	79%	Rare in <3 years of age, then levels increase
Zinc Transporter 8 (ZnT8)	63%	Positive in >25% of patients negative for IAA, GAD, IA-2; rare in <3 years of age, peak in adolescence

Note. Adapted from “Auto-antibodies in Type 1 Diabetes”, by Taplin, C.E., & Barker, J.M., 2008, *Autoimmunity*, 41, p. 13. Copyright 2008 by Taylor and Francis, Ltd.

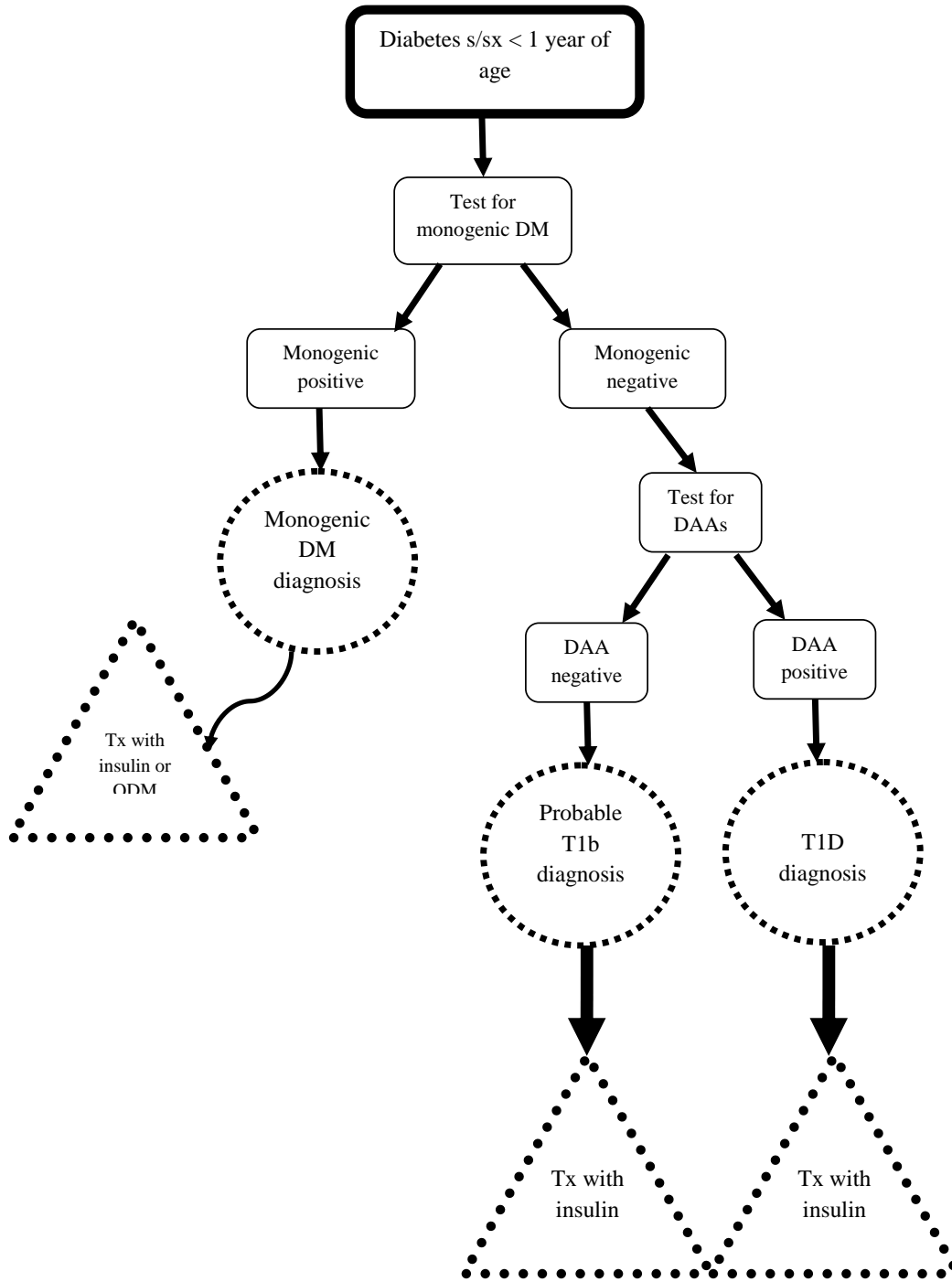
Biomarkers and the Diagnosis of Diabetes in Youth

Genetic biomarkers are used in the diagnosis of monogenic diabetes and autoimmune biomarkers are used in the diagnosis of T1D (see Figure 2.2). Healthcare providers may suspect a patient has a monogenic form of diabetes if one or more of the following are true:

1. The patient is diagnosed before 6 months of age,
2. A parent has monogenic diabetes,
3. Endogenous insulin and c-peptide levels are normal,
4. The patient is not positive for DAAs (see discussion below),

5. The patient does not have a high-risk HLA haplotype,
6. The patient is not obese and has no evidence of insulin resistance (i.e. acanthosis nigricans) (Rubio-Cabezas & Argente, 2008).

Genetic testing for monogenic diabetes has recently become widely available for clinical use in the United States and a current listing of laboratories that provide monogenic testing can be found through the National Center for Biotechnology Information (see resources section). For example, Seattle Children's Hospital provides MODY and neonatal diabetes sequencing panels for patients. The current cost is \$2,034 for the MODY panel and \$3,293 for the neonatal diabetes panel, which is covered by Medicaid and most private insurance companies with prior authorization. It is important to reiterate that an accurate diagnosis of monogenic diabetes is critical to select an appropriate treatment regimen. Patients with PNDM due to *KCNJ11* or *ABCC8* mutations may be effectively treated with oral sulfonylureas; however, mutations in the *INS* gene result in the destruction of β cells and will require life-long insulin treatment. Patients with TNDM may require insulin treatment upon initial diagnosis, but often their treatment can transition to lifestyle modifications and/or oral sulfonylureas (Rubio-Cabezas & Argente, 2008).



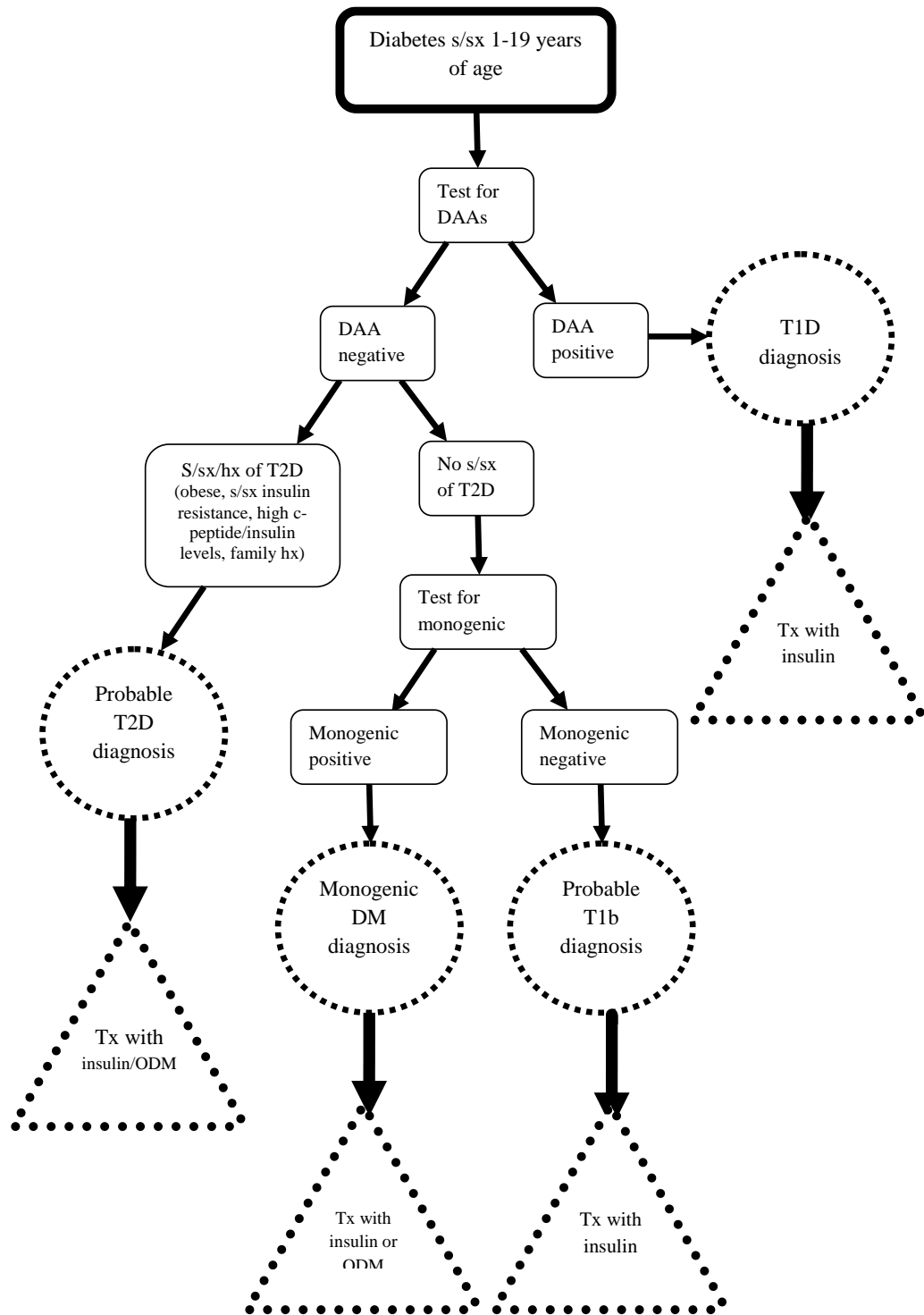


Figure 2.2. Diagnosis flow chart to determine diabetes type in youth. T1D = type 1 diabetes; T2D = type 2 diabetes; DM = diabetes mellitus; DAA = diabetes auto-antibodies; s/sx = signs/symptoms; hx = history; T1b = type 1 b diabetes (idiopathic); tx = treat; ODM = other diabetes medications (all except insulin).

Autoimmune biomarkers are widely used at the time of diagnosis to confirm the typology of T1D. When 4 DAAs are measured, 96-98% of T1D patients are positive for at least 1 DAA at diagnosis (Bingley, 2010; Taplin & Barker, 2008). T1D is by definition an autoimmune disease, so presence of DAAs confirms the diagnosis and excludes the diagnosis of monogenic or T2D (Atkinson & Eisenbarth, 2001). However, the absence of DAAs at diagnosis is not sufficient enough to rule out a diagnosis of T1D alone. A subtype within T1D is Type 1b diabetes (idiopathic autoimmune diabetes) in which patients have all the characteristics of T1D, but test negative for all currently known DAAs (Maahs, et al., 2010).

Biomarkers and Determining the Risk for Developing Diabetes in Youth

Genetic biomarkers can be used to determine the risk of an individual for developing either T1D or monogenic diabetes and autoimmune biomarkers can aid in determining the risk of developing T1D in relatives of individuals with T1D. The HLA class II haplotype *DR3/4-DQ8* is associated with the highest genetic risk of developing T1D, while other HLA class II haplotypes (*DR15-DQ6*, *DQB1*) are protective against the disease (Hewagama & Richardson, 2009; Morran, et al., 2008). Children and adolescents have an approximate risk of 6% of developing T1D by age 20 if a high-risk HLA haplotype is present, compared to 0.39% risk for the general population and 0.03% for those with a protective HLA haplotype based on studies in the United States and Europe (Bonifacio & Ziegler, 2010). However, genetic testing is not currently used clinically to assess T1D risk in individuals.

Similar to genetic biomarkers, autoimmune biomarkers play a role in determining disease risk in T1D. The total number of DAAs an individual without diabetes is positive for in serum blood tests is currently the most predictive measure of T1D risk, with greater risk correlating with a greater number of DAAs present (Bingley, 2010). Studies have found that first degree relatives of individuals with T1D who are positive for 3 or more DAAs have $\geq 50\%$ risk of developing the disease over 5 years (Bingley, 2010; Mahon, et al., 2009; Taplin & Barker, 2008). Serum blood tests for DAAs are currently only available to non-diabetic family members of individuals with T1D through ongoing research studies (see Diabetes TrialNet information at the end of this article).

Risk related to monogenic diabetes is largely determined by Mendelian inheritance patterns. The monogenic subtypes PNDM and TNDM may be caused by spontaneous mutations or by both autosomal recessive inheritance (25% chance offspring will be affected) and autosomal dominant inheritance (50% chance the offspring will be affected) (Rubio-Cabezas & Argente, 2008). The monogenic forms of MODY are autosomal dominant disorders and are passed on to offspring 50% of the time (Rubio-Cabezas & Argente, 2008).

Discussion

Implications for Nurses and Other Diabetes Care Providers

New knowledge in genetics/genomics and immunology is growing rapidly and challenges the ability of diabetes healthcare providers to integrate this knowledge into their daily practices (Jenkins, Bednash, & Malone, 2011). The speed and expanse of genetic/genomic knowledge development since completion of the Human Genome Project in 2003, including substantial developments such as the International HapMap Project (www.hapmap.org) and high through-put technologies that have enabled rapid growth of GWAS, underscores this challenge (Lea, Skirton, Read, & Williams, 2011). The American Nurses Association published “Essentials in Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators” in 2008, highlighting the importance of increasing genetic and genomic knowledge among nurses and other care providers in order to inform and support patients and families on the topic (American Nurses Association [ANA], 2008; Lea, et al., 2011).

An understanding of the genetic and autoimmune biomarkers involved in diabetes types affecting youth will enable nurses and other diabetes care providers to inform patients and families by: 1. Explaining diabetes etiology using various results from genetic and autoimmune biomarker tests to ultimately determine diabetes type; 2. Discussing the treatment implications of diabetes etiology; 3. Explaining an individual’s likelihood of developing T1D (and /or monogenic diabetes) by using genetic and autoimmune biomarkers as indicators, keeping in mind that the assessment of risk is not static (i.e. if a child is DAA positive or a sibling is diagnosed with T1D,

the calculated risk of developing the disease increases significantly); 4. Providing options for genetic and/or autoimmune testing if requested by patients or families or indicated by clinical presentation:

- Many laboratories now offer MODY and neonatal diabetes testing (including Seattle Children's Hospital, www.seattlechildrens.org); additional laboratories can be found at www.genetests.org
- DAA testing for patients diagnosed with diabetes is widely available, for example, from the Mayo Clinic, the Barbara Davis Center, and Quest Diagnostics
- Information on DAA screening of first and second degree family members of T1D patients can be found at www.diabetestrialnet.org

5. Providing additional resources for further information:

- Free online genetics course from Duke's Center for Human Genetics (www.chg.duke.edu/education/online.htm), covers basic areas of genetics
- Genetics and Genomics Series in the Journal of Nursing Scholarship (starting March 2011, 43(1)), and an upcoming special issue on genetics and genomics to include an article on the genomics of diabetes (March 2013, 45(1))
- Articles and competencies related to genetics/genomics and nursing can be found at the International Society of Nursing in Genetics website (www.ISONG.org)
- In-depth diabetes etiology and pathogenesis information can be found at www.endotext.org

- Information and guidelines regarding monogenic diabetes can be found at www.diabetesgenes.org
- Specific information on T1D-related genes can be found at www.t1dbase.org

Conclusion

The complexity of determining etiology, risk, diagnosis and treatment of diabetes affecting youth is increasing with advances in genetic/genomic and immunologic discoveries. Due to their patient advocacy role, diabetes nurses and other care providers must be knowledgeable to inform patients and families about the genetic and autoimmune biomarkers used in determining the risk, etiology, and/or diagnosis of the disease and potential implications on treatment options. This article provides diabetes care providers with the latest information on diabetes-related genetic and autoimmune biomarkers and resources for further information regarding these topics. Future updates regarding the use of genetic and/or autoimmune biomarkers for other complex diseases will be essential for nurses and other healthcare providers to offer clear and concise information to support patients and their families.

CHAPTER THREE

DIFFERENCES IN U.S. IMMIGRANT AND NONIMMGRANT BLACK YOUTH
WITH TYPE 1 DIABETES: A CASE FOR EXPANDING CLASSIFICATIONS OF
ETHNICITY**Abstract**

Purpose: The aims of this study were to (a) describe and compare demographic and clinical characteristics of U.S. immigrant and nonimmigrant Black youth with type 1 diabetes (T1D) at time of diagnosis and (b) estimating the prevalence of T1D among these two populations in King County, Washington.

Methods: In this retrospective study, all immigrant (n = 60) and nonimmigrant (n = 53) Black youth with T1D and treated at Seattle Children's Hospital from 2000 to 2011 were identified. Descriptive analyses were conducted for all demographic and clinical characteristics. T1D prevalence was estimated using study data and U. S. Census Bureau estimates.

Results: Estimated T1D prevalence rates for immigrant Black youth in King County are nearly 4 times that of nonimmigrant Black youth (6.76/1,000 vs. 1.74/1,000). Immigrant Black youth were on average younger at the time of T1D diagnosis, more likely to have government-sponsored insurance, and more likely to have a family history of diabetes. Immigrant youth had lower mean hemoglobin A1c and C-peptide

levels, and were overall less likely to present in diabetic ketoacidosis at diagnosis, but more likely to have severe DKA when present, and tested positive for diabetes-related autoantibodies less frequently than did nonimmigrant youth.

Conclusions: We found a substantial difference in estimated T1D prevalence rates as well as differences in disease trends at diagnosis between immigrant and nonimmigrant Black youth. These observations are lost within the Black/African American race classification and efforts to explore these phenomena further and advocate for a more expansive classification of ethnicity should be advanced.

Clinical relevance: Nurses and other pediatric health care providers should be aware that some ethnic groups, such as East African immigrants, may be disproportionately affected by T1D. Targeted education and screening programs may need to be implemented to mitigate the effects of disease burden.

Background

The first step in ensuring high-quality health care and addressing potential health disparities is to provide an accurate description of the population(s) served, including rich data on race and ethnicity. Race and ethnicity are complex cultural and/or political constructs that have historically been used as a basis for abuse and oppression in the United States (U.S.) (Jaja, Gibson, & Quarles, 2013). However, there

are important reasons for the thoughtful use of race and ethnicity in the health care setting in a way similar to gender or age: to identify vulnerable populations that may be adversely affected by disease and/or poor health outcomes (IOM, 2009). For example, certain ethnic groups in the U.S. are known to carry substantial disease burdens specific to their communities; examples include type 2 diabetes among Pima Indians or Tay-Sachs disease and breast cancer among Ashkenazi Jews (Brower, 2002).

The Institute of Medicine's Subcommittee on Standardized Collection of Race/Ethnicity Data states that the health care system in the U. S. "does not provide the necessary level of detail to understand which groups are experiencing health care disparities or would benefit from targeted quality improvement efforts" (IOM, 2009). Based on Census Bureau classifications, all organizations that receive federal funds in the U.S. must use five race classifications (Black or African American, White, Asian, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander) and two ethnicity classifications (Hispanic or Latino, and Not Hispanic or Latino) (IOM, 2009). Within each of these race and ethnicity categories are many heterogeneous ethnic groups whose distinct characteristics are lost to classifications that are too broad. It is important to describe populations in greater detail in order to determine if differences in disease burdens or outcomes exist based on more specific classifications and address these disparities if they are identified.

Previous studies have highlighted differences in a population's risk for developing a disease or poor health outcomes based on race or general immigrant

status. In the case of type 1 diabetes (T1D) in the U. S., prevalence rates are higher for non-Hispanic White youth than for Black youth for those diagnosed from 0–9 years of age (1.03 per 1,000 White youth, 95% confidence interval (CI) [0.97, 1.10], vs. 0.58 per 1,000 Black youth, 95% CI [0.48, 0.71]) and for those diagnosed from 10–19 years of age (2.88 per 1,000 White youth, 95% CI [2.78, 2.98], vs. 2.07 per 1,000 Black youth, 95% CI [1.87, 2.28]) (Liese et al., 2006). Black youth in the U. S. aged 0–19 have higher rates of diabetic ketoacidosis (DKA) at the time of T1D diagnosis compared to non-Hispanic White youth of the same age (25.5% vs. 10.3%) (Bell et al., 2009; Mayer-Davis et al., 2009). Higher rates of DKA at T1D diagnosis have also been reported for mixed immigrant groups elsewhere, such as among non-Western immigrant youth in the Netherlands when compared to Dutch and Western immigrant youth populations (17.4% vs. 9.6% and 7.3%, respectively; $p < 0.05$) (van Laar, Grishchenko, van Wouwe, & Stronks, 2007). Additional studies have characterized T1D in mixed immigrant youth and African immigrant youth in Europe and Israel with conflicting results (Delli et al., 2010; Eehalt et al., 2009; Neu, Willasch, Eehalt, Kehrer, Hub, & Ranke, 2001; Raymond et al., 2001; Zung et al., 2004). Limited data is available on T1D in youth in Africa, and it is widely described as incomplete and unreliable (Majaliwa, et al., 2008; Mbanya, Motala, Sobngwi, Assah, & Enoru, 2010; Oilinki, Otonkoski, Ilonen, Knip, & Miettinen, 2012).

While these broader comparisons have been made, there is a lack of research that describes how T1D affects two ethnic groups within the same race classification, such as immigrant and nonimmigrant Black youth in the U. S. The diabetes team at

SCH observed that more children from East African immigrant families were presenting with new onset T1D when compared to children from nonimmigrant Black families, and that current classifications of ethnicity in the U. S. do not allow for characterizing differences between these two populations. The specific aims of this retrospective study are (a) to describe and compare demographic and clinical characteristics between U.S. immigrant and nonimmigrant Black youth with T1D at time of diagnosis, and (b) to estimate the prevalence of T1D among these two populations in King County, Washington.

Methods

Study Design

After obtaining permission from the Institutional Review Board at Seattle Children's Hospital (SCH), data were obtained from existing electronic medical records. All pediatric patients diagnosed with T1D and seen at SCH on at least one occasion between January 1, 2000, and July 31, 2011, were identified by primary or secondary ICD-9 codes. This query resulted in 2,929 patients identified. From this population, all individual medical records for each patient whose race was classified as Black or African American, Other, or Patient Refused/Missing ($N = 760$) were reviewed by one study team member.

Sample

East African immigrants represented 94% of Black immigrant youth with T1D at SCH and as a result, inclusion in the immigrant sample for the study was restricted to this group. Patients were categorized as East African immigrant if their race was listed as Black or African American and: (a) notation in the medical record of patient or their parents' birth in an East African country (Kenya, Uganda, Ethiopia, Eritrea, or Somalia), or (b) interpreter requests were made for an East African language (Amharic, Somali, Tigrinya, Oromo, or other). While there are many definitions of 'immigrant', we have chosen to include patients or youth of parents born in East Africa because previous data suggests that parent's immigration status may affect diabetes outcomes (Jaacks et al., 2012).

Patients were classified as nonimmigrant Black if their race was listed as Black or African American and : (a) their language was listed as English, and (b) no reference to any other race or country of birth outside the U. S. was noted for the patient or their parents. All of the patients who met these criteria and whose diagnosis with T1D before the age of 20 was confirmed in their medical records were included in the study. A total of 60 East African immigrant Black youth and 53 nonimmigrant Black youth with T1D were identified.

Measures

Demographic data was collected from medical records and included age at diagnosis, gender, insurance type (a proxy for socioeconomic status), and family

medical history of diabetes. Additional demographic data collected from the medical record for immigrant youth included ethnicity, country of birth, country of T1D diagnosis, interpreter usage, and primary language.

Clinical data collected at diagnosis of T1D included mean hemoglobin A1c (HbA1c), mean C-peptide, the presence and severity of DKA, and the presence of diabetes-related autoantibodies (DAAs). For reference, normal levels for HbA1c are <6.5% (<47.54 mmol/mol) and normal C-peptide levels range from 0.5 to 2.0 ng/mL (0.17 to 0.67 nmol/L) (ADA, 2013; Topiwala, 2012). The severity of DKA is classified based on venous pH and bicarbonate levels (mild is pH < 7.30 or bicarbonate < 15 mmol/L; moderate is pH < 7.20 or bicarbonate < 10 mmol/L; severe is pH < 7.10 or bicarbonate < 5 mmol/L) (Dunger et al., 2004). Since the presence of DKA at diagnosis has been associated with a younger age at T1D onset, rates of DKA at diagnosis are reported by age group (Usher-Smith, Thompson, Ercole, & Walter, 2012).

The specific DAAs patients in this study were screened for within one month of diagnosis included glutamic acid decarboxylase 65 (GAD65), protein tyrosine phosphatase insulinoma antigen 2 antibody (IA-2, also called ICA512), insulin antibody (IAA), and islet cell autoantibody (ICA). While each DAA has its own validated cut-point, results are presented as positive or negative for each of the four markers.

The estimated prevalence of T1D in this study, reported as cases per 1,000 youth ages 0–17, is presented for King County. King County was used as the catchment area because (a) detailed denominator data is available on the county level,

(b) it is the county in which SCH is located, and (c) it is where the majority of patients in this study reside. Cases of Black youth ages 0–17 with T1D were obtained by identifying those patients whose residence was listed in King County in the medical record. Denominator numbers were obtained from the U.S. Census Bureau’s 2007–2009 American Community Survey (ACS) 3-Year Estimates. Of note, ACS data provides breakdowns of populations based on country/region of origin, so population estimates for other countries and regions of Africa are not included in these estimates.

The estimate for the total immigrant Black youth population in King County aged 0–17 is composed of foreign-born East African immigrants and U.S.-born youth whose parents were born in East Africa. The estimate of the foreign-born East African immigrant youth aged 0–17 population in King County was provided by ACS. To estimate the U.S.-born East African immigrant population aged 0–17 in King County, proportions from the immigrant Black youth population with T1D at SCH were used, assuming similar proportions were true for the entire East African immigrant youth population in King County. Accordingly, we estimated that 65% of King County’s East African immigrant Black youth (4,805) were born in the U. S. (United States Census Bureau [USCB], n.d). This number was subtracted from the nonimmigrant Black youth population numbers provided by ACS to obtain the King County nonimmigrant Black youth estimate, and added to the ACS foreign-born data (representing 35% of the East African immigrant Black youth population aged 0–17, or 2,587), for a total of 7,392 (USCB, n.d.). This assumption seems reasonable as it is similar to 2006–2010 ACS data available for the number (7,084) of King County

youth ages 0–17 in households with adults from three East African countries (Kenya, Somalia, and Ethiopia) (USCB, n.d.).

To obtain nonimmigrant Black youth population estimates for King County, the number of all foreign-born black youth and U.S.-born Black youth aged 0–17 with East African parents was subtracted from the number of single-race Black or African Americans aged 0–17 in King County (USCB, n.d.).

Data Analysis

At the completion of data collection, all data were examined to identify outliers and potential data entry errors. Descriptive analyses (including counts, proportions, means, and standard deviations) were conducted for all demographic characteristics at diagnosis. Independent *t*-tests for continuous variables and odds ratios (*ORs*) for dichotomous variables were completed for clinical characteristics at diagnosis. All analyses were completed using SPSS, version 18.0.0 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

Results

Demographic Characteristics

A total of 113 Black youth with T1D were treated at SCH during the study period. At the time of diagnosis, all were 17 years old or younger (see Table 3.1). East African immigrants made up 53.1% of Black youth with T1D seen at SCH during the study period. Both the immigrant and nonimmigrant Black youth populations were

approximately 60% female. Compared to nonimmigrant Black youth, immigrant Black youth were slightly younger at the time of T1D diagnosis, more likely have subsidized insurance, and more likely to have a first-degree relative with diabetes of any type. Immigrant Black youth were also almost twice as likely as nonimmigrant Black youth (13.3% vs. 7.5%, respectively) to have a first-degree relative with T1D. The most common ethnicities within the immigrant Black youth population were Ethiopian (41.7%) and Somali (40.0%), and the majority of immigrant Black youth were born in the U. S. (65.0%) and diagnosed in the U. S. (91.7%). Approximately one third (38.3%) of immigrant families used interpreters during medical appointments, with Somali (23.3%) and Amharic (11.7%) being the most requested languages.

Clinical Characteristics

While independent *t*-tests for continuous variables and *ORs* for dichotomous variables were completed for clinical characteristics at diagnosis, these analyses did not show statistically significant differences between groups. This was likely due to the relatively small sample sizes and missing data for nearly every variable (see discussion section); therefore, results are presented using descriptive statistics. At the time of T1D diagnosis, immigrant Black youth had a lower mean HbA1c and lower mean C-peptide and were

Table 3.1
Demographic Characteristics of Study Sample at Type 1 Diabetes Diagnosis

	Total (N=113)^a	Immigrant Black Youth (n=60)^a	Nonimmigrant Black Youth (n=53)^a
Mean age in years at T1D diagnosis (SD)	7.94 (3.96)	7.63 (4.42)	8.29 (3.50)
Gender (males/females)	46 / 67	24 / 36	22 / 31
Insurance type (n, (%))			
-Government	76 (67.3)	45 (75.0)	31 (58.5)
-Private	32 (28.3)	14 (23.3)	18 (34.0)
-None	4 (3.5)	1 (1.7)	3 (5.7)
-Other	1 (0.8)		1 (1.9)
Family history (n, (%))			
-1 st degree relative with T1D	12 (10.6)	8 (13.3)	4 (7.5)
-1 st degree relative with any diabetes type	27 (24.1)	16 (26.7)	11 (21.2)

Note. T1D= type 1 diabetes; SD=standard deviation. Sample sizes vary due to missing data.

less likely to be diagnosed with DKA when compared to nonimmigrant Black youth (see Table 3.2). The difference in the rate of DKA at diagnosis between the two groups was most pronounced for those who were diagnosed between 10 and 17 years of age (15.8% of immigrant Black youth vs. 41.2% of nonimmigrant Black youth presented in DKA). However, when DKA was present at diagnosis, immigrant Black youth were more likely to have severe DKA.

Table 3.2
Clinical Characteristics of Study Sample at Type 1 Diabetes Diagnosis

	Immigrant Black Youth^a	Nonimmigrant Black Youth^a
Mean A1c^b (SD)	11.02 (1.88)	11.71 (2.21)
Mean C-peptide^c (SD)	0.71 (0.48)	0.99 (0.92)
DKA present (n, (%))	14 (31.1)	18 (45.0)
-0-4 yrs	6 (50.0)	2 (40.0)
-5-9 yrs	5 (35.7)	9 (50.0)
-10-17 yrs	3 (15.8)	7 (41.2)
If DKA present:		
-Total severe (%)	7 (50.0)	6 (33.3)
-Mean pH (SD)	7.08 (0.17)	7.12 (0.13)
-Mean bicarbonate (SD)	8.22 (3.84)	8.98 (3.57)
Tested for any DAAs (n, (% positive))	32 (65.6)	16 (75.0)
Tested for IAA (n, (% positive))	26 (34.6)	13 (38.5)
Tested for GAD65 (n, (% positive))	24 (62.5)	13 (76.9)
Tested for IA-2 (n, (% positive))	20 (25.0)	11 (54.5)
Tested for ICA (n, (% positive))	14 (14.3)	5 (20.0)

Note. A1c=hemoglobin A1c; SD = standard deviation; DKA= diabetic ketoacidosis; DAA=diabetes auto-antibodies; IAA=insulin auto-antibody; GAD65=glutamic acid decarboxylase 65; IA-2=insulinoma-associated 2 antibody; ICA=islet cell auto-antibody. ¹Immigrant black youth as reference group. Sample sizes vary due to missing data.

Overall, diabetes health care providers tested immigrant Black youth for DAAs more frequently than they did nonimmigrant Black youth within a month of T1D diagnosis (53.3% of immigrant Black youth were tested for DAAs vs. 38.2% of nonimmigrant Black youth). When patients were tested for at least one DAA, immigrant Black youth tested positive less often than nonimmigrant Black youth did. Immigrant Black youth also tested positive less often than did nonimmigrant Black youth for each of the four individual DAAs tested: IAA, GAD65, IA-2, and ICA.

Estimated Type 1 Diabetes Prevalence Rates

East African immigrant Black youth represented 28.1% of the overall Black population between 0 and 17 years old in King County, but accounted for 60.2% of T1D cases among Black youth in the county (see Table 3.3). The estimated prevalence rate of T1D among immigrant Black youth ages 0–17 was more than 3.5 times the rate among nonimmigrant Black youth ages 0–17. No significant difference was identified in the estimated T1D prevalence between East African immigrant Black youth born in and outside the U. S.

Table 3.3
Estimated Prevalence of Type 1 Diabetes in Black Youth in King County, Washington

	Immigrant Black Youth (n)	Nonimmigrant Black Youth (n)
Total Population 0-17¹	7,392	18,935
T1D Cases 0-17²	50	33
	Per 1,000	Per 1,000
Estimated T1D Prevalence 0-17	6.76	1.74
-Foreign-born	6.57	n/a
-US-born	6.66	1.74

Note T1D = type 1 diabetes. ¹2007-2009 American Community Survey 3 Year Estimates. ²Age at diagnosis.

Discussion

To our knowledge, this is the first time that T1D among U.S. immigrant and nonimmigrant Black youth populations has been described. As previously discussed, prior studies have described how T1D characteristics differ between racial groups and mixed immigrant groups. It will be helpful to consider how results from the present study compare to current knowledge on the topic.

Demographic Characteristics

The mean age at T1D diagnosis among the immigrant Black youth in this study was similar to that of immigrant youth in general in the U. S. (8.3 years \pm 4.5 years) and in contrast to reports of a later age of onset in Africa (peak age of onset is 15–19

years of age in Tanzania) (Jaacks et al., 2012; Mbanya et al., 2010). The age of onset of T1D for nonimmigrant Black youth in our study supports the SEARCH for Diabetes in Youth (SEARCH) figures for African American youth in the U. S. (age at onset ranged from 4.7 years \pm 2.4 years to 12.2 years \pm 4.4 years) (Mayer-Davis et al., 2009).

Our findings of a female preponderance in both groups is supported by previous reports of higher T1D prevalence among young Black women in the U. S., Sudan, Ethiopia, Nigeria, and Liberia (Lipton, Drum, Greeley, Danielson, Bell, & Hagopian, 2011; Majaliwa et al., 2008). However, most previous studies of T1D in youth have found either a near-even split between genders in the U. S., Tanzania, and among East African youth in Sweden or a significant (2:1) male preponderance in Ethiopia (Liese et al., 2006; Gill et al., 2011; Hjern, Soderstrom, & Aman, 2012; Lutale, Thordarson, Holm, Eide, & Vetvik, 2007).

Compared to previous data, both groups in the current study had a greater proportion of patients with government-subsidized insurance: 75% of East African immigrant Black youth in this study vs. 30.5% previously reported (Jaacks et al., 2012); 58.5% nonimmigrant Black youth in this study vs. 49.7% previously reported (Mayer-Davis et al., 2009).

Documented family medical history of diabetes in both groups was lower in the current study than in previous reports, but direct comparisons are difficult due to varying definitions of family history and lack of available data on family medical history specific to T1D. For example, Jaacks and colleagues (2012) reported that

14.5% of all immigrant youth with T1D had a parental history of diabetes; Mayer-Davis and colleagues (2009) reported 67.7% of Black or African American youth with T1D had a family medical history of diabetes (defined as parents, grandparents, or siblings); and Lutale and colleagues (2007) reported that 44.7% of T1D patients in Tanzania had an (undefined) family history of diabetes.

Clinical Characteristics

Mean HbA1c levels at diagnosis among nonimmigrant Black youth in this study were similar to those reported in a previous study of Black or African American youth at diagnosis ($11.71\% \pm 2.21$ vs. $11.55\% \pm 1.9\%$) (104.48 vs. 102.73 mmol/mol) (Kumar & Kaplowitz, 2009). Additional data on HbA1c and C-peptide at T1D diagnosis for immigrant or nonimmigrant Black youth were not identified. The percentage of immigrant Black youth presenting in DKA at time of T1D diagnosis in this study supports previous reports from the U. S., but is much lower than reported data from Africa, where 75% of youth with diabetes in Tanzania and up to 80% of all patients elsewhere in Africa present in DKA (Majaliwa et al., 2008; Usher-Smith et al., 2012). This finding is not surprising given the severe lack of adequate health care resources in Africa, potentially leading to prolonged periods of illness prior to diagnosis and increased risk of DKA. Among nonimmigrant Black youth in the U. S., rates of DKA at diagnosis in this study appear higher than those previously reported by the SEARCH study (overall, 25.5% of Black or African American youth presented

in DKA), although the breakdown by age group is not identical (Mayer-Davis et al., 2009).

Data in the current study supports Delli and colleagues' (2010) findings that immigrant youth with T1D tested positive for DAAs less often than did nonimmigrant youth populations.

This study's findings that DAA positivity in East African youth is also similar to Oilinki and colleagues' (2012) work with Somali youth in Finland. Additional data on the presence of DAAs around the time of diagnosis varies widely among Black populations with T1D in Africa and the U. S. For example, 18.9% of African American patients ages 15–50+ tested positive for at least one DAA, while results from Tanzania are conflicting (8%–11% vs. 42.6% positive for at least one DAA at diagnosis) (Aviles-Santa, Maclaren, & Raskin, 2004; Levitt, 2008; Lutale et al., 2007).

This study's rates of GAD65 positivity in both immigrant and nonimmigrant Black youth in the U. S. are higher than previously reported, although prior results are from a mix of youth and adults after diagnosis: 29.8% of patients with T1D in Tanzania, 35.0% of insulin-treated patients in Ethiopia, 50.0% of Somali immigrant youth in Finland with T1D, and 56.4%–56.9% of Black or African American youth with T1D were GAD65 positive (Gill et al., 2011; Lipton et al., 2011; Lutale et al., 2007; Mayer-Davis et al., 2009; Oilinki et al., 2012). Rates of IA-2 positivity in this study's nonimmigrant Black youth were similar to those reported by Lipton and colleagues (51.0%), while rates in the immigrant Black youth lay between the rates reported in Somali youth in Finland and patients in Tanzania (12.8%–33.0%) (Lutale

et al., 2007; Oilinki et al., 2012). ICA positivity was significantly lower than found in Somali youth in Finland (57.0%) (Oilinki et al., 2012). No data on IAA positivity were identified in comparable populations.

Estimated Type 1 Diabetes Prevalence Rates

The estimated prevalence rate of T1D among East African immigrant Black youth in this study (6.76/1,000) was higher than that reported among East African immigrant youth in Sweden (up to 4.5/1,000 based on a national insulin registry) (Hjern et al., 2012). Our estimates in East African immigrants also represents a more than 4-fold increase over rates among the general U.S. population (T1D prevalence for all youth ages 0–19 in the U. S. is 1.54/1,000, 95% CI [1.50, 1.58]) (Liese et al., 2006). Estimates for T1D prevalence rates among nonimmigrant Black youth was similar to the SEARCH study estimates of T1D prevalence rates for Black youth in the U. S. (0.58/1,000, 95% CI [0.48, 0.71] for 0–9 year olds; 2.07/1,000, 95% CI [1.87, 2.28] for 10–19 year olds) (Liese et al., 2006).

Limitations

Missing data for nearly all variables examined in the present study affected our ability to determine if there were statistically significant differences as a result of utilizing existing medical records. Despite this fact, we found some interesting trends that suggest significant differences between the two groups. These trends support the

need for future research that would include a prospective, multisite design and thus avoid weaknesses in this study's single-site, retrospective design.

Sampling bias is also a potential concern in retrospective designs. It is possible that immigrant Black youth are overrepresented in a tertiary care center such as SCH with ample social services and interpreter support. However, overrepresentation is thought to be minimal: no other pediatric endocrinology clinic exists in King County, young patients with T1D are hospitalized at diagnosis, and are seen in outpatient clinics every 3 months. Therefore, it is highly likely that the vast majority of pediatric T1D patients in the area are seen at least once at SCH. It is also possible that immigrant Black youth with T1D could have been underrepresented in the study due to inconsistency in capturing ethnicity data in the medical records. This potential is also thought to be minimal as each medical record with a race classification of Black, Other, or Patient Refused/Missing was individually reviewed, and ethnicity was determined from three different data sources.

While our prevalence estimates are based on a relatively small number of cases, we believe they are a fair reflection of T1D in the immigrant and nonimmigrant Black youth populations in King County for several reasons. It is very likely that the vast majority of youth with T1D in King County were seen at SCH on at least one occasion over the 10+ year study period for the reasons noted above. Robust estimates of denominator data from the ACS were available in enough detail to determine not only immigrant and nonimmigrant Black youth population numbers in King County, but to also confirm some assumptions made regarding those numbers (i.e., the

percentage of East African immigrant Black youth with T1D treated at SCH who were born in the U. S. is similar to the entire East African immigrant Black youth population born in the U. S.). Additionally, our estimates of the nonimmigrant Black youth population are supported by similar U.S. rates reported by the SEARCH study group.

Conclusions

We have shown that potentially important demographic and clinical differences may exist between immigrant and nonimmigrant Black youth at the time of T1D diagnosis. More importantly, prevalence estimates suggest that in King County, immigrant Black youth are diagnosed with T1D at nearly 4 times the rate of nonimmigrant Black youth. Further research to substantiate and expand on these findings is imperative to determine the underlying cause(s) of the disparity. If these findings are validated, initial efforts must include (a) education for all diabetes and pediatric health care providers, (b) routine blood glucose screenings for East African immigrant youth, and (c) outreach programs to engage and educate the East African community regarding the signs and symptoms of diabetes and ongoing treatment requirements. Additionally, broader classifications of ethnicity, including elements such as country of origin and recent immigration status, are needed to accurately describe populations affected not only by T1D, but also by other diseases and conditions. Efforts to advocate for such expansions should be pursued.

Clinical Resources

- Endotext.org is a free, peer-reviewed Website created by physicians to provide the latest information on endocrine disorders (including diabetes etiology, treatment, and management) to physicians and other diabetes health care providers around the world: www.endotext.org
- The International Diabetes Federation's Diabetes Atlas provides extensive data on diabetes globally: <http://www.idf.org/diabetesatlas/>
- The SEARCH for Diabetes in Youth study provides access to study publications and links to many diabetes resources: www.searchfordiabetes.org
- The *African Journal of Diabetes Medicine* provides access to nearly all articles free of charge and provides links to other resources in Africa: www.africanjournalofdiabetesmedicine.com

CHAPTER FOUR
GLYCEMIC CONTROL IN U.S. IMMIGRANT AND NONIMMIGRANT BLACK
YOUTH WITH TYPE 1 DIABETES

Abstract

Background: Differences in glycemic control based on race have been reported in pediatric populations with type 1 diabetes (T1D). It is unknown if differences exist between pediatric populations within the same race classification.

Methods: This retrospective study identified all immigrant and nonimmigrant Black youth diagnosed with T1D and treated at Seattle Children's Hospital from 2001 to 2011. Demographic characteristics and hemoglobin A1c (HbA1c) levels at 12, 24, and 36 months post diagnosis were obtained from existing medical records.

Results: Immigrant youth had lower mean HbA1c levels at all three time points. The ethnicity effect on mean HbA1c levels approached significance at 36 months. When comparing 12 months and 36 months, the time effect was significant; the ethnicity effect approached significance.

Discussion: Clinically important differences may exist in glycemic control between pediatric populations with T1D from the same race classification. Additional work is needed to confirm these findings and determine potential causes.

Background

Achieving optimal glycemic control and preventing diabetes-related complications is the central focus of diabetes care. Glycemic control is especially challenging for patients with type 1 diabetes (T1D), as this population must rely on exogenous insulin to achieve optimal glucose levels. Hemoglobin A1c levels (HbA1c) are the gold standard for determining glycemic control in patients with diabetes and are a crucial indicator of risk for diabetes-related complications. The landmark Diabetes Control and Complications Trial (DCCT) established that tight glycemic control can reduce diabetes complications by up to 76%, and the current American Diabetes Association guidelines for optimal HbA1c levels in pediatric populations reflect the strength of this association (< 8.5% for children aged 0–6, < 8.0% for children aged 6–12, and < 7.5% for children aged 13–19; normal levels are < 6.5%) (DCCT, 1993; ADA, 2013). Optimal glycemic control is crucial to achieve better health outcomes and quality of life for diabetes patients, and is also necessary to decrease diabetes-related health care costs which exceed \$471 billion per year globally (IDF, 2012).

Differences in glycemic control, diabetes complications, and diabetes-related mortality based on race have been established for more than a decade (Delamater et al., 1999; Lipman et al., 2006). A recent study confirmed that mean HbA1c levels differed between Black/African American youth and non-Hispanic White youth with T1D ($9.10\% \pm 0.10$ vs. $8.30\% \pm 0.10$, $p < 0.01$, respectively) (Kamps et al., 2010). Differences in glycemic control among immigrant and native-born populations with

T1D have also been reported. In the SEARCH for Diabetes in Youth Study, participants with T1D with ≥ 1 parent born outside the U.S. (17% of participants) were less likely to have poor glycemic control (HbA1c $\geq 9.50\%$) than those with native-born parents (OR 0.70, 95% CI [0.53–0.94]) (Jaacks et al., 2012). However, higher levels of HbA1c were observed in immigrant youth in Italy and in Somali immigrant youth in Finland when compared to native-born populations (Banin et al., 2010; Oilinki et al., 2012).

While the current literature suggests differences in glycemic control exist between populations of different races and among various groups of immigrants and native populations, it is not known whether such differences also exist between immigrant and nonimmigrant groups within the same race classification. The purpose of this descriptive study was to explore whether differences in mean HbA1c levels at 12, 24, and 36 months after T1D diagnosis exist between two ethnic groups within the same race classification. We examined glycemic control in immigrant and nonimmigrant Black youth with T1D and considered potential explanations for these differences.

Methods

Participants were identified from existing electronic medical records at an academic children's hospital in Seattle, Washington, after obtaining approval from the hospital's Institutional Review Board. Inclusion criteria were: (a) T1D diagnosis before age 20, identified by primary or secondary ICD-9 codes and confirmed by a

diabetes provider; (b) having been seen at the hospital on at least one occasion between January 1, 2000, and July 31, 2011; and (c) having race listed as Black/African American. Immigration status was determined by the principal investigator, who evaluated the individual medical records ($N = 760$) that met the inclusion criteria, including those in which race was classified as Other or Patient Refused/Missing.

The immigrant group was restricted to East African immigrants, as they represented the vast majority (94%) of the hospital's Black immigrant youth population with T1D. Patients were categorized as East African immigrant if their race was noted as Black/African American and either (a) the country of birth for the patient or parents was an East African country (Kenya, Uganda, Ethiopia, Eritrea, or Somalia) or (b) interpreter requests were made for an East African language (Amharic, Somali, Tigrinya, Oromo, or other).

Patients were categorized as nonimmigrant Black if (a) their race was listed as Black/African American, (b) their primary language was listed as English, and (c) no references to any other race or ethnic group or country of birth outside the United States were identified for the patient or the patient's parents. Fifty-three nonimmigrant Black youth and 60 East African immigrant Black youth with T1D were identified, for a total patient sample of $N = 113$.

Measures

Demographic data that were collected included gender, ethnicity (defined as immigrant or nonimmigrant Black), insurance type (private vs. subsidized/no insurance), and mean age in years at T1D diagnosis. Standard of care for T1D patients during the study period included outpatient clinic visits every three months, during which patients had their HbA1c levels checked. HbA1c levels were collected from the clinical visit data closest to 12-, 24-, and 36-month time points after T1D diagnosis. All HbA1c levels were determined by the hospital's point-of-care machine (Siemen's DCA Vantage® Analyzer). Note that standard results for HbA1c analysis are presented through 14.0%, and are listed as > 14.0% for any results over 14.0%. Thus, > 14.0 results were coded as 14.1.

Data Analysis

For all demographic variables, descriptive statistics were conducted to determine proportions, means, and standard deviations (*SD*). To compare group means for HbA1c data, analyses of variance (ANOVA) were performed to examine the effect of ethnicity on the mean HbA1c at each time point (12, 24, and 36 months) and the effects of ethnicity and time on mean HbA1c for the most extreme time points (12 months vs. 36 months). The data were examined and all assumptions for the ANOVA were met. All statistical analyses were conducted using SPSS (version 19.0). Significance was set at $p < .05$.

Results

Both immigrant and nonimmigrant Black groups were approximately 60% female (60.0% vs. 58.5%), and the majority of both groups had subsidized or no health insurance (76.7% vs. 64.2%). The mean age at diagnosis was lower for immigrant Black youth than nonimmigrant Black youth (7.63, *SD* 4.42 vs. 8.29, *SD* 3.50). Nonimmigrant Black youth had higher mean HbA1c levels at all three time points when compared to immigrant Black youth (see Table 4.1). Greater variation in HbA1c levels was also observed in the nonimmigrant Black group at all three time points, shown by the standard deviations in Table 4.1 and in individual variability seen in Figure 4.1. The greatest variance in HbA1c levels for both groups was observed at the 12-month time point, likely due to a continuing “honeymoon effect” for some patients who were still producing some endogenous insulin and, as a result, were able to obtain normal levels of HbA1c (see Figure 4.1).

Table 4.1

Mean Hemoglobin A1c Levels at 12, 24, and 36 Months After Type 1 Diabetes Diagnosis

	<i>n</i> ^a	Mean (SD)	95% CI
12-month HbA1c			
Nonimmigrant	37	9.07 (2.13)	8.36, 9.78
Immigrant	51	8.75 (1.77)	8.25, 9.25
Total	88	8.89 (1.93)	8.48, 9.29
24-month HbA1c			
Nonimmigrant	34	9.57 (1.78)	8.95, 10.19
Immigrant	45	9.41 (1.69)	8.90, 9.92
Total	79	9.48 (1.72)	9.09, 9.86
36-month HbA1c			
Nonimmigrant	29	10.25 (1.91)	9.52, 10.97
Immigrant	39	9.42 (1.74)	8.85, 9.98
Total	68	9.77 (1.85)	9.32, 10.22

^a Sample sizes vary due to missing data.

While a one-way, between-groups ANOVA conducted to explore the impact of ethnicity on HbA1c levels at the three time points did not show statistical significance at the 12-month [$F(1, 86) = 0.58, p = 0.45$] and 24-month [$F(1, 77) = 0.17, p = 0.68$] time points, the effect of ethnicity did approach significance for mean HbA1c levels at 36 months [$F(1, 66) = 11.54, p = 0.07$]. The effect size, calculated as η^2 , was 0.05 (small to moderate according to Tabachnick and Fidell (2007)). The two-way between-groups ANOVA to explore the impact of ethnicity and time on mean HbA1c levels at 12 and 36 months showed a statistically significant main effect for time [$F(1, 152) = 9.01, p < 0.01$]. The calculated effect size (η^2) was moderate at 0.06. The main effect for ethnicity once again approached statistical significance [$F(1, 152) = 3.50, p = 0.06$], but with a small calculated effect size of $\eta^2 = 0.02$. As expected, the interaction

effect between time and ethnicity [$F(1, 152) = 0.706, p = 0.40$] did not reach statistical significance.

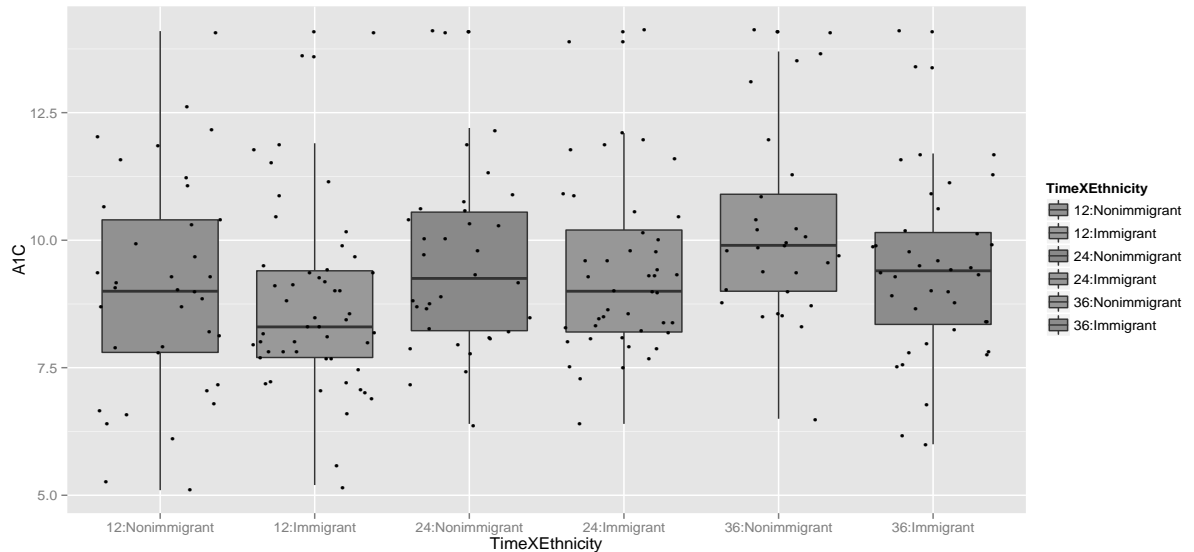


Figure 4.1. Individual Variability in Hemoglobin A1c Levels at 12, 24, and 36 Months After Type 1 Diabetes Diagnosis

Discussion

There is a great deal of individual variation in HbA1c levels in both immigrant and nonimmigrant Black youth at 12, 24, and 36 months after T1D diagnosis. Mean HbA1c levels between the two groups began to diverge considerably at the 36-month point, with immigrant Black youth achieving better glycemic control at all three time points. Several factors may be influencing HbA1c levels, resulting in the differences observed between the groups. Nonimmigrant Black youth may experience higher levels of insulin resistance compared to immigrant Black youth, which would make achieving optimal glycemic control more challenging. There may also be protective

environmental factors found in the immigrant Black youth, resulting in better glycemic control. For example, their diets may comprise fewer simple carbohydrates than the diets of nonimmigrant Black youth. There may also be a stronger nuclear family structure found in immigrant families in general given the recent experience of immigration, perhaps resulting in better adherence to diabetes care.

Limitations to the current study include missing data and small sample sizes. Because of the study's retrospective design, missing data was an issue for this data set due to the patients' time of T1D diagnosis (i.e., if diagnosed in June 2010, HbA1c levels at 24 and 36 months were missing). Additionally, T1D is a somewhat uncommon disease and efforts to explore even smaller subgroups within the affected population yields a relatively small number of cases. However, given these limitations, our data suggest that there may be statistically significant differences in glycemic control between two vulnerable populations within the same race classification. Further work is warranted, and if these findings are confirmed, efforts to determine the underlying causes should be made.

CHAPTER FIVE

CONCLUSION

A trip to Africa 14 years ago formed the core of my values and beliefs today, and ultimately led to this dissertation work. Notions of social justice were instilled in me during this time and drive my passion for addressing health disparities in vulnerable populations. A quote by Lilla Watson, an Australian Aboriginal artist and activist, encapsulates my own philosophy and approach to clinical research with vulnerable populations: “If you have come to help me, you are wasting your time. If you have come because your liberation is bound up with mine, then let us work together.” (Lilla: International Women’s Network, n.d.). Accordingly, I do not view addressing the health disparities of a particular group only about improving health outcomes for that specific community. Rather, I believe that decreasing health disparities in general furthers social justice and thus improves the human condition as a whole.

Superficial classifications such as race and ethnicity have been used to divide groups rather than bind them together as Lilla Watson suggests, but more granular classifications of ethnicity are also undeniably useful in identifying groups of individuals at risk, as discussed in Chapter Three. If we cannot identify individuals at risk, we cannot prevent disease or improve health outcomes. More specific classifications of ethnicity are needed to identify potential or address existing health disparities, but this must be done in a thoughtful way to avoid unintentionally

furthering other disparities as described by Jaja and colleagues (2013). For example, the authors argue that researchers should avoid a singular focus on race and ethnicity at the exclusion of other variables that may actually be causing the phenomena of interest (i.e. socioeconomic, lifestyle, and environmental factors) (Jaja, Gibson, & Quarles, 2013). There is also the need to include the affected population(s) in the research process using a collaborative framework rather than the normally disengaged, hierarchical relationship that the researcher and participant share. My hope is that this dissertation work will contribute to future discussions on the need to ethically expand our classifications of ethnicity in the U.S. and move beyond the narrow ‘Hispanic’ or ‘not Hispanic’ division to provide better health care to all populations.

The aim of this dissertation research was to explore if there were T1D-related differences between two populations within the same race classification. Our findings provide strong evidence to suggest that there are indeed T1D-related differences between immigrant and nonimmigrant Black youth and that these differences have gone unnoticed because both populations are conflated into the Black/African-American race classification. We first provided an in-depth examination of diabetes typology and the genetic and autoimmune biomarkers involved in diabetes affecting youth in Chapter Two. Once this foundation was laid, we were able to explore T1D differences between immigrant and nonimmigrant Black youth. Perhaps the most striking difference we identified was the fact that the estimated T1D prevalence rate for immigrant Black youth in King County is nearly four times that of nonimmigrant Black youth (6.76/1,000 vs. 1.74/1,000).

In Chapter Three, we also noted that compared to nonimmigrant Black youth, immigrant Black youth were on average younger at the time of T1D diagnosis (7.63, *SD* 4.42 vs. 8.29, *SD* 3.50), more likely to have government-sponsored insurance (75.0% vs. 58.5%), and nearly twice as likely to have a family history of T1D (13.3% vs. 7.5%). Immigrant youth were overall less likely to present in DKA at diagnosis than were nonimmigrant youth (31.1% vs. 45.0%); however, when DKA was present, immigrant youth were more likely to have severe DKA (50.0% vs. 33.3%). Immigrant youth also tested positive for diabetes autoantibodies less frequently than did nonimmigrant youth (65.5% vs. 75.0%). Additionally, both populations were approximately 60% female, in contrast to the overall population at SCH and much of the existing literature suggesting that T1D affects both genders equally.

In Chapter Four, we reported that immigrant youth had lower mean HbA1c levels at 12, 24, and 36 months after diagnosis, and the effect of ethnicity on glycemic control approached statistical significance at 36 months after T1D diagnosis [$F(1, 66) = 11.54, p = 0.07$], albeit with a small effect size of $\eta^2 = 0.05$. An exploration of the effect of ethnicity and time on mean HbA1c levels at the two extreme time points (12 vs. 36 months after T1D diagnosis) also approached statistical significance for ethnicity [$F(1, 152) = 3.50, p = 0.06$], $\eta^2 = 0.02$, and revealed that time had a significant impact time [$F(1, 152) = 9.01, p = <0.01$], $\eta^2 = 0.06$.

In this dissertation work, we found a substantial difference in estimated T1D prevalence rates, differences in disease trends at diagnosis, and in glycemic control after diagnosis between immigrant and nonimmigrant Black youth. These observations

are lost within the larger U.S. race classification of Black or African American, and efforts to explore these phenomena further and advocate for more expansive classifications of ethnicity should be advanced.

My hope is that nurses and other pediatric health care providers will become aware that some ethnic groups, such as East African immigrant youth, may be affected by T1D differently than other pediatric populations. Additionally, I hope that researchers and diabetes care providers can use CPBR values to collaborate with the East African community and create targeted education and screening programs to mitigate the effects of T1D disease burden in this population. Collaboration is also needed to design clinical studies to confirm the findings presented here and explore potential causes of the T1D disparity between immigrant and nonimmigrant Black youth. Finally, additional work is warranted to determine if our current ethnicity classifications are masking comparable trends among other populations affected by T1D and similar work should be considered for other diseases and conditions.

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