The Changing Face of Diabetes in Youth: Lessons Learned from Studies of Type 2 Diabetes

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Abstract

Youth type 2 diabetes (T2D) is increasing, linked with obesity and declining physical activity in high-risk populations. Recent multi-center studies have led to tremendous advances in our understanding of the epidemiology, pathophysiology, diagnosis, treatment and complications of this condition. As in adult T2D, youth T2D is associated with insulin resistance, together with progressive deterioration in β cell function and relative insulin deficiency in the absence of diabetes-related immune markers. However, increasing obesity in children with type 1 diabetes (T1D) blurs the clinical distinction between youth T2D and autoimmune-mediated T1D. In stark contrast to adult T2D, the decline in β cell function is 3-4 fold faster in youth T2D and therapeutic failure rates in youth are significantly higher than in adults. Whether or not the more aggressive nature of youth T2D is driven by genetic heterogeneity or by physiology/metabolic maladaptation is yet unknown. The lack of approved pharmaco-therapeutic agents for youth T2DM, besides metformin, targeting the pathophysiological mechanisms is a major barrier to optimal diabetes management. There is a desperate need for effective therapeutic options, in addition to prevention, to halt the projected four-fold increase in youth T2D by 2050 and its consequences of heightened diabetes morbidity and mortality at younger ages.

Introduction

Diabetes mellitus (DM) is a disorder characterized by hyperglycemia resulting from defects in insulin action and/or production. The most common form of DM in youth is immune-mediated type 1A diabetes (T1D) resulting from autoimmune insulitis and destruction of the pancreatic β-cells, leading to absolute insulin deficiency.[1] Diabetes-associated pancreatic autoantibodies are present in over 90% of youth with T1D at the time of diagnosis.[2] The traditional text-book description of childhood T1D is that of a normal-weight child who develops polyuria, polydipsia, and nocturia which progressively worsens resulting in weight loss, ketosis, dehydration and ultimately diabetic ketoacidosis if unrecognized and untreated in a timely fashion.[3]

In contrast, type 2 diabetes (T2D) in youth, an increasingly recognized pediatric disorder of the millennium, is primarily associated with insulin resistance together with β-cell dysfunction and relative insulin deficiency[4-7], and the absence of circulating diabetes-related immune markers.[8, 9] Globally, T2D accounts for around 90% of all cases of diabetes, but predominantly effects adults.[10, 11] T2D was rare in youth, but with the soaring trajectory of childhood obesity, T2D is now being diagnosed in an ever increasing number of youth.[12] The text-book description of youth T2D is that of an overweight and/or obese adolescent, in mid-puberty, with overrepresentation of minority ethnicity/racial groups and females.[13] These adolescents could be totally asymptomatic and/or minimally symptomatic, diagnosed incidentally during a routine checkup, or could present with significant symptoms of hyperglycemia, weight loss, metabolic decompensation and even ketoacidosis.[5]

Obesity is the hallmark of T2D in North American youth.[13] However, with the escalating rates of obesity in the general population, children with autoimmune T1D are also becoming

overweight/obese making the clinical distinction between T2D and obese T1D difficult.[14-16] In this review, we present important lessons learned from studies which have led to significant advances in our understanding of the epidemiology, pathophysiology, diagnosis, treatment and complications of T2D in youth. We will offer current-day knowledge comparing and contrasting T2D with T1D in youth, and adult T2D with youth T2D. Recent multi-center studies of T2D in youth referred to throughout this review are introduced briefly here.

Key Multi-Center Studies of T2D in Youth

The **TODAY** (Treatment Options for Type 2 Diabetes in Adolescents and Youth) is an ongoing study funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[17] TODAY was a nationwide randomized clinical trial to compare three different interventions for the treatment of T2D in youth: metformin alone, metformin plus intensive lifestyle intervention, and metformin plus rosiglitazone. Participants with T2D were recruited over 4 years at 15 clinical centers in the United States (n=704) and enrolled, randomized, treated, and followed up for 2-6 years, with a mean duration of therapy of 3.9 years. Participants had to have a BMI ≥85th percentile for age and gender, be negative for two islet autoantibodies, glutamic acid decarboxylase (GAD) and insulinoma-associated protein-2 (IA2), and have an adult family member willing to participate with them. The primary outcome was time to treatment failure, or loss of glycemic control defined as sustained elevation in HbA1c ≥8% for 6 months, or the inability to wean from temporary insulin therapy within 3 months following acute metabolic decompensation. The TODAY results advanced our understanding about the treatment of youth T2D, the natural history of β-cell failure and insulin sensitivity, the predictors of

glycemic failure, the complications of youth T2D and rates of progression, all to be discussed below.

The **SEARCH** for Diabetes in Youth study (www.serchfordiabetes.org/public/dsphome.cfm) is an ongoing, national, population-based, multi-center study, funded by the U.S. Centers for Disease Control and Prevention (CDC) and the NIDDK, aimed at understanding the epidemiology and outcomes of both T1D and T2D in youth and young adults. It was initiated in 2000 and has 5 primary participating centers. The SEARCH has been a principle source of information regarding the prevalence and incidence of T1D and T2D in U.S. youth of diverse racial/ethnic backgrounds. SEARCH has been instrumental in advancing our understanding of the burden of diabetes-related complications in youth, with important implications for ongoing health, quality of life, as well as economic implications.[12, 18-20]

The **HEALTHY** study was funded by the NIDDK with additional support from the American Diabetes Association (ADA).[21] The objective of the HEALTHY study was to decrease risk factors for T2D in youth during middle school via a school-based intervention targeting nutrition, physical education, changing behaviors, and social marketing to increase visibility of the program within participating schools. The study involved a collaborative group of institutions, 42 middle schools (21 intervention and 21 control schools), and followed students prospectively from the start of 6th grade to the end of 8th grade. The primary outcome was the percent of students with a BMI ≥85th percentile in the intervention versus control schools at the end of 8th grade. Although the comprehensive school-based intervention did not result in greater decreases in the proportion of students with a BMI ≥85th percentile, it clarified the significant

prevalence of risk factors for T2D in a targeted population, and did result in significant reductions in indices of adiposity among obese participants.[22, 23]

Epidemiology of Youth T2D

Globally, approximately 347 million people have diabetes, the majority of whom are adults with T2D.[24] Among youth, T1D is much more prevalent than T2D. Worldwide, it is estimated that nearly 500,000 children and adolescents are living with T1D, and nearly 80,000 youth under the age of 15 years develop T1D annually.[25] In the U.S., according to the 2014 National Diabetes Statistics Report, an estimated 208,000 youth under the age of 20 years have been diagnosed with diabetes (0.25% prevalence rate or approximately 1 in 400 children).[26] The incidence of T1D among youth is increasing in many countries, with the overall annual increase estimated to be ~2.5-4% in the past decade.[12, 27-29] In 2012, the annual incidence of diagnosed diabetes in U.S. youth was estimated to be 18,436 for T1D and 5,089 for T2D.[26]

As compared with T1D, information is sparse with regard to the global prevalence and incidence of T2D among youth. A recent systematic review demonstrated that the worldwide incidence and prevalence of T2D in youth vary substantially among countries, age categories and ethnic groups, caused by both population characteristics and methodological differences.[30] In the US, in the late 1970's it was documented that obese Pima Indian youth with strong family histories of T2D were developing the disease.[31] As childhood obesity increased, so has the prevalence of T2D in youth over the age of 10 years.[32, 33] Diagnosed T2D among youth was documented in 4 geographic areas and 1 managed health care plan in the U.S. from 2001 to 2009 by the SEARCH for Diabetes in Youth study (Table 1).[12] The prevalence of T2D was 0.46 per 1,000 youth aged 10-19 years (0.046%), significantly lower than the prevalence of T1D (1.93 per

1,000 children aged 0-19 years; 0.193%). The prevalence varied by race/ethnicity and was highest in American Indians (0.120%), followed by black (0.106%), Hispanic (0.079%), Asian Pacific Islander (0.034%), and white youth (0.017%). Females are predominantly effected (0.058% versus 0.035% in males). This is in contrast with T1D, where there is no gender differential and white youth are predominantly effected.[12] Between 2001 and 2009, the prevalence of T2D in youth increased by approximately 30%, while the prevalence of T1D increased by around 23%.[12] Projections of T2D burden in the US population aged < 20 years from 2010 through 2050, forecast an increase from 20,203 to 30,111 cases assuming a constant incidence over time.[34] On the other hand, modeling the projections based on a yearly 2.3% increase across all ages almost quadruples the number of youth with T2D from 22,820 in 2010 to 84,131 in 2050:- A prevalence increase from 0.27/1,000 to 0.75/1,000 (+178% increase).[34]

While factors promoting the increasing prevalence of T1D are not understood, increasing rates of T2D are linked with the obesogenic environment of developed countries, nutritional excesses and rapid increases in obesity, together with declining physical activity in high-risk populations. Concurrently, increasing obesity among youth with T1D is clouding the clinical distinction between the two conditions.[14-16] Thus, some reports of increasing rates of T2D may be muddled by including obese T1D youth as having T2D. This was illustrated in the TODAY study in which all enrolled participants with a clinical diagnosis of T2D were screened for circulating GAD-65 and IA2 antibodies using standardized assays.[35] Of the 1,206 youth screened and clinically considered to have T2D, 118 (9.8%) were antibody positive, 5.9% were positive for a single antibody and 3.9% were positive for both antibodies, making them ineligible for TODAY. In smaller scale studies the reported rates of positive pancreatic autoantibodies in youth clinically diagnosed with T2D vary from 10 to 75%.[36-41]

The transition from normal glucose tolerance to overt T2D is characterized by an intermediate state of prediabetes indicative of the relatively high risk for the future development of T2D.[42] Individuals with prediabetes are defined as having impaired fasting glucose (IFG) [fasting plasma glucose levels 100 mg/dl to 125 mg/dl], or impaired glucose tolerance (IGT) [2-hr glucose values in the oral glucose tolerance test (OGTT) of 140 mg/dl to 199 mg/dl].[42] Among U.S. adolescents 12-19 years of age the prevalences of IFG, IGT and prediabetes were 13.1, 3.4 and 16.1%, respectively.[43] Overweight adolescents had a 2.6-fold higher rate than those with normal weight.[43] The prevalence is even higher (up to 25%) among obese adolescents referred to tertiary obesity treatment centers.[44, 45] In the HEALTHY study of middle-school students (n=6,358), 40.5% of the participants had IFG and the mean FPG for the cohort was 98.2 mg/dL.[46] Less than 1% of the HEALTHY participants had a FPG in the diabetic range at the onset of the study.[46]

Pathophysiology of Youth T2D

Glucose homeostasis is maintained by a delicate coupling of insulin secretion, from the pancreatic β-cells, with insulin sensitivity (skeletal muscle, adipose tissue and hepatic)[47] (Figure 1). This relationship which is an expression of β-cell function relative to insulin sensitivity is best described by a hyperbolic function called the disposition index (DI). It is the product of insulin sensitivity and β-cell function which is a constant for a given glucose tolerance in any one individual. When insulin sensitivity declines, insulin secretion must increase to maintain glucose tolerance (Figure 1). Overweight and obesity are major contributors to the development of insulin resistance. In the presence of robust pancreatic β-cell compensatory insulin secretion, glucose homeostasis remains normal. When β-cells are no longer able to secrete sufficient

insulin to overcome insulin resistance, IGT ensues progressing to T2D (Figure 1). Abnormalities in other hormones, such as hyperglucagonemia, decreased incretin effect and raised concentrations of other counter-regulatory hormones also contribute to insulin resistance, impaired insulin secretion and hyperglycemia (Figure 2).[48, 49]

Much of the knowledge about the pathophysiology of T2D had come from studies in animals and adults. However, in the past two decades, cross-sectional and longitudinal studies in pediatrics significantly advanced our understanding of the pathophysiology of prediabetes and T2D in youth.

Studies in youth T2D using a variety of methods demonstrate highly variable degrees of insulin resistance and β-cell deficiency, the two key components in T2D pathogenesis. Gungor *et al.*, used the hyperinsulinemic-euglycemic clamp to assess *in vivo* insulin sensitivity and the hyperglycemic clamp to assess β-cell function in obese youth with recently diagnosed T2D in comparison with obese non-diabetic peers matched for BMI, body composition and abdominal adiposity.[6] Adolescents with T2D had evidence of severe peripheral and hepatic insulin resistance with ~ 50% lower *in vivo* insulin sensitivity, elevated fasting hepatic glucose production together with significantly lower adiponectin concentrations. This severe insulin resistance was accompanied with severe β-cell failure, such that first phase insulin secretion was ~ 75% lower and second phase insulin secretion ~ 55% lower in T2D adolescents. β-cell function relative to insulin sensitivity, i.e. the DI was ~ 85% lower in T2D youth compared with their non-diabetic, equally obese peers (Figure 3A). Weiss *et al*., using the hyperglycemic clamp and modeling of glucose-stimulated insulin secretion also showed that glucose sensitivity of first and second-phase insulin secretion were impaired in obese youth with T2D compared with obese non-diabetic peers.[50] A Japanese study using an insulin-modified frequently sampled intravenous

glucose tolerance test (IVGTT) and the minimal model analysis, also demonstrated lower first phase insulin release in obese adolescents with T2D compared with the non-diabetic group.[51] In this study, insulin sensitivity was not different; however, body composition and fat topography were not evaluated. In another study using IVGTT, acute insulin release, insulin sensitivity and DI were lower in obese adolescents with T2D compared with non-diabetic controls.[52] Interestingly, β-cell failure in T2D adolescents was not reflected in an elevated proinsulin to insulin ratio.[52] A study from France, evaluated adolescents with T2D without a comparison group and concluded that all patients showed decreased peripheral glucose uptake to the same extent, but highly variable insulin responses under graded glucose infusion and arginine stimulation (a sixty-four fold difference in DI between the lowest and the highest).[53] Using the same approach of graded glucose infusion and after intravenous arginine at ≥ 22 mM of blood glucose concentration, insulin responses and acute insulin release were blunted, 85% and 55% respectively, in adolescents with T2D compared with non-diabetic controls.[54]

In the TODAY cohort, using fasting and OGTT-derived surrogate indices of insulin sensitivity and secretion, it was observed that with increasing HbA1c quartiles β-cell function declined both at screening and randomization, implying that glycemic control was associated with residual β-cell function and not insulin sensitivity.[55] Lastly, a recent study from our group using mathematical modeling of β-cell function during an oral glucose tolerance test established that β-cell function parameters were 40-65% lower in obese youth with T2D compared with NGT[7], consistent with our prior clamp data.[6] Additionally however, and for the first time, evaluation of incretin effect demonstrated that youth with T2D exhibit ~ 38% reduced incretin effect compared with NGT without reduction in incretin hormones (Figure 3B).[7]

With regard to hyperglucagonemia and its pathophysiological role,[48,49] the limited data in pediatric T2D are controversial.[7, 52, 56, 57] In one study, fasting plasma glucagon and the degree of suppression after glucose ingestion did not differ among adolescents with T2D, obese controls and lean controls.[52] In contrast, a study using mixed-meal tolerance tests showed relative hyperglucagonemia in adolescents with T2D compared with BMI and puberty-matched normal controls and no suppression in glucagon concentrations despite their hyperglycemia.[56] In a recent study of ours with a large number of obese youth with NGT, IGT and T2D, glucagon concentrations after an OGTT were highest in T2D followed by IGT and lowest in NGT indicative of relative hyperglucagonemia in the face of higher plasma glucose concentrations in T2D and IGT adolescents.[7] In yet another study, glucagon concentrations before and after a hyperinsulinemic-euglycemic clamp were higher in obese IGT and obese-insulin resistant subjects compared with nonobese NGT subjects.[57] In the same study, a longitudinal follow up of a subsample revealed that those who converted from NGT to IGT increased their fasting glucagon concentrations in comparison with those who remained NGT. All these studies, point to an important pathophysiologic role of hyperglucagonemia in youth T2D consistent with adult findings.

Pathophysiology of Prediabetes in Youth

Pre-diabetes, defined as IFG, IGT, or both, is associated with high risk of progression to T2D in adults.[42] Cross-sectional and longitudinal studies in youth along the spectrum of dysglycemia from obese-normoglycemic, to obese dysglycemic/prediabetic, to obese T2D, show that it is β-cell failure that results in prediabetes and T2D in high-risk youth (Figure 3A), as has been shown in adults.[58, 59] Using both the hyperinsulinemic-euglycemic clamp, to measure

insulin sensitivity, and the hyperglycemic clamp, to measure 1st- and 2nd phase insulin secretion; or, the intravenous glucose tolerance test and oral glucose tolerance test (OGTT) methodologies, pediatric researchers have demonstrated declining insulin secretion relative to insulin sensitivity as the principle pathophysiologic mechanism associated with the development of dysglycemia and T2D in youth (Figure 3A).[7, 50, 60-67] Additionally, there appears to be α-cell up-regulation with hyperglucagonemia in obese insulin resistant and IGT youth compared with lean youth.[57] Importantly however, and even prior to reaching the universally accepted glycemic cut-points for the diagnosis of prediabetes, youth demonstrate declining β-cell function relative to insulin sensitivity along the continuum of what is considered to be normal fasting and stimulated plasma glucose concentrations. Tfayli *et al*. studied obese youth with normal glucose tolerance and found that there is a significant and gradual decline in β-cell function relative to insulin sensitivity (DI, measured with clamp methodology) as fasting plasma glucose concentrations increased from ≤ 90 mg/dl to ≥100 to toward the threshold for diabetes (<126 mg/dL).[62] At fasting glucose concentrations between > 90 to < 100 mg/dl, (the glycemic cut-point for impaired fasting plasma glucose 100 mg/dL), DI was ~49% lower than when fasting glucose was below 90 mg/dl. Similarly, Burns *et al*., using clamp-derived DI and OGTT-derived DI elicited that youth with 2-hr OGTT glucose concentrations between 120 to <140 mg/dL (technically considered normal glucose tolerance values) had DI values that were 40% lower than youth with 2-hr OGTT glucose concentrations below 120 mg/dL.[63] Youth with OGTT 2-hr glucose concentrations ≥ 200 had DI values up to 75% lower than youth with glucose concentrations below 120 mg/dL.[63] Thus, even prior to developing glucose intolerance or prediabetes, there is evidence of β-cell dysfunction in obese youth. In a longitudinal study, Giannini *et al*. showed that across rising categories of normal 2-hr glucose concentrations, obese NGT adolescents had

significant impairment of β-cell function relative to insulin sensitivity associated with the development of IGT.[64] Age and DI were the best predictors of 2-hr glucose after two years of follow up.[64] Similar observations regarding β-cell function were made when youth were categorized according to their HbA1c levels. Overweight/obese adolescents with HbA1c in the at-risk/pre-diabetes category (5.7 to <6.5%), had impaired β-cell function relative to insulin sensitivity compared with the normal HbA1c (<5.7%) category.[68] Lastly, our cross sectional studies in obese youth reveal that not only there is impairment in β-cell function in prediabetes, but also there is significantly impaired incretin effect (Figure 3B).[7] To summarize, even though insulin resistance is the earliest abnormality in obese adolescents[69] there is evidence of impaired β-cell function in obesity, even in the so called normal glucose tolerance categories. This impairment gets progressively worse with worsening glycemia ultimately resulting in glucose intolerance and T2D. It is likely that a combination of obesity, genetics, the hormonal milieu, incretins and/or their effect, and metabolic alterations, such as glucotoxicity and/or lipotoxicity promote progressively deteriorating β-cell function against the backdrop of insulin resistance eventually culminating in prediabetes and T2D in at risk youth.

Natural History of Insulin Sensitivity and β-cell Function in Youth T2D and Effects of Treatment

In 2004, in a preliminary case report we examined the progression in insulin sensitivity and secretion over a 6-year period in an adolescent with T2D.[70] Her *in vivo* insulin sensitivity remained relatively stable but 80% lower than her peers. However, her first phase insulin secretion and β-cell function relative to insulin sensitivity declined precipitously over time to

~10% of her initial value. This translated to ~15%- per-year decline in β-cell function. This was the first indication that the deterioration in β-cell function in youth T2D might be more accelerated than in adults.[71, 72] Results of our follow up study, using the clamp method, concurred with the prior findings by demonstrating that there is rapid deterioration in β-cell function over time in youth T2D, but no significant change in peripheral or hepatic insulin sensitivity in the absence of weight or BMI change.[73] After a median follow up of 20 months, β-cell function declined ~ 20% per year. Such rapid deterioration in β-cell function could explain the clinical observation of worsening glycemic control and increasing insulin requirements by 1.5-2 years after diagnosis of T2D in youth.[74] Another observation in our study was the considerable inter-individual variability in the deterioration of β-cell function ranging from ~5-50%.[73] This is in agreement with the wide between-subject variability in C-peptide concentrations over the course of clinical follow up.[74] This C-peptide variability was partly related to whether or not patients presented with ketoacidosis, in which case they had overall low C-peptide concentrations at presentation and follow up. Thus, the variability in β-cell function at diagnosis and follow up may be related to different degrees of disease severity, how early or late a diagnosis is made, and how much β-cell reserve is left.

The results of the TODAY study are in harmony with the above observations. Surrogate estimates of insulin sensitivity and β-cell function in the large TODAY cohort of 699 youth with T2D revealed rapid deterioration in β-cell function, around 20-35% per year.[75] Furthermore, there was a significant difference in β-cell deterioration between those who failed to maintain glycemic control vs. those who did not fail but no difference in insulin sensitivity (Figure 4). Additionally, initial β-cell reserve and HbA1C at randomization were significant independent predictors of glycemic failure. Such observations suggest that efforts to reduce HbA1C and

preserve β-cell function before significant loss occurs may prove beneficial in the treatment of youth T2D. The effects of the TODAY treatments, metformin alone, metformin plus rosiglitazone, and metformin plus lifestyle, on insulin sensitivity and β-cell function were also examined.[75] The results were as follows: 1) during the initial six months of therapy in youth with T2D, metformin plus rosiglitazone significantly improved insulin sensitivity and the oral disposition index (oDI) vs. the other two groups, 2) after the first 6 months and up to 4 years the changes in glucose homeostasis parameters (insulin sensitivity, insulinogenic index and oDI) were not different among the 3 treatment groups, 3) insulinogenic index and oDI were ~ 40-50% lower at baseline in those who failed to maintain glycemic control vs. those who did not fail, and 4) while insulin sensitivity over time was not different between those who failed vs. those who did not fail, insulinogenic index and oDI deteriorated rapidly and progressively in the former group (Figure 4).

The SEARCH study also examined prospectively β-cell function, assessed by fasting C-peptide in antibody negative youth (diagnosed before or after age 10) with and without evidence of genetic susceptibility to autoimmunity based on HLA DR/DQ genotypes.[76] In youth diagnosed after the age of 10, the rate of decline in β-cell function was steeper in those with susceptible HLA DR/DQ genotypes, suggesting the possibility of undetected autoimmunity in these participants: ~30% per year in non-Hispanic white youth; ~20% per year in minority youth. Youth without susceptible HLA DR/DQ genotypes had lower rates of β-cell decline: ~15% per year in non-Hispanic white youth; ~5% per year in minority youth. On average, the estimated rate of decline among SEARCH youth with non-autoimmune, insulin-resistant diabetes was ~8% per year in the first 30 months following diagnosis; lower than the rate observed in TODAY. The reasons for these differences in rates of β-cell deterioration among the aforementioned

studies could be methodological differences, clamps in our studies vs. OGTT-derived estimates of insulin secretion adjusted for insulin sensitivity in TODAY vs. fasting C-peptide in SEARCH. Population differences and referral biases could also contribute given a well-controlled and protocol-driven clinical trial of diabetes treatment in TODAY vs. a population--based epidemiologic study in SEARCH.

Risk Factors for T2D in Youth

Non-modifiable Risk Factors

There are modifiable and unmodifiable risk factors for T2D. Unmodifiable risk factors include genetics/epigenetics, manifested in the presence of a strong family history of T2D in first- or second-degree relative, or mother with gestational diabetes, minority race/ethnicity, and puberty.

The presence of dysglycemia in a first-degree relative is associated with dysglycemia in offspring, even in the absence of obesity.[77-79] Adults who have one parent with T2D have approximately 30-40% lifetime risk of developing diabetes and those who have both parents with T2D have 70% risk.[80] Moreover, risk of developing T2D is 2-4 fold increased in an individual who has a sibling with T2D compared to the normal population. This is likely due to common genetic variations which have been linked with β-cell dysfunction and decreasing DI, conferring risk for prediabetes and T2D.[81] Our studies demonstrate that the genetic heritability of T2D manifests metabolically in the first decade of life by impaired insulin sensitivity and reduced β-cell function relative to insulin sensitivity in healthy youth with family history of T2D compared with those without a family history of diabetes.[82] This metabolically evident genetic

susceptibility when combined with environmental factors conducive to obesity and a sedentary lifestyle may ultimately translate to T2D. Indeed, in a study of obese youth, a genetic risk score for β-cell dysfunction from five SNPs known to modulate insulin secretion was associated with progressive worsening of the dynamic phase of insulin secretion and a higher chance of progression from NGT to IGT/T2D.[83] Genome wide association studies (GWAS) in adults have identified more than 64 genetic variants associated with T2D and 53 genetic variants associated with glycemic traits of fasting glucose, fasting insulin, and 2-hour OGTT glucose concentration, most pointing to genetic risk for β-cell dysfunction.[84] However, it is estimated that the currently identified genetic variants account only for approximately 10% of the heritability of T2D.[85, 86] Thus, common genetic variants are not yet useful for clinical prediction, and much work remains to discover the "missing heritability". Progress to date on the genetics of T2D in youth is limited. In the Oji-Cree Native Canadians, the genetic variant, G319S, a variant of HNF1A strongly predisposes to diabetes in children and adults.[87] Common variants in the transcription factor 7-like 2 (TCF7L2) gene have been associated with T2D, increasing the odds for T2D nearly 2-fold in African American youth.[88] Both SEARCH and TODAY are participating in a T2D Genetic Consortium that should provide novel information regarding the genetic background of T2D in youth.

Evidence from both animal and human studies suggests that maternal obesity and gestational diabetes mellitus (GDM) is contributing to the increase in obesity and T2D in youth.[89, 90] Since up to 10% of pregnancies are affected by GDM, and this percentage has been increasing, it poses increasing unmodifiable risk for affected youth.[91] In the TODAY cohort of adolescents with T2D one third was born after a pregnancy complicated by pre-existing diabetes or GDM.[13] In the SEARCH for Diabetes in Youth study, exposure to maternal diabetes and

exposure to maternal obesity were independently associated with T2D in adolescents and overall, 47.2% of T2D in the cohort (n=79) could be attributed to intrauterine exposure to maternal diabetes and obesity.[92]

As stated above under the epidemiology section, incidence and prevalence of T2D is highest among minority youth (Table 1).[12] This is most likely of multifactorial nature, including genetics, cultural/environmental influences, and metabolic characteristics. A detailed discussion is beyond the scope of this review except to state that several groups have demonstrated significant racial differences in insulin sensitivity and secretion that might heighten the risk of T2D compared with their white peers.[93-98]

T2D typically occurs in adolescents at mid puberty (mean age 14 years in the TODAY study).[13] Puberty is a vulnerable period for the development of dysglycemia, due to puberty-related transient insulin resistance. Cross sectional and longitudinal studies show that insulin sensitivity declines by around 25-30% as youth transition from pre-puberty to puberty.[99, 100] In the presence of normally functioning β-cells, puberty-related insulin resistance is compensated by increased insulin secretion/hyperinsulinemia. In youth who are genetically predisposed to develop prediabetes and/or T2D, β-cell compensation is inadequate due to impaired β-cell function with a progressive decline in the DI ultimately resulting in dysglycemia.[97, 101]

Modifiable Risk Factors

The major modifiable risk factor for T2D is obesity and lifestyle habits of excess nutritional intake and decreased energy expenditure and consequent insulin resistance.

Widespread obesity, especially in minority race/ethnicity populations in the U.S., is a result of nutritional factors associated with a surplus of "Western diet" and overall decline in physical activity and increased sedentary behaviors. Other potentially modifiable risk factors for T2D in adolescents and young adults which may be associated with obesity include chronic stress and/or depressed mood[102-108] and sleep-related disorders.[109-117] Our studies in obese adolescents show that obstructive sleep apnea and poor sleep quality are associated with visceral adiposity, reduced insulin sensitivity, cardiometabolic and T2D risk markers.[111, 117, 118] Treatment and or prevention of obstructive sleep apnea or interventions to improve sleep quality may decrease risk for T2D, but this is yet to be determined. We also found that depressive symptoms, particularly negative mood, anhedonia, and negative self-esteem are associated with risk markers for T2D including higher fasting and OGTT-stimulated glucose concentrations, and lower insulin secretion relative to insulin sensitivity.[103] Moreover, a prospective pediatric study found depressive symptoms to be a significant predictor of fasting markers of insulin resistance after a mean follow-up of 6-years, even after controlling for change in BMI and other confounding variables.[107] ~~It is yet to be determined though whether interventions to improve depressive symptoms could reduce risk for T2D.~~

Diagnosis of T2D in Youth

The laboratory glycemia-based diagnostic criteria for DM and prediabetes are the same for youth and adults, regardless of type of diabetes, as shown in Table 2.[119] Screening for T2D in high-risk youth is generally recommended, as prediabetes and early T2D are asymptomatic.[120, 121] Expert Committees and the American Diabetes Association have endorsed the use of fasting

plasma glucose or HbA1C for screening of overweight or obese (BMI ≥85th percentile) youth who have at least two additional T2D risk factors, starting at the age of ten years or at the onset of puberty, if this occurs first.[42, 120] The rationale for beginning screening at the age of 10, or sooner if puberty begins earlier, stems from the association of pubertal insulin resistance with increased blood glucose concentrations during adolescence. The recommended frequency of screening is every other year, or sooner if risk factors increase or diabetes symptoms are present.

The diagnostic criteria for DM were developed based on lower-end glycemic thresholds predicting the presence of retinopathy in adult populations.[122-127] Because the risk for progression from a prediabetic state to DM is a continuum, a defined glycemic cut-off cannot adequately reflect the earliest stages of the disease in development, but must reliably predict undesired outcomes, such as retinopathy, that could be improved with treatment. There is an absence of pediatric data on the relationships between these universally applied glycemic thresholds and the development of long-term complications in youth. Thus, the applicability of these cut-points (particularly HbA1C) in pediatric and adolescent patient populations has been questioned.[128-130] The transient rise in blood glucose concentrations during puberty, as seen in the HEALTHY study cohort (mean fasting plasma glucose of 98.2 mg/dL), may not indicate pathology if it reverses spontaneously and β-cell function isn't compromised. Indeed, studies have shown that abnormal β-cell function is evident in advance of meeting accepted criteria for the diagnosis of prediabetes or diabetes as elaborated above.[63, 68] As youth with T2D mature over the next few decades, it will be particularly important to further explore glycemic predictors of development of diabetes-related complications. This will allow pediatric-specific diagnostic cut-points, if this is deemed necessary.

Islet Autoantibody Positivity in Youth with Phenotypic T2D

In making a clinical diagnosis of T2D, the major diagnostic criterion is overweight/obesity. However, with the increasing rates of obesity in children with autoimmune T1D, the clinical distinction between youth with T2D and obese youth with autoimmune T1D is difficult and imperfect without measuring pancreatic autoantibodies.[5, 40, 131-133] Between two periods, 1979-1989 and 1990-1998, the prevalence of overweight at diagnosis of T1D in children tripled.[14] The SEARCH for diabetes in youth study revealed that among youth with T1D, 22.1% were overweight compared with 16.1% without diabetes and 12.6% were obese.[15] In the Pediatric Diabetes Consortium, among 857 participants, 10% were overweight and 9% obese at diagnosis.[16] This phenomenon is not unique to the U.S. because it has been reported from other parts of the world too.[134-136] The distinction between youth with T2D and obese youth with autoimmune T1D is further blurred because not infrequently youth with T2D present in DKA.[137, 138] Moreover, and as stated under the Introduction and Epidemiology sections, a number of youth clinically diagnosed with T2D have evidence of islet-autoimmunity, with autoantibodies present in 10-75% of patients.[35-41, 132] Several theories and terminologies have been proposed, such as hybrid diabetes, double diabetes, diabetes type 1.5, and latent autoimmune diabetes of youth, to refer to this subset of young patients with a clinical phenotype consistent with T2D and evidence of autoimmunity consistent with T1D.[37, 39, 139, 140]

SEARCH described four categories of diabetes using autoimmunity (at least 1 of two autoantibodies, GAD and IA2) and insulin sensitivity (estimated using an equation which includes waist circumference, HbA1C, and triglycerides).[132] Most subjects fell into either the autoimmune insulin sensitive (54.5%) or nonautoimmune insulin resistant categories (15.9%) and had characteristics associated with the traditional description of type 1 or 2 diabetes. The

group classified as autoimmune insulin resistant (19.5%) had similar prevalence of autoantibodies and similar distribution of HLA risk genotypes to those in the autoimmune insulin sensitive group, suggesting that it includes individuals with type 1 diabetes who are obese. The group categorized as nonautoimmune insulin sensitive (10.1%) likely included subjects with undetected autoimmunity and possibly those with monogenic diabetes. Considering that insulin sensitivity in normal humans is a wide spectrum, driven by genetics and strongly modulated by obesity, it is not surprising to see the same hold true for individuals with diabetes with or without autoimmunity especially when the formula used to estimate insulin sensitivity is based on waist circumference, a major determinant of insulin sensitivity.[141, 142]

We used a variety of experimental methods, including the hyperinsulinemic-euglycemic clamp together with the hyperglycemic clamp, the OGTT and the mixed meal to probe ~~assess~~ pathophysiological differences in insulin sensitivity and β-cell function between islet autoantibody-negative (Ab^-) and –positive (Ab^+) (GAD65 and IA2) ~~in~~ youth with clinically diagnosed T2D in comparison with non-diabetic matched-peers.[8, 9, 143] As depicted in Figure 5A, insulin-stimulated glucose disposal was significantly lower in Ab^- compared with Ab^+ and compared with obese non-diabetic adolescents, with no difference between the latter two groups.[9] This is suggestive of an inherent (genetic/epigenetic) insulin resistance in Ab^- youth which is not the case in Ab^+ youth whose insulin resistance appears to be consequent to their obesity. On the other hand, Ab^+ youth had severe first and second phase insulin deficiency, while Ab^- youth had relative deficiency[9] (Figure 5B). There also appeared to be an autoantibody dose effect phenomenon on first and second phase insulin secretion both of which were significantly lower in double-antibody vs. single-antibody positive patients.[9] β-cell function relative to insulin sensitivity, DI, was similar between Ab^- and Ab^+ groups (Figure 5C), but

obviously mediated through different mechanisms; through severe insulin resistance in the former and through severe insulin deficiency in the latter.[9] Moreover, youth who were Ab^- exhibited features of the metabolic syndrome (elevated systolic blood pressure and ALT) typically seen with insulin resistance while youth who were Ab^+ had significantly more frequent ketonuria at initial presentation.[9] State-of-the-art clamp studies were required to detect these metabolic/pathophysiological differences, as OGTT-derived surrogate indices of insulin sensitivity and insulin secretion were not different between Ab^- and Ab^+ patients, except for lower fasting and stimulated C-peptide in the latter group.[8] During a liquid mixed-meal test, C-peptide indices of β-cell function were lower and insulin sensitivity higher in Ab^+ vs. Ab^- phenotypic T2D patients.[143] Though fasting and stimulated C-peptide, which were significantly different between the two groups, had high sensitivity and specificity as markers of Ab^+ status, there was appreciable overlap between Ab^- (fasting C-peptide mean: 4.1 and range 1.3-10.1 ng/ml) and Ab^+ (fasting C-peptide mean 2.4 and range 1.4-3.5 ng/ml) patients. In agreement with our findings, the TODAY study showed that the 10% of clinically diagnosed youth with T2D who had positive autoantibodies, had lower fasting C-peptide concentrations, fewer cardiometabolic risk factors (lower blood pressure and triglycerides), higher HbA1C, lower BMI, and less acanthosis nigricans at screening.[35] In addition Ab^+ T2D patients were mostly non-Hispanic whites, with less female predilection and less frequent family history of DM. An evaluation of our clinic population of obese Ab^+ vs Ab^- T2D patients at diagnosis and their clinical course over time revealed similar findings; Ab^+ youth were younger, had higher rates of ketosis, higher HbA1C and glucose concentrations, and lower insulin and C-peptide concentration compared with Ab^- patients.[40] The latter patients had higher BMI z scores and cardiometabolic risk factors at diagnosis and such differences persisted over time. Longitudinal

data analysis uncovered that deterioration in BMI z-score significantly affected systolic blood pressure and ALT, but the lipid profile was mostly impacted by HbA1C and glycemic control regardless of antibody status.[40]

These important pathophysiologic differences in insulin sensitivity and secretion in Ab^+ vs. Ab^- youth with obesity and diabetes, and the contrast in their presentation and clinical course imply that the former is autoimmune T1D against the backdrop of obesity and the latter is "garden variety" T2D. Both forms of diabetes are heterogeneous but the distinction between the two may have important implications for treatment.[144] In Ab^+ youth, the progression to insulin dependency is significantly faster and glycemic control is inferior compared with Ab^-youth.[35, 37] While laboratory assessment for islet autoantibodies could be of value in distinguishing the two types of diabetes, currently available commercial assays are not always sufficiently sensitive to detect low antibody titers yielding negative results when in fact the patient may have autoimmune diabetes.

Treatment of T2D in Youth

The implications of developing T2D at a young age are worrisome, due to the risk of microvascular and macrovascular complications ensuing early in life. Therefore, it is imperative that T2D be treated aggressively to glycemic goals similar to those for youth with T1D as the risks due to hyperglycemia are present regardless of the type of diabetes. The treatment of youth T2D necessitates a multi-faceted approach to alleviate both the insulin resistance and β-cell failure, achieve glycemic control, and prevent acute and chronic complications. This could only be achieved through a diabetes team which includes the patient, family, physician, behavioral specialist, nurse educator, dietician, and school personnel. This approach should focus on family-

based behavioral lifestyle intervention together with pharmacotherapy with the objectives of weight loss or prevention of continued weight gain, adoption of healthier lifestyle habits, normalization of glycemia, and control of comorbidities such as hypertension, dyslipidemia, nephropathy and hepatic steatosis.[145] Efforts should be geared to individualize therapy in T2D not only based on the heterogeneity of the disorder but also based on ethnic/cultural beliefs and traditions.[144] Until recently, and before the TODAY study results were unraveled, there were few data to guide treatment. Most pediatric recommendations were based on studies in adults with T2D. However, in stark contrast to adult T2D a major barrier in treating youth T2D is the lack of approved oral pharamco-theraputic options besides metformin which is the only approved oral antidiabetic agent in youth T2D.[146]

In adults, lifestyle change leading to better nutrition, weight control, and increased physical activity effectively prevents or delays the onset of T2D.[147] In youth, cardiorespiratory fitness is directly associated with insulin sensitivity, and supervised exercise intervention in obese non-diabetic youth improves insulin sensitivity, even in the absence of weight loss.[148-150] The effects of similar interventions in youth T2D with or without weight loss remain to be shown. Weight reduction and individualized nutrition therapy is important since, by definition, all youth in North America with T2D are overweight/obese. Ideally, care should include guidance by a nutritionist with elimination of sugar containing beverages and high-fat, high calorie foods, and establishment of a regular meal schedule, portion control, and improvement in food choices and encouragement of high fiber intake.[151] Despite the overall belief that lifestyle intervention could be beneficial in glycemic control in youth with T2D, the TODAY study, described in detail above, revealed that the addition of intensive lifestyle intervention to metformin was not superior to metformin alone in maintaining glycemic durability nor in achieving better weight loss.[17] At 6

months the proportion of participants with meaningful weight loss (defined as a reduction of at least 7 percentage points in percent overweight) in the metformin plus lifestyle intervention group (31.2%) was not significantly different from the metformin alone group (24.3%).[17] Furthermore, the average change in percent overweight at 24 months was similar between the metformin plus lifestyle intervention group (-5.02 percentage points) and the metformin alone group (-4.42 percentage points).[17] Additional evaluation revealed that even though there were significant but small differences in the change in adiposity parameters (BMI, percent body fat and absolute fat mass) between metformin vs. metformin plus lifestyle at 6 months, there were none at 24 months.[152] The reasons why intensive lifestyle intervention did not prove more effective in TODAY remain to be investigated.

Recommendations for treating youth T2D include initiating therapy with metformin, in escalating doses up to a maximum therapeutic dose of 1000 mg twice a day, combined with lifestyle intervention, aiming for a target HbA1C < 7% by some organizations and < 6.5% by others.[5, 145, 153] If and when the HbA1C target is not achieved, basal insulin treatment is added to the regimen. In TODAY, the overall treatment failure rate (defined by either an HbA1C ≥8% for 6 months or inability to wean from temporary insulin therapy within 3 months of acute metabolic decompensation) was high. After a median of 11.5 months (mean follow-up 3.86 years) 45.6% of participants had glycemic failure.[17] Treatment failure rates were greatest in the metformin alone group (51.7%), and lowest in the metformin plus rosiglitazone group (38.6%, p=0.006). Metformin plus lifestyle group demonstrated an intermediate failure rate (46.6%) which was not statistically different from either of the other two interventions (Figure 6). While BMI increased during the trial for the entire study group, the metformin plus rosiglitazone group had a clearly significant BMI increase. Subgroup analysis revealed significant racial/ethnic disparities. Overall

failure rates, regardless of treatment assignment, were greatest in non-Hispanic blacks (52.8%), Hispanics (45.0%), and lowest in non-Hispanic whites (36.6%).[17] Non-Hispanic blacks fared poorly when assigned to metformin alone (66.2% failure rate) versus non-Hispanic whites (44.9%) or Hispanics (44.0%). Racial/ethnic contrast in these failure rates were not related to difference in insulin sensitivity or secretion parameters at randomization.[55, 75] Additionally, there were gender related differences in response to treatment. Metformin plus rosiglitazone was more effective in girls than in boys (p=0.03), and boys met the metabolic endpoint more often than girls (48.2% vs. 44.3%, p=0.02) regardless of therapeutic assignment.[17] These race-related observations in TODAY are in agreement with diabetes clinic reports demonstrating higher HbA1C in black vs. white youth with T2D.[154]

When compared with adults, the failure rate on metformin monotherapy in youth despite better than 80% adherence during the first year was startlingly high.[72, 155, 156] Treatment failure rates of monotherapy with metformin in adults have been reported as 21%[156]- 42%[155] over similar time periods. The findings from the subgroup analysis and comparison with adult trials indicate a need for different strategies to prevent and treat T2D in youth, which may vary according to race / ethnicity. It will be critical to evaluate safety and efficacy of additional agents targeted to T2D, including incretin-mimetics, in adolescents and young adults to ensure adequate treatment of this disease with devastating complications. Given the knowledge that β-cell failure is a primary feature of the pathophysiology, there is broad interest in investigating therapies directed toward the preservation or restoration of β-cell function.

At the moment the only approved oral antidiabetic medication for youth T2D is metformin. The progress in successfully completing regulatory trials for various pharmacotherapies has been painfully slow due to the still low numbers of youth with T2D, the stringent inclusion/exclusion

criteria imposed by the regulatory agencies and the frequent use of insulin even at the time of diagnosis. The dire need for quick action to address the lack of therapeutic options which target the various pathophysiological mechanisms for T2D in youth has led to the formation of collaborative efforts. Involved parties are the U.S. Food and Drug Administration, European Network of Pediatric Research at the European Medicines Agency, Eunice Kennedy Shriver National Institute of Child Health and Human Development's Diabetes Working Group, and pharmaceutical companies to collect efficacy and safety clinical trial data to inform treatment algorithms.[157]

T2D Complications in Youth

Microvascular Complications

In adults, diabetes-related microvascular complications - retinopathy, nephropathy and neuropathy result in major disabilities.[158-162] It is well-known that diabetes duration and glycemic control are closely associated with the development of these complications. Evidence of microvascular complications and risk markers for macrovascular complications in youth with T2D are present early in the course of the disease within the first 5 years and progress rapidly (Table 3).[163-169] Both SEARCH and TODAY have contributed to advancing our knowledge regarding complications in youth with T2D and their burden.[163-167, 169] Vigilant attention to glycemic control, blood pressure management, dyslipidemia, insulin sensitization, and regular screening are recommended for early detection and for reducing diabetes-related complications in youth with T2D.[170]

In adults, retinopathy is a frequently identified complication associated with newly diagnosed T2D[171], and is not uncommon in adolescents with T2D. Studies in Pima Indians show that the risk of developing retinopathy is lower in those diagnosed before 20 years of age compared with those diagnosed later in life.[172] The SEARCH study estimated a 42% prevalence of diabetic retinopathy in youth with T2D, with a mean diabetes duration of 7.2 years, vs. 17% in patients with T1D.[20] In contrast, the TODAY study, using fundus photography, revealed a lower prevalence of 13.7% in youth with T2D with a mean time of diagnosis of 4.9 years.[164] Most of these youth had early signs of retinopathy, with 90.1% classified as "very mild nonproliferative retinopathy" (microaneurysms or other vascular pathology such as intraretinal hemorrhage or cotton wool infarct), and 9.8% classified as "mild nonproliferative retinopathy" (microaneurysms plus other vascular pathology).[164] The prevalence of retinopathy in TODAY increased with increasing HbA1C, increasing age at the time of fundus photography and increasing diabetes duration.[164] Interestingly however, lower BMI appeared to be a risk factor for retinopathy in TODAY youth.[164] This association remains unexplained, and there are conflicting reports in the adult literature about the relationship between obesity and retinopathy.[173, 174] While in adults it is clear that the presence of even mild retinopathy is predictive of cardiovascular disease and stroke [175-180], youth T2D has not been around long enough to provide this crucial information which requires long-term observations. The TODAY extension study will address the long-term follow up and outcome of youth with T2D.

Youth with T2D also have higher rates of microalbuminuria, which heralds nephropathy, than peers with T1D.[181] In the Australian experience microalbuminuria (defined as $\geq$ 20 μg/min) was present in 28% of youth with T2D vs. 6% with T1D.[181] In SEARCH 22% of youth with T2D had abnormal albumin to creatinine ratio ($\geq$30 μg/mg), as opposed to only 9.2% of patients

with T1D.[18, 182] The Japanese data show 44.4% incident nephropathy in youth T2D vs. 20.2% in T1D.[183] In TODAY the prevalence of microalbuminuria was 6.3% at baseline and soared to 16.6% by the end of the study (mean follow-up of 3.9 years, mean age 14.0 [SD 2.0]) (Table 3).[166] This increasing prevalence was regardless of treatment modality but closely related to glycemic control, HbA1c. In the Pima Indian experience, end stage renal disease and consequent mortality were higher in youth onset (< 20 yrs. of age) vs. older onset (20-<55 yrs.) T2D (25 vs. 5.4 per 1000 patient-years for end-stage renal disease and 15.4 vs 7.3 for death rate, respectively).[184] Canadian First Nation Children with T2D have a fourfold increased risk of renal failure versus youth with type 1 diabetes.[185] Some studies have also shown associations between reduced insulin sensitivity and microalbuminuria or established nephropathy, potentially related to a proinflammatory state accompanied by insulin resistance leading to microvascular damage.[18, 186, 187] Further, adult data exhibit that blood pressure variability plays a role in the development of nephropathy and atherosclerosis.[188-190] Whether or not similar observations will hold true in youth T2D remains to be learned. Lastly, against this backdrop of increased risk of nephropathy in adolescents with T2D, the recommendation is to screen at diagnosis and annually thereafter for microalbuminuria by measuring the albumin-to-creatinine ratio in a random urine sample.[145, 151, 185] Patients with elevated albumin-to-creatinine ratio should have repeat confirmation on at least two of three samples during the subsequent six months.[153] If elevated urine albumin to creatinine ratio is confirmed, it is recommended to initiate an angiotensin converting enzyme (ACE) inhibitor and titrated every 3 months until the ratio is normal. Additionally, vigilant control of glycemia and other comorbidities must be implemented.[145, 151, 153]

Precursors of Macrovascular Complications

Adults with T2D have increased cardiovascular disease and event rates (myocardial infarction, stroke), despite treatment of hypertension and lipid abnormalities.[191] Unfortunately, hypertension and dyslipidemia are common in youth with T2D (Table 3) and predict cardiovascular disease events in adults.[163, 166, 169, 192] Patterns of dyslipidemia conducive to macrovascular disease are high and more prevalent in youth with T2D compared with T1D.[169, 193] In SEARCH youth with T2D had: elevated triglycerides (65%), decreased HDL cholesterol (60%), elevated apoB (36%) and dense LDL cholesterol (36%).[169] Hypertension too is more prevalent in youth T2D compared with T1D: 26% vs. 16%, in Canadian First Nation population[194] and 73% in youth with T2D in SEARCH between 2006-2013.[169] In the TODAY study, 11.6% of the participants were hypertensive at baseline and this escalated to 33.8% by the end of the study (mean follow-up 3.9 years) (Table 3).[166] The greatest risk for hypertension was male sex and higher BMI, with no relationship to treatment modality or glycemic control.[166] Dyslipidemia and chronic inflammation were common in TODAY youth too, and worsened over time (Table 3).[163] Diabetes treatment per se was generally inadequate to control this worsening risk.[163] These data are in concert with observations in adults showing that treating to glycemic goals of adults with T2D didn't improve cardiovascular event risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[195] Nevertheless, in patients with T1D there is evidence that intensive diabetes therapy with attention to glycemic control has long-term beneficial effects on the risk of cardiovascular disease.[191, 195]

Data from our laboratory regarding early subclinical biomarkers of atherosclerosis exhibited that adolescents with T2D have significantly higher pulse wave velocity, a measure of arterial stiffness, compared with obese and normal-weight healthy peers, suggestive of premature aging of their cardiovascular system.[196] Additionally, the SEARCH study demonstrated that

youth with T2D have worse arterial stiffness than youth with T1D, and that increased central adiposity and blood pressure were associated with arterial stiffness, independent of diabetes type.[197] In a follow up study of obese adolescents with normal and abnormal glucose tolerance including T2D, we examined coronary artery calcification in addition to pulse wave velocity and intima-media thickness.[198] These different biomarkers of subclinical atherosclerosis appeared to be differentially modulated; adiposity being the major determinant of coronary artery calcium independent of glycemia, while hyperglycemia/HbA1C was for intima-media thickness, and insulin sensitivity for arterial stiffness.[198] Considering that all T2D youth harbor obesity, insulin resistance and hyperglycemia, it is imperative to implement longitudinal follow up of these subclinical biomarkers of atherosclerosis in this high risk population. In the meantime, current recommendations for youth T2D include blood pressure surveillance and management, and treatment of dyslipidemia according to American Heart Association recommendations.[199]

Bearing in mind the significant differences in prevalence of hypertension, microalbuminuria and dyslipidemia between youth T2D and T1D, it is not surprising that the overall outcome is much worse in T2D than T1D. A population-based cohort study from Canada demonstrated that youth with T2D had an increased risk of any complication with a hazard ratio of 1.47.[200] Kaplan-Meier statistics revealed an earlier diagnosis of renal and neurologic complications in the T2D cohort manifesting within 5 years of diagnosis. Neuropathy, nephropathy, dialysis, blindness and amputation free survival rates were significantly lower in T2D compared with T1D with no difference in retinopathy.[200] Such data were corroborated with Australian observations showing that case fatality is increased in young-onset T2D compared with T1D of similar age and diabetes duration, driven by cardiovascular deaths with a death

hazard ratio of 2 (p=0.003).[201] Further, death occurred after shorter diabetes duration and at a younger age in T2D vs. T1D.[201]

~~Comparision~~Comparison and Contrast between Adult T2D and Youth T2D

While T2D in adults has been around for a long time, youth T2D is relatively in its toddler stage. Though our knowledge of youth T2D has increased tremendously over the last 1-2 decades, a lot still remains to be learned. Even though there are no head-to-head comparisons, data extracted from the literature would suggest that youth T2D may be a more aggressive disease than adult T2D. Therapeutic failure rates appear to be higher in youth compared with adults when comparing TODAY results with ADOPT (A Diabetes Outcome Progression Trial), and with other adult studies.[17, 156, 202] Keeping in mind that the definition for glycemic failure may differ in these studies, the failure rate on metformin in youth was 51.7% vs. 21% in ADOPT.[17, 156] The failure rate on metformin plus rosiglitazone in youth was 38.6% while in adults from the US Department of Defense data base was 14.3%.[17, 202] Further, the higher failure rates to metformin in black youth in TODAY is in contrast to the reported greater effectiveness of metformin in black adults with T2D.[17, 203] The change in insulin sensitivity with metformin monotherapy in TODAY youth was remarkably lower (-4.93%) than that in ADOPT (~13%).[75, 204] Moreover, the deterioration in β-cell function in youth with T2D in TODAY appears to be 3-4 fold faster compared with adults. Our clamp-generated data and TODAY data show on average 20-35% decline per year in β-cell function in youth with T2D,[73, 75] while the decline in adults is on average 7-11%.[71, 156, 202] In the United Kingdom Prospective Diabetes Study (UKPDS), the estimated rate of decline of β-cell function, using the Homeostasis Model Assessment (HOMA

%B) index, was about 7% per year.[71, 205] The ADOPT study of drug naïve adults with T2D with up to 3-yr duration utilized the insulinogenic index, similar to TODAY, as a measure of β-cell function.[204] The insulinogenic index declined at a rate of ~ 7-11% per year in the total cohort. Other prospective studies of adult T2D have shown either stable fasting C-peptide concentrations over a 20 year follow up or insulin use required in only 1/3 of the patients over a 12 year follow up.[206, 207] Whether or not such stark contrast between youth and adult T2D is driven by genetic heterogeneity of the disease, or susceptibility to autoimmunity driving declining β-cell function, or physiologic/metabolic maladaptation to childhood growth and development remains to be investigated.

Summary

The trajectory of childhood obesity not only is giving rise to youth T2D but also is clouding the phenotype of T1D making the distinction between the two difficult along the diabetes spectrum. Over the last 1-2 decades there has been tremendous advancement in our understanding of youth T2D, its risk factors, its pathophysiology, its clinical course and its complications. The TODAY results paint a very gloomy picture of youth T2D, showing high therapeutic failure rates with rapid deterioration in β-cell function necessitating initiating insulin treatment early in the course of the disease. Further, the TODAY showed high rates of comorbidities and complications with progressive and rapid worsening. Last, but not least, the preliminary impression is that youth T2D is a more aggressive disease than adult T2D. Against this backdrop, youth with T2D and their health care providers are up against a giant barrier, the lack of approved therapeutic agents to be used when metformin, the only approved therapy, fails

in these youth. There is an urgent need for effective and safe pharmacotherapy in youth with established T2D, to help achieve target HbA1C, to reverse one or more of the underlying pathophysiological aberrations, to enhance energy expenditure and weight control, to sustain metabolic control, and ultimately reduce diabetes-related micro and macro vascular complications and death at a young age. There is also a dire need for interventions in youth with prediabetes to preserve β-cell function and protect it from progressive failure. Lastly, there is a desperate societal need for the prevention of youth obesity and diabetes for those at risk, to halt the projected four-fold increase in the number of youth with T2D by 2050.[34] The burden of prevention does not fall only on the health care profession, but starts with the family, the school, the neighborhood, the society, the food industry, health care policy makers, economists and the government. The National Institutes of Health and the American Diabetes Association have called for the development of diabetes prevention approaches for positive lifestyle changes in adolescents.[208, 209] The successful smoking stoppage campaign should be the prototype for a successful obesity and T2D prevention campaign starting *in utero*.

Figure Legends

Figure 1: The hyperbolic relationship between insulin secretion and insulin sensitivity. Lean, insulin sensitive e individuals require lower levels of insulinemia/insulin secretion; obese, insulin resistant but normoglycemic individuals compensate with increased insulin secretion. Impaired glucose tolerance develops when insulin secretion is insufficient to overcome insulin resistance, and the disposition index (DI) which is β-cell function relative to insulin sensitivity (insulin secretion × insulin sensitivity) declines. T2D occurs when insulin secretion further deteriorates, resulting in prevalent hyperglycemia.

Figure 2: Pathogenic features of hyperglycemia in T2D. Adapted with permission from Defronzo, R.A.[8] and Tahrani, A.A. *et al*.[9]

Figure 3: (A) Disposition index (DI) which is β-cell function relative to insulin sensitivity in obese adolescents with NGT, IFG, IGT, IFG/IGT, and T2D. Letters are significant post hoc analysis (a: T2D vs. NGT; b: T2D vs. IFG; c: T2D vs. IGT; e: NGT vs. IFG/IGT; f: NGT vs. IGT). Adapted with permission from Bacha, F. *et al*.[61] (B) Incretin effect in obese youth with NGT, IGT and T2D. Letters are significant post hoc analysis (a: NGT vs. IGT; b: NGT vs. T2D). Adapted with permission from Michaliszyn, S. *et al*.[7]

Figure 4: OGTT-derived measures of (A) insulin sensitivity, (B) insulinogenic index and (C) oral disposition index (oDI) by treatment failure (red: failed, blue: did not fail) with the three treatment groups combined (metformin alone, metformin plus rosiglitazone, metformin plus lifestyle) in the TODAY study. The P value refers to the overall effect of

failed vs. not failed group assignment in longitudinal models. Copyright © 2013, American Diabetes Association, Arslanian, S. *et al*.[75]

Figure 5: (A) Insulin-stimulated glucose disposal (Rd) during the hyperinsulinemic-euglycemic clamp. (B) First- and second-phase insulin secretion during the hyperglycemic clamp. (C) Disposition index (DI), i.e. β-cell function relative to insulin sensitivity. Antibody negative (Ab^-: red), antibody positive (Ab^+: orange), obese non-diabetic controls (OBCN: blue), normal-weight controls (NWCN: green). Post hoc Bonferroni correction: Ab^- vs. Ab^+, and Ab^- vs. OBCN subjects. Adapted with permission from Tfayli, H. *et al*.[9] Copyright © 2009, American Diabetes Association.

Figure 6: Overall TODAY study primary outcome results. Survival curves by treatment group for the proportion of study participants free of glycemic failure (HbA1c <8.0%).[17] Copyright © 2012 Massachusetts Medical Society.

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Table 1. Prevalence of Type 1 and Type 2 Diabetes in Youth by Demographic Characteristics in the U.S.[12]

	Type 1 Diabetes	Type 2 Diabetes
Prevalence per 1000 by Age (years)		
All ages; 0 - ≤ 19	1.93	0.46
0 - ≤ 4	0.29	-
5 - ≤ 9	1.35	-
10 - ≤ 14	2.69	0.23
15 - ≤ 19	3.22	0.68
Prevalence per 1000 by Gender		
Male	1.93	0.35
Female	1.93	0.58
Prevalence per 1000 by Race/Ethnicity		
American Indian	0.35	1.20
Asian Pacific Islander Black	0.60	0.34
Hispanic	1.29	0.79
Black	1.62	1.06
White	2.55	0.17
Change in Prevalence (2001 – 2009)	+0.45	+0.12
Adjusted Prevalence Increase	23%	30%

Table 2. American Diabetes Association Criteria for the Diagnosis of Diabetes Mellitus or Prediabetes

DIABETES	
HbA1C ≥ 6.5%*	Method should be NGSP certified, standardized to the DCCT assay.
OR	
FPG ≥ 126 mg/dL (7.0 mmol/L)*	Fasting is defined as no caloric intake for at least 8 hr.
OR	
OGTT** 2-hr PG ≥ 200 mg/dL (11.1 mmol/L)*	
OR	
Random PG ≥ 200 mg/dL (11.1 mmol/L)	Applicable for a patient with classic symptoms (polyuria, polydipsia) or hyperglycemic crisis.
PREDIABETES	
HbA1C 5.7 - <6.5%	
OR	
FPG 100 - <126 mg/dL (5.5 - <7.0 mmol/L)	Impaired fasting glucose (IFG)
OR	
OGTT 2-hr PG 140 - <200 mg/dL (7.8 - <11.1 mmol/L)	Impaired glucose tolerance (IGT)

*In the absence of unequivocal hyperglycemia, this should be confirmed by repeat testing.

** OGTT with a glucose load containing the equivalent of 1.75 g/kg up to a maximum of 75 g anhydrous glucose dissolved in water.

Abbreviations: FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; OGTT, oral glucose tolerance test; PG, plasma glucose.

Table 3. Complications and cardiovascular risk in youth T2D in the TODAY trial at baseline and follow up.[158, 159, 161]

	Prevalence
Hypertension	
Baseline	11.6%
End of Study	33.8%
Microalbuminuria	
Baseline	6.3%
End of Study	16.6%
LDL ≥ 130 mg/dl or LLM	
Baseline	4.5%
Month 36	10.7%
Triglycerides ≥ 150 mg/dl or LLM	
Baseline	21.0%
Month 36	23.3%
hsCRP > 0.3 mg/dl	
Baseline	41.2%
Month 36	46.3%
Retinopathy	
At diabetes duration of 4.9 ± 1.5 y	13.7%

LLM: Lipid lowering medication

Figure 1.

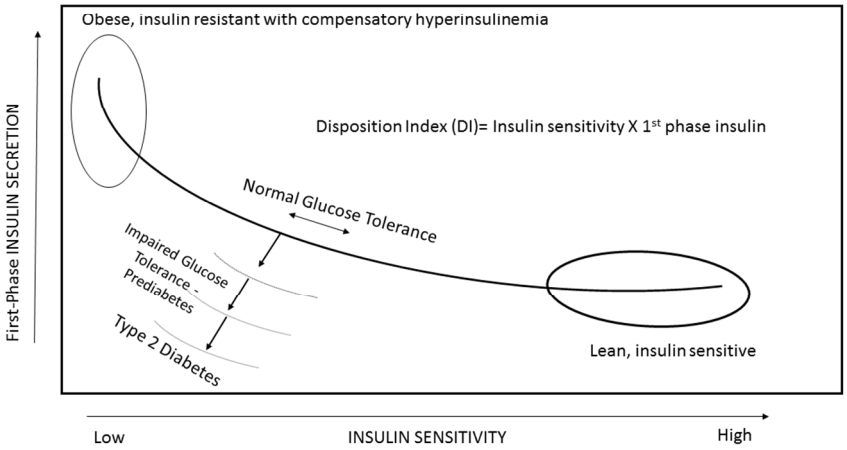

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Figure 2.

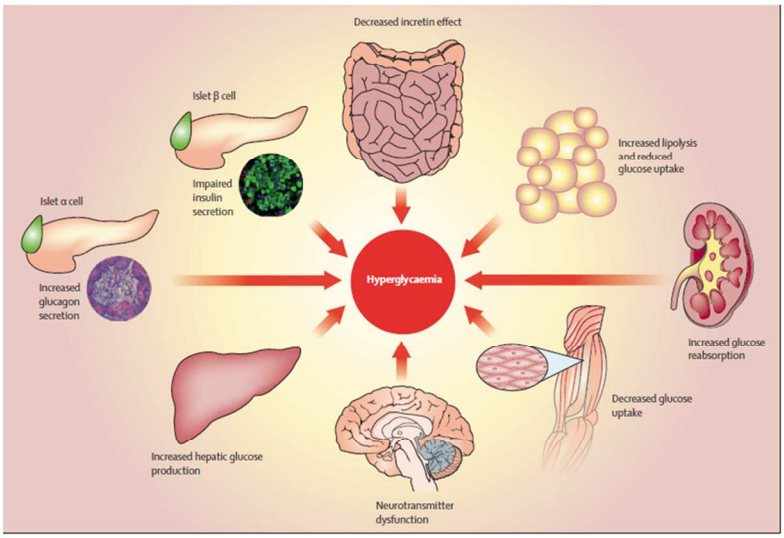

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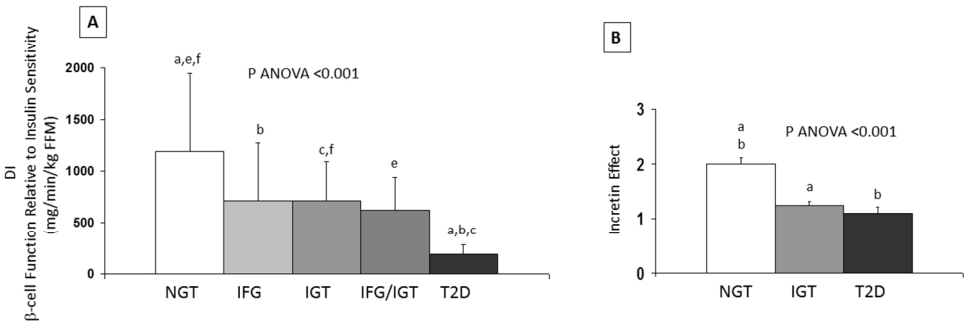
Figure 3.



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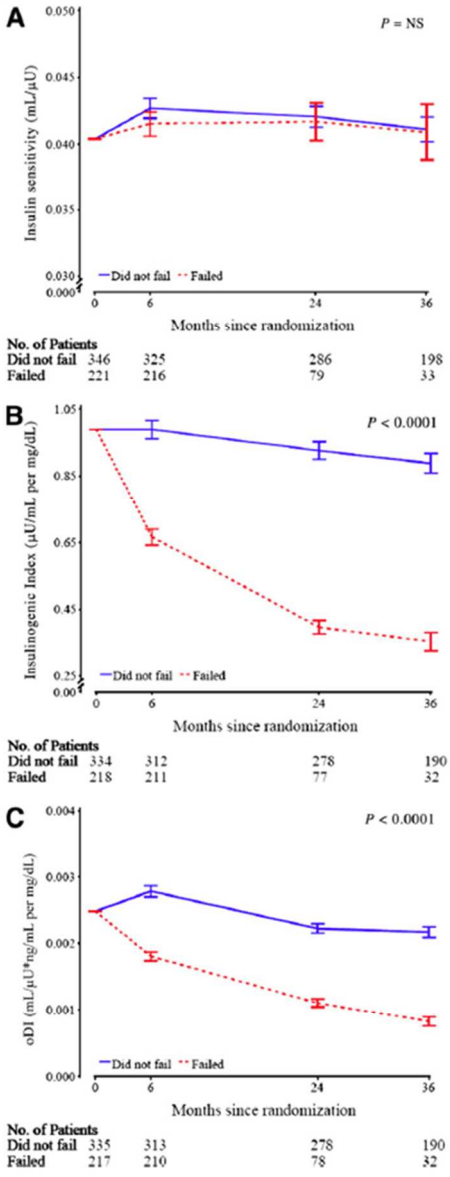

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Figure 5.

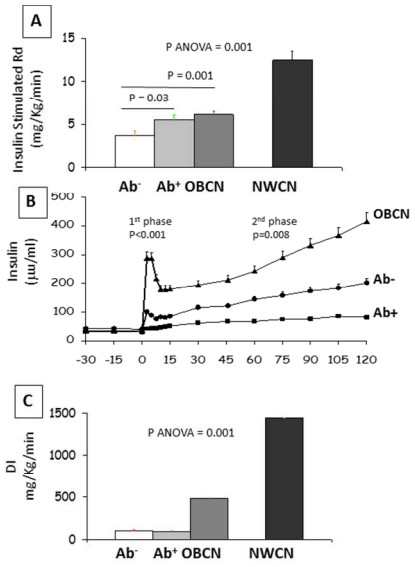

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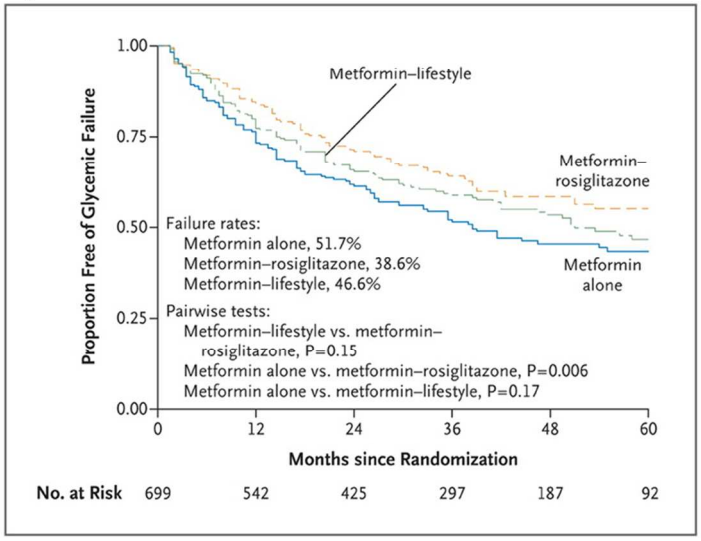
Figure 6.



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