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Evaluation and treatment of youth-onset Type 2 Diabetes mellitus

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EVALUATION AND TREATMENT OF YOUTH-ONSET TYPE 2 DIABETES MELLITUS

by

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a widespread metabolic disorder that continues to grow in prevalence both in the United States and worldwide. T2DM is an immense public health crisis and has been declared an epidemic by the United States Centers for Disease Control and Prevention. T2DM is a heterogeneous disease that is characterized by chronic hyperglycemia that is caused by dysfunction of the insulin transduction pathway. Particularly in T2DM, individuals with the disease experience a progressive loss of insulin production by pancreatic β cells in the setting of peripheral insulin resistance. Due to the dysfunction of insulin's actions, glucose in circulation is unable to enter insulin's target cells and remains in the bloodstream.

Formerly known as adult-onset diabetes, T2DM has recently become more commonplace in youthful populations, particularly in adolescents during puberty. Several risk factors have been identified for T2DM, which defines a population of study to determine the underlying pathogenesis of T2DM and possible therapeutic interventions. While extensive research on T2DM has been performed, the heterogeneous nature of the disease makes it difficult to understand the relationship between genetic susceptibility and environmental triggers.

The trend of reaching younger populations is extremely worrying as the loss of glycemic control in T2DM is associated with various medical complications. The most commonly seen complications in T2DM include neuropathy, nephropathy, retinopathy, and cardiovascular disease. These complications come with a significant burden that greatly increases mortality and reduces one's quality of life. One of the underlying causes of the growing prevalence of youth-onset T2DM is the growing pediatric obese population. The increasing prevalence of pediatric obesity, in turn, is likely tied to adolescents getting less sleep, having diets high in carbohydrates, and having insufficient physical activity.

Compared to T2DM that precipitates later in life, youth-onset T2DM appears to have a more aggressive nature, where glycemic control is quickly lost, and complications arise sooner in the disease course than adults. Unfortunately, compared to the various drug classes available to adults, options for youths with T2DM are limited. Currently, the only pharmacologic therapies available to youths are metformin and insulin and given that youths quickly lose metabolic control, new therapies are desperately needed to combat this epidemic. Lifestyle interventions are also widely used in pediatric populations, but success with lifestyle monotherapy is limited. Adherence to treatment plans is a barrier to positive outcomes in youthful populations, which may be improved by having patients and their families attend diabetes education programs. The aggressive nature of youth-onset T2DM and the limited amount of available therapies make it difficult to maintain control diabetes in this youthful population, which is concerning given the huge costs associated with diabetes for both individuals and health care systems. To combat this epidemic of youth-onset T2DM, aggressive monitoring is needed to identify high-risk populations and to prevent and delay T2DM in these populations. Reducing the prevalence of youth-onset T2DM will require efforts to increase the physical activity of youths and to reduce the consumption of foods that greatly increase blood sugar. Additionally, efforts should be made to ensure that youths are getting adequate amounts of sleep. Bariatric surgery has been demonstrated positive results in remission of T2DM in youths, but such an invasive procedure may be an extreme solution in a vulnerable population.

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
ATP	adenosine triphosphate
BMI	body mass index
Ca2+	calcium
cAMP	cyclic adenosine monophosphate
CDC	Centers for Disease Control and Prevention
CVA	cerebrovascular accident
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
DN	diabetic nephropathy
DPN	diabetic peripheral neuropathy
DR	diabetic retinopathy
FFA	free fatty acids
FPG	fasting plasma glucose
GI	glycemic index
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
GLUT-2	glucose transporter type 2
GLUT-4	glucose transporter type 4
HbA1C	glycated hemoglobin
IFG	impaired fasting glucose

K+	potassium
kg/m2	kilograms per square meter
mg/dl	milligrams per deciliter
MI	myocardial infarction
OGTT	oral glucose tolerance test
PG	plasma glucose
PKA	protein kinase A
RYGB	Roux-en-Y gastric bypass
SES	socioeconomic status
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
Teen-LABS	Teen-Longitudinal Assessment of Bariatric Surgery
TODAY	Treatment Options for type 2 Diabetes in Adolescents and Youths
TV	television
US	United States
WHO	World Health Organization

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is on the rise worldwide, which includes pediatric populations.[1] The increasing prevalence of diabetes has been declared an epidemic with significant public health impacts.[2] In the past, T2DM was referred to as adult-onset diabetes mellitus as the disease was typically seen later in life, but the use of this term is declining as the disease has recently begun reaching younger populations.[3] T2DM was also formerly called non-insulin dependent diabetes mellitus due to the continued presence of insulin in patients with the disease as opposed to the absolute lack of insulin seen in insulin-dependent diabetes mellitus, or type 1 diabetes mellitus (T1DM).[3] T1DM was previously called juvenile-onset diabetes mellitus because it typically began in childhood, but adult-onset T1DM cases do occur.[3] Both forms of diabetes are a serious metabolic condition that comes with a severe burden on those with the disease and on health care systems.[3] This thesis will investigate the causes of the trend of T2DM reaching younger populations, how the disease differs in youths compared to adults, treatment options available for youths, and the significance of the disease reaching younger populations.

Insulin Signaling Transduction

Diabetes mellitus is a disease that is characterized by hyperglycemia, or elevated plasma glucose (PG).[3] Hyperglycemia is caused by the inability of glucose to enter its target cells from circulation due to the dysfunction of the insulin transduction pathway.[3] Insulin is a hormone necessary for glucose to enter adipose and muscle cells where it is either metabolized into energy or stored for later use, which results in a decreased PG concentration.[4] Insulin is a protein hormone that is produced by the β cells of the islets of Langerhans in the pancreas.[5] It is formed by proteolytic cleavage of a larger precursor molecule, proinsulin, that also produces a peptide known as C-peptide in a 1:1 ratio with insulin.[5] C-peptide has been used clinically to estimate the amount of secretion of insulin in patients that have antibodies against insulin that interfere with standard techniques used to measure endogenous insulin secretion.[5] C-peptide has also been used to measure β cell function in patients that use exogenous insulin as treatment, where exogenous insulin would interfere with the assessment of endogenous insulin production.[5]

Insulin regulates body fuel metabolism and its secretion is stimulated by body fuels such as glucose, amino acids, and free fatty acids (FFAs).[4] The concentration of these fuel sources is increased following a meal, which is referred to as the postprandial state.[4] Glucose enters pancreatic β cells via the insulin-independent glucose transporter type 2 (GLUT-2) channel and the increased levels of glucose lead to increased glucose metabolism, which increases levels of adenosine triphosphate (ATP).[4] Increased ATP leads to a closure of ATP-sensitive potassium channels, which depolarizes the cell and opens voltage-gated calcium channels.[4] Calcium then flows into the cell and induces insulin secretion.[4] Insulin secretion occurs in 2 phases, where the first phase occurs quickly and lasts about 10 minutes, which represents the release of preformed and stored insulin.[4] The second phase has a more gradual onset and lasts the duration of the elevated PG following a meal, which is mediated by newly synthesized insulin.[4] During the postprandial period, the gastrointestinal tract releases hormones known as incretins into circulation that also stimulate insulin secretion.[4] The two predominant incretins are known as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1).[6] Incretins are released in response to the presence of food in the gastrointestinal lumen and act on their receptors on pancreatic β cells to induce insulin secretion by a separate signaling cascade from glucose-mediated insulin secretion.[6] Glucose-mediated insulin secretion and how incretins act on a distinct signaling pathway are shown in **Figure 1**.[7] The synergistic effect of incretins and glucose on insulin secretion is indicated by a higher level of insulin secretion in response to an oral dose of glucose compared to an intravenous dose of glucose that would not stimulate incretin secretion.[6] Studies have demonstrated that incretin secretion could be responsible for 50%-70% of postprandial insulin secretion.[6]

Once released into circulation, insulin primarily acts on muscle tissue and adipose tissue by binding to the insulin receptor.[4] The insulin receptor is a transmembrane glycoprotein receptor, which consists of 2 α-subunits and 2 β-subunits.[4] The α-subunits bind insulin with high affinity and specificity, which induces a conformational change that activates the catalytic β-subunits.[4] The β-subunits contain tyrosine-kinase domains that autophosphorylate upon binding insulin and induce a signaling cascade that ultimately leads to the translocation of cytoplasmic storage vesicles containing glucose transporter type 4 (GLUT-4), the insulin-dependent glucose transporter, to the cell membrane, which

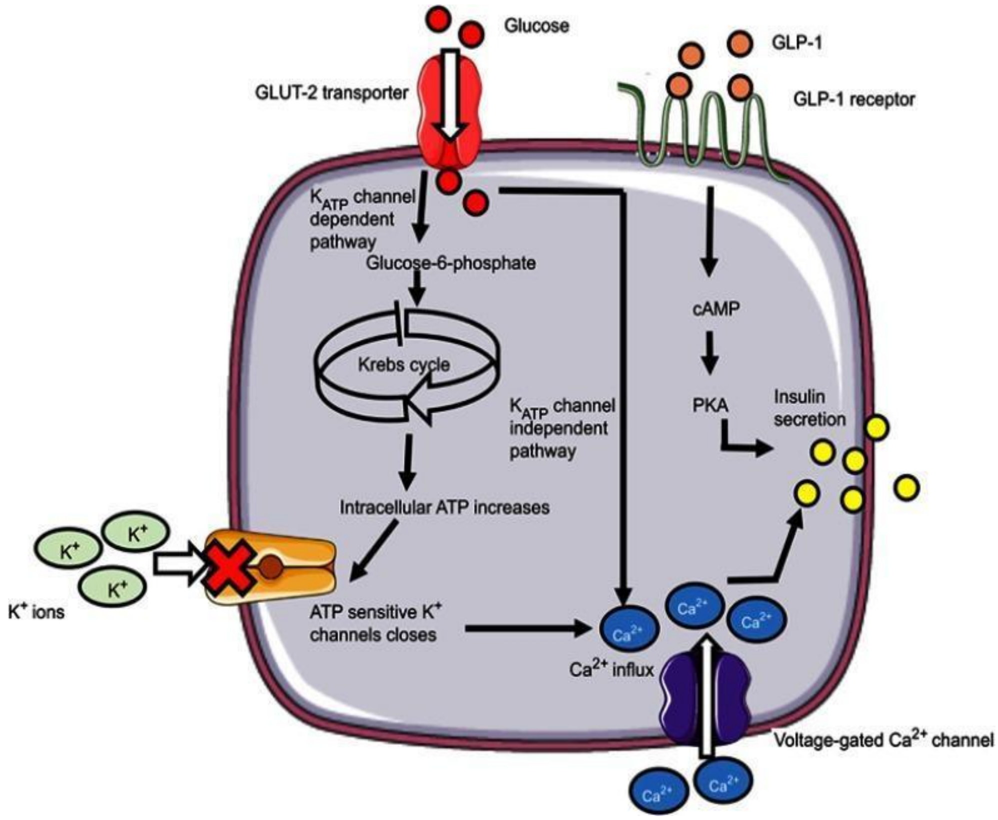

Figure 1. Mechanism of insulin secretion from pancreatic β-cells in response to glucose (left) and GLP-1 (right). In the glucose mediated insulin secretion pathway, glucose enters the cell via the glucose transporter type 2 (GLUT-2 transporter) and increases cellular adenosine triphosphate (ATP) via the Krebs cycle. The increased ATP levels closes ATP sensitive potassium (K^+) channels, which depolarizes the cell. Cellular depolarization opens voltage-gated calcium (Ca^{2+}) channels, where Ca^{2+} influx induces insulin secretion. In the incretin mediated insulin secretion pathway, glucagon-like peptide 1 (GLP-1) acts on the GLP-1 receptor, which increases cellular cyclic adenosine monophosphate (cAMP). Increased cAMP levels activate protein kinase A (PKA), whose downstream phosphorylation events induce insulin secretion (adapted from Ojha et al. 2019).[7]

allows glucose to enter the cell where it can be metabolized or stored.[4] Many of the subsequent actions of insulin are mediated by phosphorylation and dephosphorylation events.[4]

Glucose is then metabolized via the glycolytic pathway to produce ATP for the cell.[4] Insulin stimulates glycolysis by inducing transcription of key glycolytic enzymes and stimulating enzymes used later in glucose metabolism, such as pyruvate dehydrogenase.[4] Insulin also inhibits gluconeogenesis by inhibiting the transcription of a key enzyme in the pathway, phosphoenolpyruvate carboxykinase, which also contributes to a lower PG concentration.[4] Glucose storage is also regulated by insulin.[4] Insulin stimulates glycogen synthesis in liver and muscle cells while also inhibiting glycogenolysis.[4] Also in the liver, insulin stimulates the conversion of glucose to fatty acids that are exported out of hepatocytes into the bloodstream as lipoproteins.[4] Lipoproteins are broken down into FFAs in capillaries proximal to adipose tissue.[4] Adipose cells then uptake the FFAs and use them to synthesize triglycerides that are stored for future energy demands.[4] Insulin also prevents the breakdown of triglycerides in adipose cells by inhibiting enzymes involved in lipolysis, which results in the accumulation of triglycerides in adipose cells postprandially.[4] Due to insulin's effects on increasing fuel storage, it is considered an anabolic hormone.[4]

Diabetes Mellitus Pathophysiology

There are different points of dysfunction in the insulin transduction pathway that differentiate T1DM from T2DM. T1DM is estimated to represent 5%-10% of all diabetic cases.[8] T1DM is recognized as an absolute deficiency of insulin that is caused by autoimmune destruction of pancreatic β cells.[3] The loss of mass and function in pancreatic β cells leads to a depletion of insulin secretion.[3] The lack of insulin prevents the transport of glucose to insulin's target cells and produces a chronic hyperglycemic state that usually presents clinically by polyphagia, polydipsia, and polyuria.[3] Other symptoms of T1DM include fatigue, vision changes, numbness in the extremities, and slow healing wounds.[3] These symptoms typically appear rapidly in T1DM, in the span of weeks.[3] T1DM may also present with diabetic ketoacidosis (DKA), which is a serious complication of diabetes.[3] Insulin's target cells are unable to metabolize glucose, which causes the body to seek alternative fuel sources.[4] Without insulin, gluconeogenesis in the liver is disinhibited and hepatic cells release glucose into circulation to further elevate PG levels.[4] Adipose tissue lipolysis releases FFAs into circulation that are converted to ketone bodies and glucose by the liver via β oxidation and gluconeogenesis respectively.[4] Ketone bodies can be used as an alternative fuel source during periods of starvation.[4] Ketone bodies are acidic and lead to metabolic acidosis that is slowly compensated by the release of acetone in the breath, which has a distinctive sweet smell.[4] T1DM is usually differentiated from T2DM by the presence of two or more autoantibodies against components of pancreatic β cells and insulin.[3] While the presence of autoantibodies does not guarantee a progression to T1DM, the likelihood of diagnosis increases with the number of autoantibody types.[3]

Compared to T1DM, T2DM is a metabolic disorder that is typically categorized by peripheral insulin resistance, where cells do not respond to insulin in a normal fashion.[3] T2DM accounts for the vast majority of diabetic cases, representing 90% to 95% of all diabetic cases.[8] Insulin resistance may occur due to dysfunction in any part of the insulin receptor transduction cascade, but it has been largely associated with a decrease in the recruitment of GLUT-4 from cytoplasmic storage vesicles, which results in a decreased rate of glucose translocation from circulation.[9] Studies have demonstrated that expression of GLUT-4 is reduced in T2DM, which also results in decreased glucose uptake.[10] In addition to a decreased amount of glucose transporters, the function of the remaining transporters is also decreased in T2DM where the rate of glucose transport is significantly decreased.[9] While the exact mechanism of reduced GLUT-4 function remains unclear, it has been hypothesized that a reduced affinity for glucose may be responsible.[9] Most of the glucose in circulation is taken up and used by skeletal muscle and insulin resistance is largely due to the dysfunction of insulin transduction in this tissue.[11] However, insulin resistance has also been demonstrated in hepatic tissue. Due to this resistance, gluconeogenesis in hepatocytes occurs at a higher rate and further contributes to a hyperglycemic state.[11]

Another defining feature of T2DM is the progressive loss of pancreatic β cell function that leads to reduced insulin secretion.[3] This loss is a relative deficiency in insulin as opposed to an absolute deficiency seen in T1DM, where circulating levels of insulin may appear to be normal or even elevated, but unable to compensate for insulin resistance and leads to a loss of glucose homeostasis.[3] Pancreatic β cells are forced to produce more insulin to compensate for peripheral insulin resistance, which acts as a source of stress and induces apoptosis.[12] Another source of decreased β cell function appears to be due to the increase in circulating FFAs seen in T2DM, which occurs due to the disinhibition of lipolysis in adipose cells.[13] Elevated levels of circulating FFAs have been demonstrated to stimulate insulin secretion and chronically elevated levels may act as a source of stress similar to glucose.[14] The elevated circulating FFAs have a lipotoxic effect on pancreatic β cells and induces apoptosis.[13] Studies have demonstrated that dysfunction of autophagy in pancreatic β cells may be responsible for the loss of β cell mass and function.[15] Autophagy is a process where cells degrade damaged organelles and proteins as a method to maintain cellular homeostasis.[15] Fasting PG (FPG) is significantly elevated in patients with T2DM and those with impaired fasting glucose (IFG), which is an intermediary state where glucose metabolism is abnormal but not yet considered T2DM (**Figure 2A**).[12] β cell mass is significantly reduced in T2DM and IFG patients, which corresponds with the elevated FPG and occurs in obese and lean patients (**Figure 2B**).[12] The observation that decreased β cell volume occurs in both lean and obese diabetics is significant because obesity is a risk factor for T2DM, and this observation shows that β cell deficits are not solely attributable to body weight.[12]

T2DM presents clinically with the same symptoms as T1DM, but the appearance of these symptoms occurs more gradually than T1DM, over the course of a few years.[3] Many patients with T2DM are asymptomatic, which can delay the diagnosis and treatment of T2DM.[3] DKA is not typically seen in T2DM due to the presence of insulin being sufficient to prevent the formation of ketone bodies.[3] Related to T2DM is the condition prediabetes, IFG, or impaired glucose tolerance, where there is an impaired response to glucose and insulin, but not significant enough to warrant a diagnosis of T2DM.[3] Individuals with prediabetes are at high risk of progressing to T2DM even with therapeutic

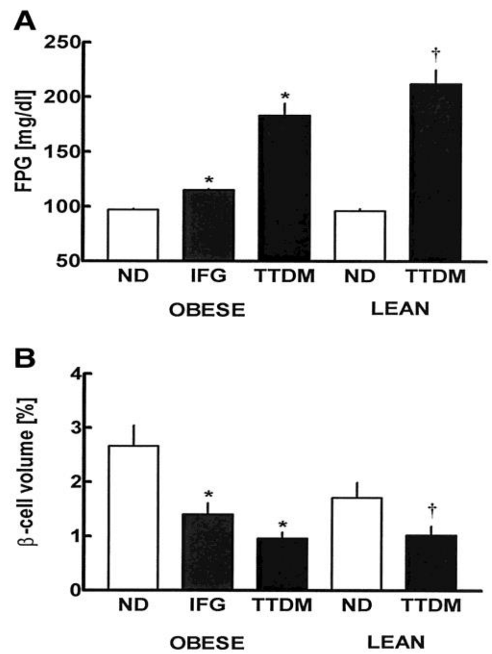

Figure 2. Fasting plasma glucose and β-cell volume in obese and lean subjects The mean FPG concentration (A) and the mean relative β-cell volume (B) in obese (nondiabetic [ND], impaired fasting glucose [IFG], and type 2 diabetic subjects [TTDM]) and lean cases (nondiabetic and type 2 diabetic subjects) (adapted from Butler et al. 2003)[12].

intervention.[3] Insulin resistance may be apparent in prediabetes and circulating insulin levels may be higher than normal to overcome insulin resistance.[3] These patients are unable to return to normal PG concentration after consuming dietary glucose.[3] Prediabetes is often asymptomatic and is recognized due to testing in patients that are at high risk of diabetes.[3]

Detection and Diagnosis of Diabetes Mellitus

Both T1DM and T2DM are detected and measured in similar ways.[16] A patient would be tested if they present with symptoms of diabetes or are determined to be at high risk of diabetes.[16] There are several tests that are used clinically to diagnose diabetes, but the most prevalent are measuring fasting PG or glycated hemoglobin (HbA1C).[16] Fasting PG is a measure of PG concentration following an 8 hour fast or more.[16] Normally, a patient's fasting PG would be less than 100 milligrams per deciliter (mg/dl), whereas a diabetic patient would have a PG greater than 126 mg/dl and a prediabetic patient would fall between those two ranges.[16] HbA1C gives a measure of the patient's PG over the past 3 months due to the lifespan of red blood cells, which is about 100 to 120 days.[18] Glucose can non-enzymatically bind to the hemoglobin in red blood cells and the higher amount of HbA1C is correlated with the degree of hyperglycemia.[18] The amount of HbA1C is often expressed as a percentage of total hemoglobin and the American Diabetes Association (ADA) recommends a diagnosis of diabetes with an HbA1C greater than 6.5%.[16] The normal range for HbA1C is below 5.7% and prediabetic patients will have an HbA1C between these two ranges.[16, 17] The ADA recommends the HbA1C test as the preferred measure of diabetes due to PG concentration estimates being highly variable amongst individuals and there is a high degree of variability in the collection and storage methods of PG used in the other tests[18]

In addition, clinicians can also test a random PG concentration, where a diabetic patient will have a PG concentration greater than 200 mg/dl and a normal patient will be below that value.[16] Another test available to clinicians is the oral glucose tolerance test (OGTT), which requires a fast of at least 8 hours before the test and measures PG concentration.[16] The patient will then ingest a known amount of glucose, usually 75 grams, and then have their blood tested 2 hours after ingestion. A normal patient will have a PG concentration less than 140 mg/dl, while a diabetic patient will be above 200 mg/dl and a prediabetic patient will have an intermediate value.[16] Even with these detection methods, many cases of diabetes are asymptomatic and an estimated 29.3% of all diabetes cases are undiagnosed, which suggests that there needs to be an improvement in the detection and awareness of diabetes.[19] **Table 1** summarizes the diagnostic criteria for prediabetes and diabetes of the ADA.[16]

Risk Factors of Type 2 Diabetes Mellitus

While the exact cause of T2DM remains unclear, several risk factors have been identified that include genetic and lifestyle components. It is thought that genetic predisposition interacts with environmental factors that result in the emergence and progression of the disease.[3] There are large discrepancies in the prevalence of T2DM between different ethnicities, which supports a genetic factor in the disease.[8] In the United States (US), the prevalence of T2DM is higher in ethnic minorities, which includes African Americans, Asian Americans, Latino Americans, and Native Americans.[8] Among these groups, Native Americans are at the highest risk of T2DM.[8] While no single gene guarantees a diagnosis of T2DM, several genes have been identified that increase susceptibility to T2DM, many of which influence β cell function and are speculated to have a role in β cell proliferation and apoptosis.[20] There have also been various genes identified that affect the function of the GLUT-4 transporter.[20] The genes associated with T2DM have

Prediabetes
HbA1C 5.7% to <6.5%
IFG: fasting glucose ≥100 but <126 mg/dL
IGT: 2-h plasma glucose ≥140 but <200 mg/dL during an OGTT
Diabetes
A1C ≥6.5%
or
FPG ≥126 mg/dL
or
2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT.
or
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >200 mg/dL

Table 1. Criteria for the diagnosis of prediabetes and diabetes (adapted from Arslanian et al., 2018)[16].

been shown to have a cumulative effect, where the number of genes present is positively correlated with the likelihood of a diagnosis.[20]

A family history of diabetes with first-degree relatives has also been established to increase the risk of T2DM, even more so than T1DM.[21] One study demonstrated that having one parent with a history of diabetes conferred a 3.5-fold higher risk of T2DM and two parents increased the risk by 6 fold.[22] Other studies have demonstrated that maternal transmission of the disease is a stronger risk factor than paternal transmission.[22, 23] This differential effect between maternal and paternal disease transmission may be linked to the intrauterine environment during pregnancy. A younger age of diagnosis of T2DM has been associated with a hyperglycemic intrauterine environment, as it has been demonstrated that T2DM is diagnosed earlier in offspring if their mother was diagnosed with diabetes before pregnancy compared to a diagnosis after pregnancy.[21] This association was not seen in T1DM.[21] It is important to note when assessing family history as a risk factor of T2DM that families also share environments, such as their socioeconomic background or diet. However, studies have demonstrated that T2DM has 72% concordance among monozygotic twins compared to 41% concordance among dizygotic twins, which strengthens the evidence of a genetic background for T2DM.[24]

Advanced age is also associated with an increased prevalence of T2DM. In 2012, the prevalence of diabetes in those older than 65 was about 19%, which is significantly higher than the prevalence of the general population at 8.3%.[8] Studies have demonstrated that insulin secretion decreases with age in a linear fashion between the ages of 20 and 70, where there is a loss of about 0.7% of insulin secretion per year.[25] This rate of loss shows that aging by itself is not enough to induce T2DM, but it can exacerbate dysfunction of glucose homeostasis in those with other risk factors. However, insulin sensitivity was not shown to decrease with age, which supports the hypothesis that the development of T2DM in old age is multifactorial.[25] As age increases, the pancreatic β cell turnover rate decreases, which would ultimately result in decreased β cell function and less insulin production.[26]

With advanced age, there is also a decrease in β cell proliferation, and they are more probable to undergo apoptosis in hyperglycemic environments.[27] Thus, in older individuals, the pancreatic β cells experience reduced mass and are more vulnerable to stress, which results in a reduced capacity to compensate for insulin resistance.

In addition to these uncontrollable risk factors, several modifiable risk factors for T2DM have been identified. Among these, the relationship between obesity and T2DM is well documented and obesity is considered to be one of the primary factors in developing T2DM.[28] Approximately 86% of all T2DM cases are overweight or obese.[29] The World Health Organization (WHO) and Centers for Disease Control (CDC) both define obesity as a body mass index (BMI) above 30 kilograms per square meter (kg/m^2) and a BMI between 25 and 30 kg/m^2 is considered overweight.[29] Obesity features an excessive accumulation of adipose tissue, particularly around the abdominal area.[29] Obesity is associated with insulin resistance, but many obese patients secrete enough insulin to overcome insulin resistance and maintain glucose homeostasis.[29] Increased circulating levels of FFAs are another hallmark of obesity, which has been shown to reduce insulin-stimulated glucose uptake in a dose-dependent manner.[30] It has been proposed that elevated levels of FFAs in the intracellular compartment interfere with the transduction cascade of the activated insulin receptor.[31, 32] This interference leads to decreased trafficking of GLUT-4 to the cellular surface and reduced insulin-stimulated glucose uptake.[31] Another aspect that needs to be considered in understanding the relationship between obesity and T2DM is the distribution of body fat. A higher degree of insulin impairment is associated when there is a higher level of adiposity in the chest and abdomen compared to adiposity in the extremities.[33] Abdominal fat, or central fat, has been shown to have a strong relationship with insulin resistance in both skeletal muscle and liver tissue and this relationship has been shown to occur even in non-obese individuals.[33] There is not only a higher prevalence of T2DM with increasing BMI, but there are significantly higher rates when central obesity and blood lipids are present (**Figure 3**).[34] Another distinction within central adiposity is the observation that abdominal visceral fat appears to have a stronger relationship with insulin resistance than subcutaneous fat.[35] It is hypothesized that visceral adiposity produces more FFAs into the liver portal circulation and this increase may lead to hepatic insulin resistance, which would interfere with insulin's inhibition of hepatic gluconeogenesis.[35] As noted, elevated FFAs may also induce apoptosis of pancreatic β cells, which contributes to the progressive loss of insulin secretion seen in T2DM.[13] However, the link between obesity and T2DM is still widely researched and the exact mechanism is a topic of debate.

Diet is another factor that influences the risk of developing T2DM. Glycemic index (GI) is a term used to describe a food's ability to raise PG concentration, where a high GI will significantly increase the PG level.[36] Less processed grains have a low GI and maintain their original fiber content, while more refined grains with low fiber have a higher GI Foods with a high GI increase the demand for insulin and increase insulin secretion, which is a well-understood feature of T2DM.[36] As previously noted, increased insulin demand acts as

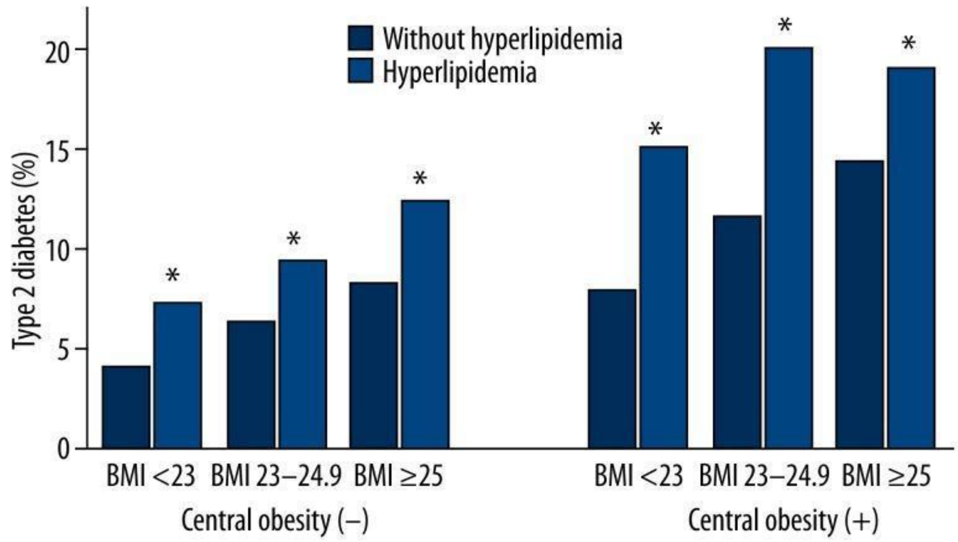

Figure 3. Prevalence of T2DM for increasing BMI and with or without the presence of central obesity (adapted from Chen et al., 2015).[34]

stress for pancreatic β cells and can induce apoptosis to reduce mass and function.[12] Studies have demonstrated that a diet that consists of foods with a high GI is positively correlated with the risk of T2DM, whereas total carbohydrate intake did not noticeably increase the likelihood of T2DM.[37] In particular, a high ratio of refined grains to whole grains in dietary intake appears to substantially increase the risk of T2DM.[38] Additionally, the amount of dietary fiber present in a diet is inversely associated with the risk of T2DM.[37] Dietary fiber has been shown to reduce a rise in PG and insulin following a meal.[39] Whole grains tend to have higher levels of fiber that may slow their rate of digestion and absorption, which would contribute to their low GI.[40] Surprisingly, total energy intake was not independently correlated with an increased risk of T2DM, which indicates that dietary content is a more significant influence on T2DM risk than the amount of food eaten.[36]

Sleep loss has also been identified as a risk factor for T2DM.[41] Glucose tolerance has been shown to fluctuate throughout the day, where it is highest in the morning and decreases throughout the day where it is lowest in the middle of the night.[41] This decreased sensitivity to glucose is due to a reduction in insulin sensitivity where there is a decreased secretion of insulin in response to a glucose load.[41] In the morning, elevated glucose levels quickly return to normal due to an increased output of insulin.[41] This pattern is in part mediated through the circadian pattern of cortisol secretion, which has a high secretion in the morning and a decreased secretion in the evening.[42] This pattern is counterintuitive due to the well-documented effect of cortisol to decrease glucose sensitivity and insulin secretion, the high level of cortisol secretion in the morning would be expected to elicit a decreased tolerance to glucose.[42] However, while there is a decrease in insulin secretion, PG levels remain constant, which suggests that the actions of insulin are enhanced, possibly due to increased binding of insulin to its receptor.[43] Studies have demonstrated that loss of sleep, which is categorized by sleeping less than 6 hours per night, is associated with increased body weight and diabetes.[44] While the effect on T2DM may be mediated in part by the effect on body weight, the increased incidence of T2DM with decreased amounts of sleep still occurred after controlling for body weight.[44] Decreased amounts of sleep significantly increase insulin resistance without an accompanying increase in insulin secretion, which suggests that there may be multiple mechanisms that decrease glucose tolerance with reduced sleep.[44] A decrease in the amount of sleep has been shown to increase levels of evening cortisol, which may play a part in decreased glucose tolerance by antagonizing the effects of insulin.[45] Sleep deprivation has also been associated with both an increased appetite and an increased desire for foods with a high glycemic index.[46, 47]

Another risk factor for T2DM is sedentary behavior, where leisure time has increased amounts of time sitting or lying down and a decreased amount of physical activity.[48] Sedentary behaviors do not greatly increase energy expenditure above resting basal metabolic rate.[48] Exercise has been shown to be protective against T2DM independently of age and obesity.[49] Increased physical activity enhances insulin sensitivity and improves glucose tolerance and this effect arises whether or not changes in body weight occur.[50] Exercise mediates its effect on insulin sensitivity by increasing the amount and activity of GLUT-4 transporters.[51] The protective effect of exercise may also be due to not only a general decrease in fat mass but also an increased loss of visceral fat compared to subcutaneous fat.[52] While decreased amounts of physical activity are associated with obesity and T2DM, sedentary behavior is associated with T2DM independently of physical activity and body weight.[53] Particularly, television (TV) watching is positively correlated with an increased risk of obesity and T2DM.[53] TV watching also influences dietary patterns; those who watch more TV also eat more processed foods and fewer vegetables and fruits.[53] TV watching is associated with a significantly higher risk of T2DM, even compared to other sedentary behaviors (**Figure 4**).[54] While sedentary behavior as a risk

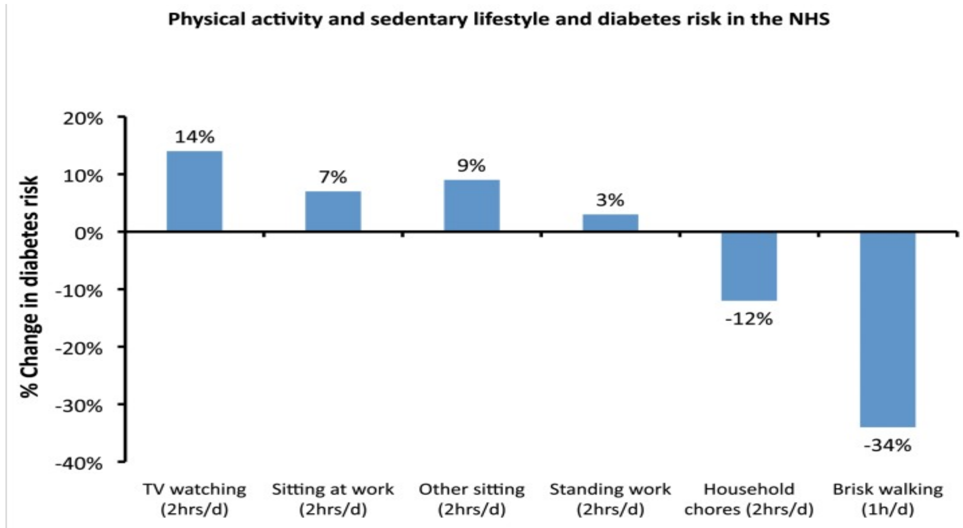

Figure 4. The relative risk of developing type 2 diabetes in nondiabetic women. Sedentary habits result in an increased risk of developing T2DM, while more vigorous activities result in a decreased risk of developing the disease (adapted from Hu et al., 2011)[54].

factor of T2DM may mostly mediate its effect through obesity, there appear to be several means where such behavior decreases insulin sensitivity and glucose tolerance.

Socioeconomic status (SES) is another area that needs attention when considering the risk of T2DM.[55] SES describes the economic and social position that one holds within a social structure and is typically measured by some combination of educational attainment, amount of income, and occupational prestige.[55] The risk of T2DM has been shown to have an inverse correlation with SES and this relationship does not exist for T1DM.[55] This discrepancy between social classes is likely multifactorial and may arise from several causes, such as access to health care services, health education, availability of healthy eating options, and free time available for exercise. Access to health care refers to the availability of health care services and if those services are used by patients.[55] People with lower SES have more barriers that limit their access to care, such as financial constraints or lack of proximity to medical facilities.[56] These barriers reduce the likelihood of an early diagnosis of T2DM and limits access to the resources necessary to slow the progression of the disease.[56]

Those with low SES have a higher tendency to use avoidance coping during stressful events, which refers to dealing with stress by ignoring that it exists or to give up trying to deal with stressors.[57] Much of the burden associated with low SES is due to a lack of financial power and how that can influence all aspects of life.[57] Living with T2DM is extremely stressful as it is difficult to maintain a balance of medication adherence in a setting of increased stress associated with low SES.[58] The stresses associated with treating T2DM may receive a lower priority and could explain why low SES is associated with higher rates of loss of glycemic control.[57] Studies have shown that low SES is associated with less capacity to engage in healthy decisions, which both exacerbates existing health conditions and increases the risk of developing more health issues.[58] A higher usage of avoidance coping could explain why low SES is associated with behaviors that increase the risk of T2DM. Those who are preoccupied with the stresses of low SES would have less capacity to engage in healthy eating habits, which could lead to higher consumption of high GI foods.

Complications of Type 2 Diabetes Mellitus

T2DM is associated with several complications that arise during the course of the disease.[59] Diabetic complications are associated with loss of glycemic control and a chronic hyperglycemic state, which causes damage to blood vessels.[60] The complications of diabetes are widely grouped as microvascular complications, which arise due to damage to small blood vessels, and macrovascular complications, which are due to damage to arteries.[60] The most common microvascular complications include retinopathy, neuropathy, and nephropathy.[60] Macrovascular complications typically manifest as a form of cardiovascular disease (CVD) and often lead to myocardial infarction (MI) or cerebrovascular accidents (CVA).[3, 60]

Diabetic retinopathy (DR) is the degeneration of the retina and is one of the leading causes of vision loss and blindness.[61] It is estimated that among diabetic patients in the US, the prevalence of DR is 33.7%.[61] There is an increased risk of DR associated with a longer duration of diabetes and loss of glycemic control.[61] Studies have shown that intense intervention to maintain glycemic control can delay the onset and progression of DR.[62] Hyperglycemic conditions damage the small blood vessels of the retina, which includes changes in vascular permeability, capillary degeneration, microaneurysms, and excessive growth of new blood vessels.[63] DR progresses in two stages called nonproliferative diabetic retinopathy and proliferative diabetic retinopathy. In the nonproliferative stage elevated PG levels induce the death of retinal capillary cells, which cause microaneurysms to form.[60] The microaneurysms can cause fluid to leak out of the capillaries, which is called macular edema and contributes to visual impairment. Hyperglycemia can also cause a thickening of the basement membrane of retinal capillaries, which can result in the closure of the capillaries.[64] These changes in the microvasculature of the retina can result in a lack of perfusion that leads to retinal hypoxia.[65] Hypoxia induces a release of inflammatory cytokines from retinal endothelial cells, which recruit leukocytes to the retina and contribute to further blockage of retinal microvasculature.[65] This damage results in a chronic hypoxic condition that causes retinal endothelial cells to release angiogenic growth factors that induce vascularization of the retina and leads to the proliferative stage of diabetic retinopathy.[66] The abnormal new vessels lead to scar tissue in the retina and further contribute to vision loss.[66]

Diabetic neuropathy is a form of progressive nerve damage that can affect different parts of the nervous system in various forms of neuropathy but primarily affects the extremities as diabetic peripheral neuropathy (DPN).[67] DPN is very common and affects up to 50% of diabetic patients.[67] It typically manifests with abnormal sensation, pain, weakness, and poor wound healing, but there is a high degree of variability of symptoms between patients.[67] Typically, symptoms begin at the distal extremities and progressively spread more proximally.[67] DPN is often described as persistent pain and often interferes with everyday activities, which results in a significantly reduced quality of life.[68] DPN is associated with the duration of diabetes, age, and poor glycemic control (**Figure 5**).[69, 70] While the prevalence of neuropathy increases with age and disease duration in both T1DM and T2DM, it has a higher association with T2DM at all ages (**Figure 5**).[70] However, DPN

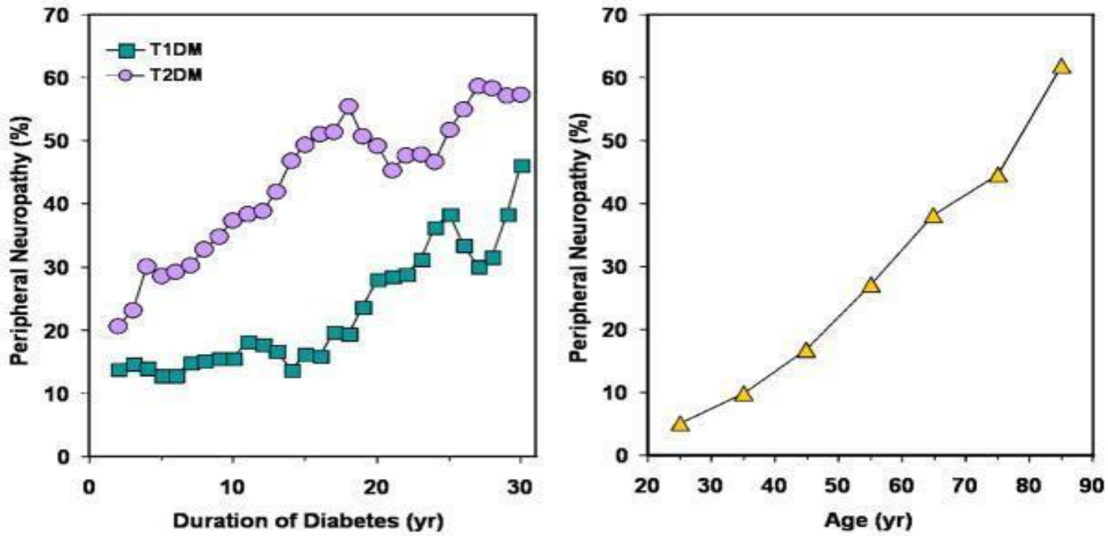

Figure 5. Effect of disease duration and age on prevalence of diabetic neuropathy For both T1DM and T2DM, duration of diabetes (left) as well as age of patient (right) is correlated to the incidence of diabetic neuropathy (adapted from Edwards et al., 2008).[70]

can develop in patients that have good control of their PG, which indicates that other factors outside the duration of disease and glycemic control influence the development of DPN.[69] Hyperglycemic conditions cause glucose to enter metabolic pathways that ultimately result in free radicals that cause oxidative damage to neurons and to endothelial cells surrounding the nerves.[71] For example, it has also been proposed that elevated PG levels cause glucose to react non enzymatically with structural and functional proteins in peripheral nerves and these glycated end products cause oxidative stress and damage.[72] The damage to endothelial cells reduces blood flow to nerves and results in further nerve damage.[72] The lack of sensation caused by DPN is associated with wounds that eventually develop into ulcers in the lower extremities, which is one of the leading causes of lower extremity amputations.[73] The poor wound healing associated with DPN plays a role in the formation and progression of diabetic ulcers.[74] Lower extremity amputations greatly impede one's ability to perform daily tasks and significantly lower the quality of life for diabetic patients.

Diabetic nephropathy (DN) is one of the leading causes of kidney disease and is estimated to affect 40% of diabetic patients.[75] Like other microvascular complications of diabetes, diabetic nephropathy is associated with hyperglycemia and duration of disease, with an average onset of 10 to 20 years after diabetes diagnosis.[75] Hyperglycemia increases glucose flux into mesangial cells of the kidney's filtration unit, the glomerulus, and induces metabolic dysfunction in these cells.[76] The increased flux into mesangial cells is through the insulin-independent glucose transporter type 1.[77] The metabolic changes in glomerular cells induce thickening of the basement membrane of the glomerulus and expansion of mesangial cells.[77, 78] Nephropathy is clinically diagnosed by the presence of albumin or proteins in the urine and by a progressively diminishing glomerular filtration rate.[78] As the kidneys lose their ability to filter blood, it may progress to end-stage kidney disease where the patient requires hemodialysis to live, which greatly reduces their quality of life.[78] Hemodialysis is a treatment where a machine filters waste products and water from the blood in replace of the kidneys.[78]

Complications of diabetes that affect the arteries are collectively called macrovascular complications.[79] Macrovascular complications lead to CVD, which is one of the leading causes of mortality in T2DM and is estimated to account for half of T2DM related deaths.[79] As seen with microvascular complications, hyperglycemia induces metabolic changes in endothelial cells, which results in oxidative stress and inflammation of endothelial cells.[80] The inflammation and damage to endothelial cells result in smooth muscle proliferation and collagen accumulation.[80] Oxidized lipids accumulate in immune cells drawn to the area by inflammation, which together with the smooth muscle cells and collagen form an atherosclerotic lesion and narrow the artery.[81] Atherosclerosis associated with diabetes greatly increases the risk of coronary artery disease, which in turn increases the risk of an MI.[82] One study found that a diabetic patient without a history of MI has a comparable risk of MI to a nondiabetic patient with a history of CVD.[82] Additionally, diabetic atherosclerosis has been found to significantly increase the risk of CVA by 35%.[83] Macrovascular complications are serious outcomes of diabetes that negatively impact the quality of life and significantly increase mortality in diabetic patients by increasing the risk of acute life-threatening cardiac events.

Trends of Type 2 Diabetes Mellitus

The prevalence of diabetes has increased dramatically in the United States, increasing from 4.5% to 12.2% of the total population from 1995 to 2017, which demonstrates a 171.1% increase.[84, 85] Studies predict that the prevalence of diabetes will continue to increase throughout the US and a significant portion of the country is predicted to have a 20% prevalence of diabetes by 2030 (**Figure 6**).[2] However, while the prevalence

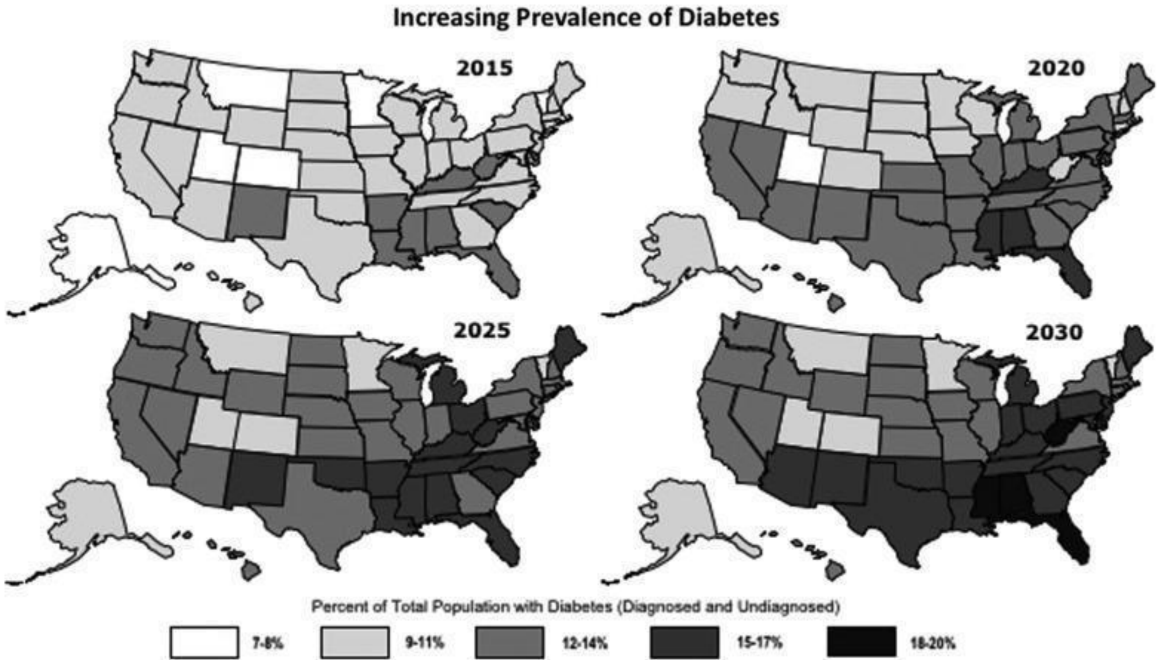

Figure 6. Trends and predictions of prevalence of total diabetes as a percent of total population for each state for 2015, 2020, 2025, and 2030 (adapted from Rowley et al., 2017).[2]

of T2DM continues to increase, the incidence of the disease appears to be stabilizing.[86] Between 1970 and 2000, the rate of diabetes per 1000 people increased from 3.0 to 6.0, but between 2000 and 2010 the rate of diabetes per 1000 people decreased to 5.5.[86] While prevalence describes the number of people with the disease, incidence describes the rate of people being diagnosed with T2DM.

One of the main causes of the increased amounts of patients with T2DM is the increased number of obese individuals. In 2000, the prevalence of obesity among adults in the US was 30.5% and by 2014 it had risen to 37.7%.[87] The increased prevalence of obesity coincides with the increased prevalence of T2DM.[2] Obesity is also associated with a sedentary behavior and a diet with a higher GI, which both increase the risk of T2DM independently of obesity as previously stated.[36, 53] This trend in obesity is expected to continue to increase and in 2030 about half of the adults in the US are expected to be obese.[88] In the US, there has also been an increased prevalence of people sleeping less than 6 hours per night, which would be expected to be associated with an increased prevalence of T2DM as well.[89] Another explanation is that the treatment of T2DM has improved, which results in better outcomes and extends the lifespan of those living with T2DM.[2] Also, increased physician recognition of T2DM has led to an increase in diagnosed T2DM, which is significant given that an estimated 23.8% of T2DM cases are undiagnosed.[8, 84] Shifting demographics for the US is another source of the increasing prevalence of T2DM.[90] Between 1980 and 2012 the population of the US became both older and more racially diverse, which both have a higher prevalence of T2DM and contribute to a greater prevalence in the general population.[8]

Within the trend of a growing prevalence of T2DM, T2DM has become increasingly common in adolescents.[1] Nearly half of the newly diagnosed cases of diabetes in children and adolescents are classified as T2DM, which has greatly increased from 4% of newly diagnosed pediatric diabetic cases in 1994.[91] The incidence rate of T2DM has been projected to increase by 49% through 2050 among youths and a four-fold increase in the prevalence of youths with T2DM.[1]

CAUSES OF INCREASING PREVALENCE AMONG YOUTHS

As with the increasing prevalence of T2DM among adults, the trend of T2DM increasing within a younger population is likely tied to the trend of increasing childhood obesity. Between the 1960s and 2010, the prevalence of childhood obesity increased from 4% to 17%, but recent studies show that this increase in prevalence may be stabilizing around 17%.[92, 93] A high proportion of children today are predicted to be obese by the time they reach 35 years of age and trends show an increasing prevalence of obesity in the future (**Figure 7A**).[94] Obesity prevalence also increases with age through childhood and in young adulthood, which may represent two critical periods of developing obesity (**Figure 7B**).[94] Children and adolescents with a high BMI often become obese adults and most obese adults were classified as obese during adolescence.[95] Most obese adolescents had body weights that fell within the normal range as infants, but by age 5 they were classified as overweight or obese.[95] The period between ages 2 through 6 was found to have the most rapid weight gain, but BMI continued to rise throughout childhood and adolescence.[95] Additionally, as in adulthood, childhood obesity has been strongly correlated with the level of insulin resistance and decreased β cell function.[96] Therefore, in order to understand the causes of increasing cases of childhood T2DM, it is critical to understand the causes of increased childhood obesity.

There are many overlapping risk factors between obesity and T2DM and there has been an increasing prevalence of these risk factors among youths. While genetics plays a

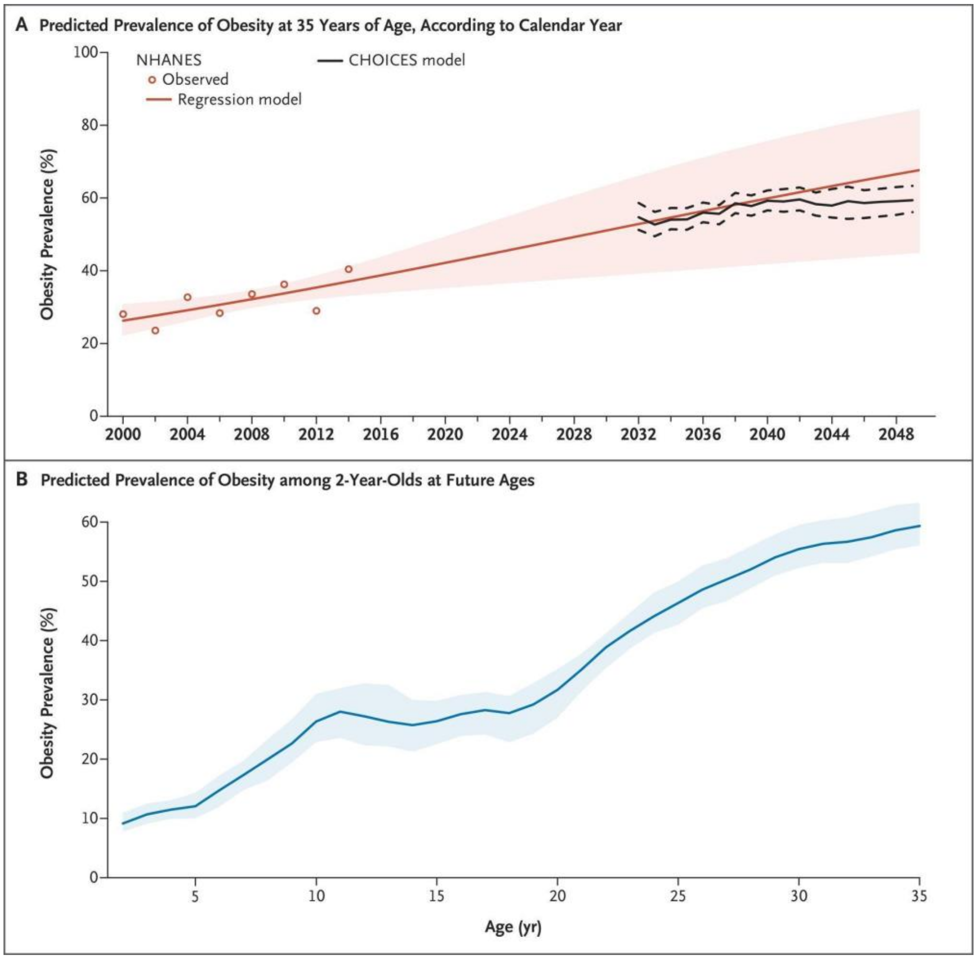

Figure 7. Predicted Prevalence of Obesity at the Age of 35 Years. Panel A shows the predicted prevalence of obesity at the age of 35 years among today's children. The 95% uncertainty intervals are indicated by a shaded area and by dashed lines for two different models. Panel B shows the projected prevalence of obesity at future ages among 2-year-olds in 2016. The shaded areas indicate 95% uncertainty intervals (adapted from Ward et al., 2017).[94]

role in the development of obesity, it is estimated that less than 5% of childhood obesity cases can be attributed to genetic factors.[97] One possible cause of the rise in childhood obesity is the trends seen in nutrition and diet. In recent years, portion sizes have increased dramatically and the larger portions lead to increased energy intake, which is a likely factor of childhood obesity.[98] As noted, the amount of energy intake is not independently associated with the risk of T2DM, but it may indirectly influence the development of the disease with obesity as a mediating factor. In support of this notion, obese children have been shown to have significantly higher energy intake and increased amounts of fat in their diet.[99] The US is trending towards healthier eating patterns with lower consumption of refined grains (i.e. high GI), but the US still eats a disproportionate amount of high GI carbohydrates compared to other food sources.[100] Interestingly, this pattern of decreased intake of refined grains did not occur in individuals with low SES and provides another association between low SES and T2DM.[100] Youths in the US have decreased the number of empty calories they consume, but their intake of empty calories is still considered high compared to recommendations.[101] Empty calories are foods that are digested quickly and often contain solid fats or added sugars that lead to a high GI.[101] Therefore, larger portions of foods with a high GI probably plays a role in the trend of childhood obesity, but diet composition seems to be trending in a healthier direction despite a continued high prevalence of childhood obesity.

In addition to eating patterns, the amount of sedentary behavior plays a role in the likelihood of developing childhood obesity and it also influences the risk of T2DM independently of obesity. Between 2003 and 2016, the amount of leisure time spent watching TV remained stable, but at a high level where 65% of individuals under 20 years of age watched TV for over 2 hours per day.[102] In this same time period, the number of youths spending more than an hour on the computer outside of school increased from 53%

to 57%.[102] Sedentary behavior reduces energy output by reducing the amount of time available for physical activity.[103] The reduced energy output contributes to an energy imbalance where there is more energy intake than output, which is associated with weight gain.[103] Similar to the trend of healthier diets, adolescents are becoming more active than they were in previous years, but the number of adolescents that are not meeting recommended activity levels remains high.[104] In 2016, 72% of adolescents in the US were not meeting the recommended amount of physical activity, which is at least 60 minutes of moderate physical activity per day.[104] This lack of physical activity removes exercise's protective effect against insulin resistance and promotes childhood obesity, which would both contribute to the increasing prevalence of T2DM in youths.

A trend of sleep deprivation is also a likely cause of the increased prevalence of childhood T2DM. As noted, decreased amounts of sleep are associated with an increased risk of T2DM and recently children and adolescents have been getting less sleep than in past years.[105] There is also a trend of decreasing sleep as development progresses, where those at the end of high school sleep less than their younger counterparts and also have an increased perception as not getting enough sleep (**Figure 8**).[105] The National Sleep Foundation currently recommends that adolescents get between 8 to 10 hours of sleep per night and in 2015 only 27.3% of adolescents slept a sufficient amount.[106, 107] There is evidence that the decrease in adolescents getting sufficient sleep could be associated with an increase in time spent looking at screens.[108] Since sleep deprivation is linked to insulin

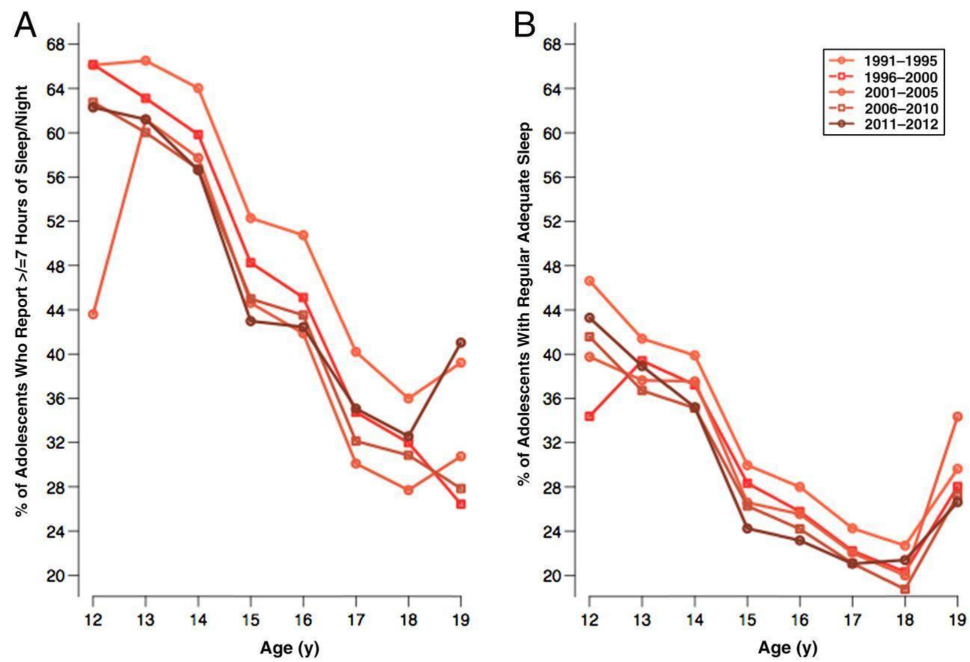

Figure 8. According to age and time period, percentage of adolescents who regularly report: A, ≥7 hours of sleep per night; and B, getting adequate sleep per night (adapted from Keyes et al., 2015).[105]

resistance and glucose intolerance, the pattern of decreased amounts of sleep for children and adolescents is another plausible factor in the increased prevalence of T2DM.

The concerning trend of an increased prevalence of T2DM among youths is caused by multiple factors and the complex interactions of these risk factors. The trend of increasing childhood obesity parallels the increase in T2DM cases in this population and many of the causes of obesity are linked to T2DM independently of their obesity association. Obesity and its associated metabolic dysfunctions arise in part from an energy imbalance between energy expenditure and energy intake.[103] Trends have shown that youths today have a greater energy intake of high GI foods and less energy expenditure than in past generations.[100, 103] Given that T2DM has shown strong associations with a family history of the disease, the increased prevalence of T2DM may have inertia into the future, where a greater population of diabetic individuals increases the likelihood of diabetic offspring. Studies have found that a younger age of T2DM onset is more likely to have a positive family history of diabetes than those with an older age of T2DM onset.[109] A younger age at the time of T2DM diagnosis is associated with a hyperglycemic intrauterine environment and the increased prevalence of T2DM itself may be linked to the trend of increased T2DM in youth, but further studies are needed to make this association.[21]

YOUTH AND ADULT-ONSET TYPE 2 DIABETES MELLITUS DIFFERENCES

Overall, the pathophysiology of T2DM is similar in youths and adults. Like adult T2DM, the main features of pediatric T2DM are increased peripheral insulin resistance and progressive impairment of pancreatic β cell function.[3] In T2DM in youth, there is also a period of impaired glucose tolerance, or prediabetes, that precedes T2DM.[3] It has been observed that obese youths that go on to develop T2DM have a lower pancreatic β cell function at baseline compared to their counterparts that do not develop the disease despite having similar levels of insulin resistance.[110] Therefore, youths with a higher risk of T2DM may have less ability to overcome insulin resistance due to an early defect in β cell function and eventually the inability to overcome insulin resistance leads to T2DM. Interestingly, puberty in both sexes and various ethnicities has been associated with an increase in insulin resistance and a compensatory increase in insulin secretion.[111] This increased insulin resistance occurs in healthy, lean adolescents at the beginning of puberty and can result in a loss of 50% of insulin sensitivity.[112] This rise in insulin resistance during puberty would act as an additional risk factor of developing T2DM, especially among obese youth already at an increased risk. Typically, the insulin resistance seen in puberty disappears after development and insulin sensitivity returns to prepubertal levels.[111] However, it is unknown if this return of insulin sensitivity occurs in adolescents with T2DM and illustrates another area in need of further study. T2DM in youths generally begins during puberty with a mean age of onset of 13.5 years, which coincides with the pubertal rise in insulin resistance.[113] Given that adult-onset T2DM occurs after the pubertal rise in insulin resistance, this period of increased risk for youths could demonstrate a difference in the underlying pathogenesis of youth-onset T2DM. Youths have been shown to have significantly more insulin resistance compared to matched adults, but it is unknown if this difference can be attributed to the pubertal rise in insulin resistance.[114]

The most striking difference between in T2DM in youths and adults is that the progression of the disease appears to be significantly faster in youths.[115] The disease progression from prediabetes to T2DM typically lasts from 5 to 10 years in adults, while obese youths have been shown to have an average progression period of 21 months.[116] This accelerated pace is concerning as prediabetes is often asymptomatic and provides a smaller time frame to prevent or slow down the progression of the disease.[3] Children with prediabetes shown to have a progressive decline of 20-35% in pancreatic β cell function per year compared to adults who experienced a 7-11% decline in pancreatic β cell function per year, which represents a 3 to 5-fold difference.[115]

Additionally, the β cells of youths with prediabetes secrete more insulin than comparable adults and this pattern persists across a range of insulin sensitivities, which demonstrates that the difference in insulin secretion has an underlying pathology that is not attributable to different insulin sensitivities.[114] The enhanced insulin response is also greater than what would be needed to compensate for their reduced insulin sensitivity.[114] This observation indicates that the β cells in youths with prediabetes have an increased workload compared to adults and may demonstrate that a higher level of stress on the β cells results in a quicker pace of deterioration. β cell deterioration is largely affected by the degree of glycemic control, which highlights the importance of establishing glycemic control early in order to prevent the progression of the disease.[115] This task is more difficult in youths, as they tend to lose glycemic control rapidly and a higher percentage of youths progress from prediabetes to T2DM compared to adults.[115, 116, 117] Increased stress on β cells acting as a mediator to the faster disease progression in youths is an attractive theory, but further studies are needed to determine the cause of the hypersecretion of insulin found in youths.

In support of a faster progression of youth-onset T2DM, youths with the disease also have complications related to T2DM that appear quicker compared to adult counterparts.[109] As previously noted, T2DM is associated with a vast amount of complications that arise due to loss of glycemic control that results in hyperglycemia. It was previously thought that the earlier appearance of diabetes-related complications in youth-onset T2DM was due to increased duration of the disease, as a longer duration provides more opportunities to be exposed to hyperglycemic conditions that promote the development of complications.[116] However, when matched for the duration of disease, youth-onset T2DM patients have a significantly higher prevalence of complications compared to those with an older age of onset.[109] Also, T2DM in youths is associated with a higher prevalence of complications compared to youths with T1DM when controlled for age and duration of disease.[118] This association suggests that some factor besides the duration of exposure to hyperglycemic conditions influences the accelerated progression of T2DM in youths. While it is apparent that there is an accelerated disease progression in youth-onset T2DM, further studies are needed to illuminate the underlying causes that lead to loss of glycemic control and the development of complications.

TREATMENT OF TYPE 2 DIABETES MELLITUS IN YOUTHS

Current treatment options for youths with T2DM include lifestyle interventions and pharmacological intervention.[119] Treatments focus on maintaining normal PG levels in order to delay the progression of the disease and intensification of treatment, which also prevents and delays complications related to T2DM.[119] The goal of therapy is to enhance or preserve β cell function and tries to achieve this enhancement by increasing peripheral sensitivity to insulin to decrease β cell stress.[119] The ADA recommends an HbA1C goal of below 7% for children and adolescents, but targets should be individualized and open to more rigorous HbA1C goals of below 6.5% given that youths with T2DM infrequently experience hypoglycemia from pharmacological interventions.[16, 120] HbA1C at the time of diagnosis is the best predictor of durable glycemic control, which reflects baseline β cell function and indicates the severity of T2DM prior to therapy initiation.[121] Failure to reduce HbA1C to nondiabetic ranges within the first few months of treatment indicates a significant loss of β cell function at baseline and is indicative of an increased risk of losing glycemic control.[121] Therefore, baseline HbA1C should be considered an important criterion when individualizing goals of treatment. When individualizing glycemic target ranges the clinician needs to consider the risk of the therapy compared to the potential benefits to the patient. Other considerations that differ between patients is the presence of comorbid conditions, mental health status, and economic factors, which influence what therapies are available and convenient for the patient and their family. Given the more aggressive nature of T2DM in youths, intensive interventions aimed at maintaining near-normal PG levels are recommended for youths. This recommendation is especially true for recently diagnosed T2DM, as older patients with a longer duration of T2DM have been shown to have less benefit from intensive glucose-lowering therapies.[122]

Lifestyle interventions are often the initial therapy presented by clinicians and aim to reduce body weight and increase physical activity.[119] These lifestyle interventions target increasing education regarding T2DM for both patients and their families, increasing physical activity, reducing sedentary behaviors, and improving diet and nutrition.[119]

Lifestyle interventions have been shown to be most effective at preventing progression to T2DM in those with prediabetes, but they are still encouraged in all patients with T2DM.[119] A general reduction in body weight is one of the typical goals seen in lifestyle interventions. A 10% decrease in body weight has been associated with an 80% decrease in the occurrence of type 2 diabetes in children and adolescents with obesity.[123] Changes in diet and nutrition are also aimed at lowering body weight but also independently influence insulin resistance and glucose tolerance[123]. For example, one study found that a diet with low carbohydrate intake significantly improved insulin resistance compared to a low-fat diet.[124] It has been demonstrated in adolescents that lowering the amount of added sugar to a diet can decrease insulin secretion, which may slow disease progression during the period of increased insulin secretion in prediabetes.[125] The GI of foods is also an important factor when considering changes in diet. A low GI diet has been shown to decrease insulin resistance and improve glucose tolerance in adolescents.[126] A diet that significantly decreases energy intake has also been shown to be effective in slowing the progression of T2DM.[127] A very low energy diet is a diet that aims to limit energy intake to less than 800 kilocalories per day and is typically high in protein intake.[127] A very low energy diet has been shown to decrease many of the risk factors for T2DM by lowering blood glucose, HbA1C, and body weight.[127] One downside of the very low energy diet is that the strict calorie intake makes adherence to the diet difficult and may be difficult to sustain for long periods of time.[128] The very low energy diet can acutely reduce BMI, insulin requirements, and HbA1C, but only BMI is significantly durable, while HbA1C and insulin requirements increase with time (**Figure 9**).[127] Related to low energy diets, intermittent fasting diets have become more popular recently.[129] This diet consists of 2 to 4 fasting days, which limits energy intake to less than 600 kilocalories per day, and then 3 to 5 feeding days, where one can eat as they desire or follow additional dietary restrictions on an individual basis.[129] One study showed that intermittent fasting significantly lowered body weight and improved HbA1C, but this reduction was difficult to maintain over long periods of time.[129] Overall, diet modifications try to limit the glycemic load following a meal and reduce glucose-induced stress on pancreatic β cells.

In addition to diet, lifestyle interventions aim to increase physical activity levels and decrease the amount of sedentary behavior. The ADA currently recommends that patients with T2DM try to incorporate daily physical activity or to allow no more than 2 consecutive days without exercise.[130] Additionally, it recommends that sedentary behavior should be limited and to interrupt long sitting periods with light activity.[130] Even light exercise has been shown to increase insulin sensitivity by enhancing peripheral glucose uptake for a prolonged period after the conclusion of exercise.[131, 132] Reducing the amount of sedentary time by periodic standing decreases postprandial PG levels, which may have a protective effect on pancreatic β cells.[133] The main goal of the exercise is to increase glucose utilization in skeletal muscle, which reduces accumulated glucose and lipids to reduce stress on β cells.[130]

Another lifestyle modification that gets less attention is improving education regarding T2DM in patients and their families. This improvement aims to increase the

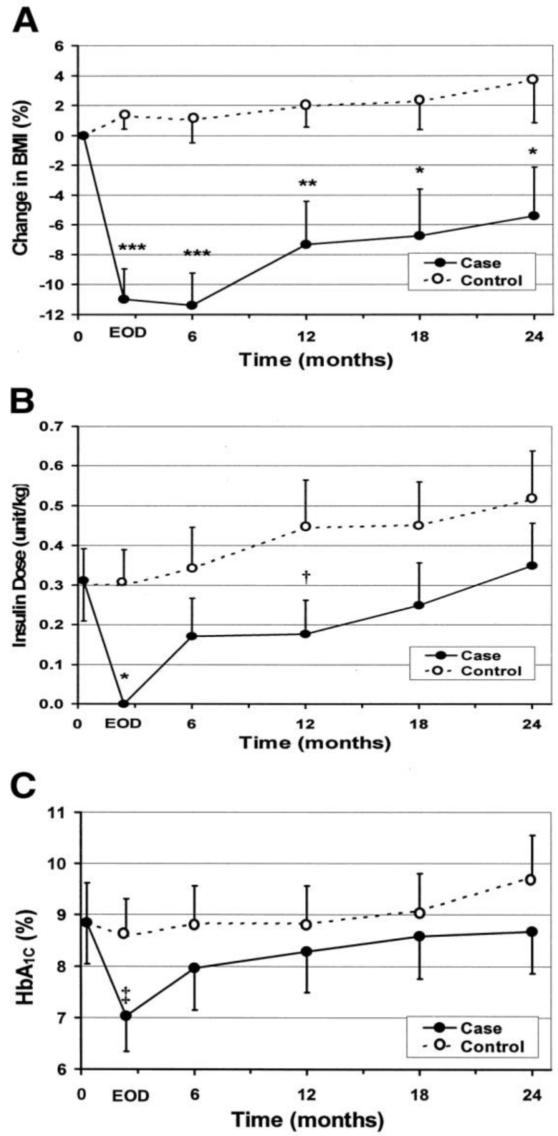

Figure 9. Long-term effects of the very low-calorie diet (VLCD) on BMI (*A*), insulin dose (*B*), and HbA1c (*C*). In comparison with a matched control group (○ with dashed lines), subjects compliant with the VLCD for >6 weeks (• with solid lines) experienced sustained decreases in BMI, but only transient reductions in insulin requirements and glycohemoglobin (adapted from Willi et al., 2004).[127]

patient's understanding of the causes of T2DM, how it is assessed clinically, the complications of T2DM, and how to manage the disease. There is little data on the effectiveness of diabetes education in youths, but the Treatment Options for Type 2 Diabetes Available to Youth (TODAY) study provided an education program to the patients who were enrolled in their study and to their families.[134] The TODAY study was the first and largest randomized clinical trial that studied treatment outcomes in youth-onset T2DM.[115] The program provided information regarding the physiology and treatment of T2DM and worked in a progressive, interactive manner to build skills related to T2DM.[134] The program was available in English and Spanish and was culturally sensitive in their handout materials.[134] The program was supervised by an educator and periodic quizzes were issued to assess mastery of the material.[134] Unfortunately, there are no experimental trials available to test the efficacy of diabetes education in regard to improving glycemic control among youths with T2DM. However, in adults, self-management of T2DM education has been associated with a modest increase in glycemic control measured by a decreased HbA1C.[135] Further studies are needed to demonstrate the effectiveness of diabetes education among their family but given that improving social support increases adherence to diabetes treatment, getting families involved and educated in T2DM management will likely have positive benefits.[136]

Unfortunately, it appears that lifestyle intervention as a monotherapy is often insufficient to manage T2DM in youths.[137] One study demonstrated that only 54% of pediatric patients with T2DM reached their HbA1C goals one year after diagnosis with lifestyle modification alone.[137] Lifestyle modification is more successful in milder cases of hyperglycemia and more intervention is needed when glycemic control is lost.[137] The accelerated progression of T2DM may play a role in the lack of success with lifestyle monotherapy in youths. Another study found that 77% of patients on lifestyle monotherapy required antidiabetic medication initiation within a 2-year period and that 65% of patients on monotherapy alone failed to follow up in subsequent appointments.[138] It is possible that when presented with lifestyle changes as a monotherapy, patients and their families feel that not enough is being done by the clinician to treat the disease and lose motivation to adhere to treatment. Another possible reason is that the stresses associated with adolescence and T2DM are overwhelming for youths and coping with stress with avoidance prevents adherence.

When lifestyle adjustments fail to correct glycemic control, pharmacological interventions are then considered.[16] Better glycemic control is obtained when lifestyle changes are used in conjunction with pharmacological interventions.[115] Currently, the only medications approved for youths are insulin analogs and metformin.[16] Metformin is an oral antidiabetic agent known as a biguanide antihyperglycemic agent.[139] It decreases PG through several mechanisms, which include decreasing hepatic gluconeogenesis to reduce liver glucose output, reducing intestinal absorption of glucose, and enhancing insulin sensitivity by increasing peripheral glucose utilization.[139] Metformin is generally tolerated fairly well, with minor gastrointestinal side effects such as nausea, vomiting, and diarrhea appearing in 40% of patients.[120] The ADA recommends that patients that are considered metabolically stable with an HbA1C less than 8% can be started on metformin alone in addition to lifestyle modification.[16] The initial dose of metformin is 500 to 1000 milligrams per day based on patient tolerance and to gradually increase the dosage to 1000 milligrams twice per day.[16] In the TODAY study, 48.3% of youths with T2DM were able to maintain an HbA1C under 8% for up to 6 years on metformin alone, while the rest of the participants had to have their treatment intensified.[140] This information shows that durable treatment of youth-onset T2DM is possible with metformin monotherapy, but a significant population requires more intensive therapy.[140] However, the use of metformin improved glycemic control in almost all cases and many patients that were treated with insulin at the beginning of the study were capable of being weaned off with metformin alone.[119]

The ADA recommends that exogenous insulin therapy should be started in patients that initially present with severe loss of metabolic control or when metformin monotherapy is not adequately maintaining glucose tolerance.[16] Severe loss of metabolic control is considered an HbA1C over 8.5%, PG over 250 mg/dl, or presentation with symptomatic T2DM or DKA.[16] There are various types of insulin available that differ in their time of onset, peak time of maximum strength, and duration.[141] Basal insulin is a long-acting insulin that takes several hours to reach circulation but lowers PG for a day or longer.[141] Rapid or short-acting insulin is generally taken before meals.[141] It takes about 15 to 30 minutes to begin its action and lasts for 2 to 4 hours[141]. Intravenous or subcutaneous insulin should be used to achieve glycemic stability while also titrating the dosage of metformin.[16] Patients may be weaned off insulin if glycemic control is regained, as extended insulin therapy in addition to metformin is not shown to significantly improve β cell function compared to metformin alone.[142] This observation is another contrast to adult-onset T2DM, who show improved β cell function with intensive insulin therapy and this improvement was sustained for a significant period without medication.[143] If the patient is unable to maintain metabolic control, then they will require extended use of long-acting insulin analogs in addition to metformin and lifestyle interventions.[16] Given that youths with T2DM have severe insulin resistance even compared to adults, they may require rapid-acting insulin with meals in addition to the maximum dose of basal insulin, which is 1.5 units per kilogram per day.[16]

Unfortunately, outside of insulin and metformin, pharmacologic treatments are extremely limited for youths as the Food and Drug Administration has not approved any other medications for pediatric diabetics.[16] However, recent results with GLP-1 receptor agonists in youths are promising. One study demonstrated that exenatide, a GLP-1 receptor agonist approved for adult diabetics, was well tolerated in adolescent patients and significantly lowered postprandial PG concentrations.[144] Exenatide is a twice-daily injection and has been shown to preserve β cell mass and function in adults by protecting against oxidative stress, but this effect has yet to be studied in adolescents.[145] Further studies are needed to see if the different classes of medications available to adults are safe and effective in pediatric populations. Presently, there are several studies examining different classes of drugs in youths, but the data are not yet available.

Another more extreme option available to pediatric T2DM patients is bariatric surgery to reduce weight. Roux-en-Y gastric bypass (RYGB) is a surgical technique that creates a stomach pouch out of the patient's stomach and attaches it directly to the small intestine bypassing most of the stomach and duodenum.[146] The stomach pouch does not allow for much food to be held and bypassing the duodenum reduces the absorption of dietary fats.[146] RYGB has been shown to significantly improve β cell function and insulin sensitivity by increasing postprandial GLP-1 concentrations.[146] Currently, RYGB is the only bariatric surgery recommended for adolescents and other surgeries are currently an area of study.[147] The current criteria for bariatric surgery for adolescents are to have finished puberty and to have a BMI greater than 35 kg/m^2 with significant comorbidities, such as T2DM, or a BMI greater than 40 kg/m^2 regardless of complications[147] RYGB has been shown to cause the remission of T2DM in adolescents with significant improvements in many parameters of T2DM.[148] In one study, BMI was reduced by 34%, fasting PG was decreased by 41%, and HbA1C was reduced by 1.7%.[148] While these results are certainly promising, the study had a small sample size of 11 people and further studies should be performed to support the results. A comparison of improvements after bariatric surgery and pharmacological interventions in adolescents found that surgical intervention significantly improved metabolic control, weight loss, and reduced risk of CVD over medical treatment.[149] Surgical participants of the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) study had more significant and durable reductions of HbA1C compared to the medical participants of the TODAY study (**Figure 10**).[149] While bariatric surgery appears to have positive outcomes on T2DM and its related complications, given that it is an extremely invasive procedure for a vulnerable population, other options should be explored before resorting to surgery.

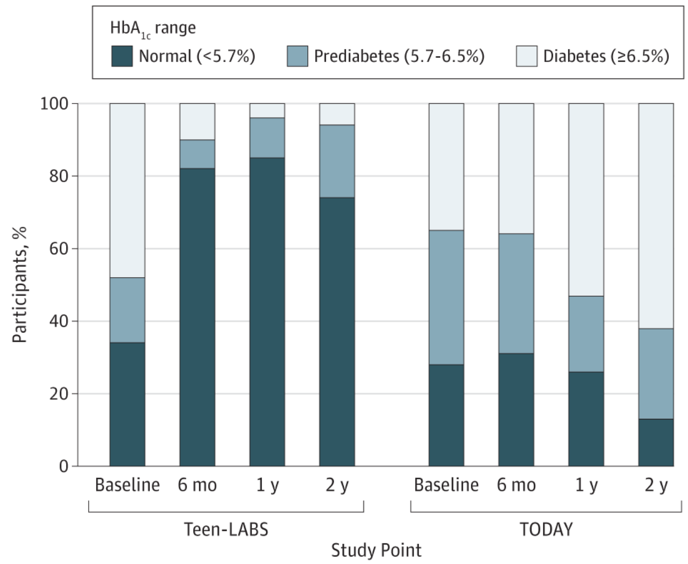

Figure 10. Changes in the Proportion of Participants With Hemoglobin A_{1c} (HbA_{1c}) Concentrations Teen-LABS indicates Teen–Longitudinal Assessment of Bariatric Surgery; TODAY, Treatment Options of Type 2 Diabetes in Adolescents and Youth (reproduced from Inge et al., 2018).[149]

Adherence to treatment is difficult to maintain in pediatric patients with T2DM and lack of adherence is one of the largest causes of loss of glycemic control.[138] Increased adherence has been shown to be a positive predictor of lower HbA1C and a lower prevalence of diabetic complications.[150] Positive social support and family relationships have been shown to increase adherence to therapy and to improve glycemic control, which demonstrates the importance of getting families involved in diabetic care.[136] One possible way of improving family support and education is through joint training and education programs that have been shown to improve adherence and increase glycemic control.[136] However, patients should not be shamed for noncompliance, but rather the factors that lead to noncompliance should be investigated on an individual basis. Like T2DM in adults, the disease in youths disproportionately affects those with lower SES.[91] Lower SES comes with an additional set of stresses such as lack of health care access, housing instability, employment difficulties, and lack of economic resources, which adds on to the already substantial stresses of living with T2DM. Treatment plans that integrate a patient's cultural influences, available resources, and core values have been shown to have more success in maintaining glycemic control.[151] Clinicians should be aware of the burdens related to low SES and should try to minimize barriers to care when possible to enhance adherence to prescribed therapies, whether lifestyle or pharmacological.

Diabetes distress is a term that refers to the stresses related to caring for diabetes, which includes medication compliance, PG monitoring, diet, exercise, and complications related to T2DM.[152] Higher levels of diabetes distress have been associated with worse metabolic outcomes and a lower perception of being able to successfully manage diabetes.[152] Higher rates of diabetes distress result in higher HbA1C, less healthy diet, less physical activity, and less perceived self-efficacy, which increases the risk of developing diabetes-related complications (**Figure 11**).[152] Research regarding diabetes distress in youths is extremely limited, but about one-third of adolescents with T1DM are prone to diabetes distress that impairs their ability to manage their disease.[153] Additionally, caregivers of youths with T1DM are also prone to diabetes distress, which limits their ability to support their dependent.[153] Given that T2DM has a higher prevalence in youths

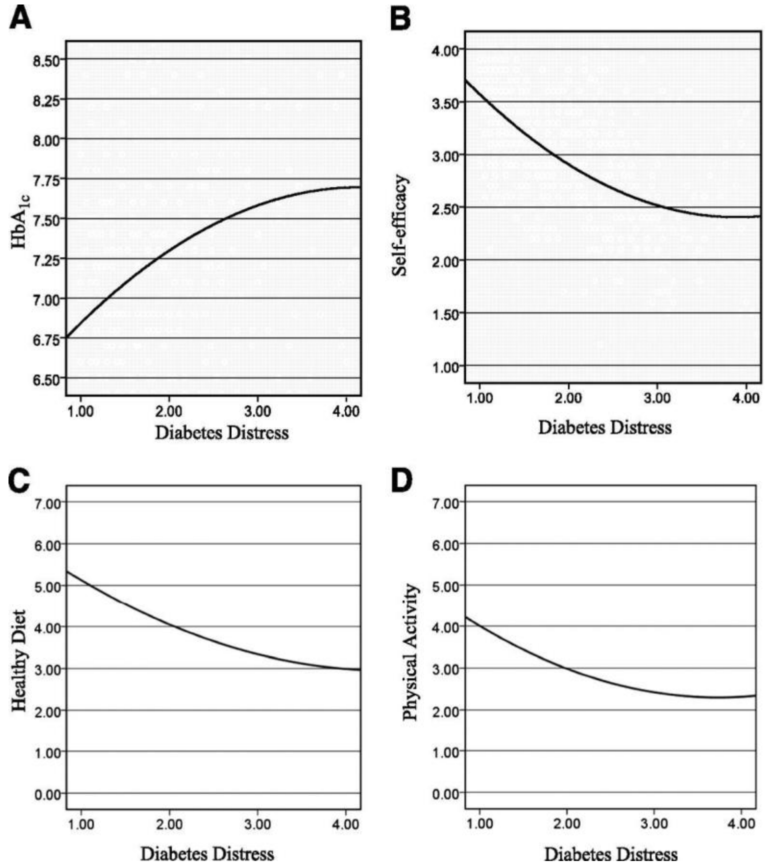

Figure 11. Associations between diabetes distress scores and the key diabetes variables of HBA1c (*A*), self-efficacy (*B*), healthy diet (*C*), and physical activity (*D*). Diabetes distress was assessed by a 17-item survey where patients rate each item 1-6, where 1 means the item is no problem and 6 means the item is a serious problem. The mean value represents the patient's diabetes distress score. HbA1C was measured as a percentage of total hemoglobin. Self-efficacy was assessed by a 10-item survey regarding their confidence in managing their diabetes. Scores were on a 1-4 scale, where 1 is the least confident and 6 is the most confident. Healthy diet was scored by the mean number of times per week that the patient ate certain unhealthy foods. Physical activity was scored as the mean number of physical activities per week (adapted from Fisher et al., 2012).[152]

with low SES, it is likely that they and their families are a part of a population that is susceptible to diabetes distress, which should be considered when constructing a care plan.

CONSEQUENCES OF TYPE 2 DIABETES MELLITUS REACHING YOUTHS

T2DM affecting younger populations has resulted in a significant economic burden on both the individuals living with the disease and on society. T2DM is a costly disease that requires an increased number of medical appointments, supplies for PG monitoring, medications, and additional costs from the complications that arise from T2DM.[154] The cost of these diabetic expenditures for an individual in 2017 was $9,600 per year, which is a factor of 2.3 more than a medical patient with a similar age and sex would pay without the disease.[154] One study created a model that estimated the annual direct medical cost on a healthcare system for T2DM and its related treatments and complications.[155] The model is based on surveys of diabetic patients to assess their demographics, treatments, medications, and complications, which were then assessed for cost using insurance company data.[155] For a white male with a BMI of 30 kg/m^2 that has T2DM controlled by diet alone and has no risk factors for additional complications is $1,684.[155] Women cost an extra 25% annually and African American males amounts to 18% less than his white counterpart.[155] However, given that the model relies on data of past treatments, differences

Disease Status	**Baseline cost ($1,684) x (multiplier)**
Sex	
Female	1.25
Race	
African American	0.82
BMI (kg/m^2)	
Every unit >30 kg/m2	1.01
Diabetes Intervention	
Oral antidiabetic medication	1.10
Insulin	1.59

Table 2. Direct medical costs of type 2 diabetes mellitus associated with demographic characteristics and treatments (adapted from Brandle et al., 2003).[154]

in costs between demographics may reflect differences in access to health care. Oral medications come with a 10% increase and insulin increases the annual cost by 59%.[155] There is also an increased cost associated with increased BMI and every 1 kg/m^2 over 30 kg/m^2 increases the annual cost by 1%.[155] **Table 2** summarizes how demographic characteristics and treatments can substantially increase the direct costs of T2DM.[155]

Complications related to T2DM drastically increase the cost of the disease and one study estimated that complications related to T2DM cost $47,240 per patient over a 30-year period.[156] Most of the costs incurred by complications can be attributed to the management of macrovascular complications, which represent 52%, but a substantial amount of the cost was related to treating microvascular complications.[156] Nephropathy made up 21% of the costs related to complications, neuropathy was 17%, and retinopathy was 10%.[156] Better glycemic control is associated with a lower cost, which is related to a slower progression of the disease and delaying the appearance and progression of related complications.[156] In total, this problem leads to huge costs on the healthcare system, which in 2017 was estimated to be $327 billion and included $237 billion in direct medical costs and $90 billion in reduced productivity, which arise due to time spent in medical appointments and inability to work due to the burdens of T2DM.[154] While the loss of productivity is probably not as significant in pediatric populations because they are in school, there will still be a significantly increased economic burden since the younger age of diagnosis leads to a longer duration of the disease. Additionally, given that youths frequently and rapidly lose glycemic control, there will likely be an increased cost due to the complications that arise from metabolic dysfunction, which appear sooner due to the rapid progression of T2DM in youths. However, few studies have studied the cost of youth-onset T2DM and none to date have studied how the trend of T2DM reaching younger populations will influence future costs. The TODAY study estimated that the cost to the health care system for treatment with metformin alone to be $1,798 in the first year of treatment, while metformin with lifestyle intervention cost $2,092 and metformin with additional medication cost $2,971.[157] The TODAY study is limited due to the study being a clinical trial, where study participants may not necessarily represent the general population with youth-onset T2DM. Further investigations are needed to study how a growing pediatric population with T2DM will influence the economic burden on health care systems and how costs will change as new therapies are approved for pediatrics.

In addition to economic costs, T2DM has a significant burden on the individual's mental well-being and quality of life. Increasing prevalence of T2DM among youths is likely to lead to higher rates of associated mental health disorders. Adults with diabetes are twice as prone to have depression than adults without diabetes and depressive symptoms are estimated to be present in 26% of adults with diabetes.[158] Youths with T2DM have a higher association with depressive symptoms than youths with T1DM.[159] The higher prevalence of depression in youths with T2DM is probably caused in part to T2DM association with obesity, where obesity may lead to a negative self-body image and depressive feelings. Additionally, youths with less glycemic control were associated with higher rates of depressive symptoms, which may be a bidirectional relationship as depressive feelings have been associated with worse metabolic outcomes.[160, 161] Adolescence is already a difficult period associated with many changes in a youth's life and clinicians caring for youth-onset T2DM should be alert for depressive symptoms.

As previously noted, T2DM is associated with several complications that significantly impair one's ability to perform everyday tasks and leads to a lower quality of life. A higher prevalence of T2DM among youths will lead to a higher prevalence of associated comorbidities in a susceptible population. Indeed, a younger age of diagnosis of T2DM is associated with higher rates of complications compared to duration-matched adults and naturally leads to higher mortality in this population as well.[109]

CONCLUSIONS

It is apparent that the epidemic of T2DM is going to continue to be a significant burden for both individuals and health care systems for the foreseeable future. An extremely worrying trend of an increased prevalence of T2DM among youths should make the treatment and management of T2DM a top priority for future research and focus of health care policy. T2DM comes with huge costs to the individual suffering from the disease as they have to pay for the expenses to manage the disease, but less recognized is the amount of time spent on medical appointments that make it more difficult for one to take care of their daily tasks. Likewise for health care systems, there are huge expenses associated with T2DM as direct medical costs, but there are also immense costs that arise from the loss of productivity associated with living with T2DM. Not only are the economic costs of T2DM tied to diabetic complications, but the significant loss of quality of life that comes with T2DM are as well. Since youths with T2DM will spend a larger proportion of their life managing the disease compared to adults, finding ways to delay the appearance and progression of diabetes-related complications will significantly alleviate the economic and personal stresses of T2DM.

It appears that T2DM is much more aggressive in youths and decreasing the prevalence of T2DM in youths should focus on prevention and delaying the progression of the disease. The increased prevalence of T2DM among youths is probably tied to the increasing rates of obesity and efforts to limit rates of T2DM should focus on combating the obesity epidemic as well. Since a significant amount of T2DM cases are undiagnosed, there needs to be improved diagnosis of the disease in those at high risk. Individuals that are overweight and have a family history of the disease should have their HbA1C routinely monitored, as HbA1C has been shown to have a considerable predictive power of progressing from prediabetes to T2DM. Given that T2DM appears to disproportionately affect those with low SES, there should be greater efforts to decrease barriers to diabetic treatment and improve health-related education. Another goal of improving access to healthcare for those with low SES would be to improve motivation to maintain a healthier lifestyle with more physical activity and a healthier diet. A healthier diet would aim to decrease the overall GI of the diet by increasing the amount of dietary fiber and decreasing portion sizes. In addition to increasing physical activity, there should be an effort to decrease the amount of time spent watching TV, as TV watching appears to increase the risk of T2DM through several different mechanisms. Another manner of preventing T2DM in youths would be to ensure that adolescents are getting enough sleep, which would consist of at least 8 hours. This result might be accomplished by shifting school schedules to start later in the day or by researching the cause of the reduced sleep in adolescents and addressing the cause.

Another way of combatting the increased prevalence of T2DM among youths would be to increase the number of treatments available to this population. Numerous different drug classes are available to adults but testing for new drugs should study safety and efficacy in pediatric populations as well in future drug development. Currently, only insulin and metformin are approved for pediatric diabetics and increasing the options available will increase the ability of clinicians to individualize treatment plans of this heterogeneous disease. Also, it appears that adherence to treatment plans is a challenge in this population and efforts should be made to enhance adherence. This outcome could be accomplished by having a professional more involved with lifestyle interventions, as coaches have been shown to improve adherence and increase the success of treatment goals. Also, insufficient adherence should not be shamed or criticized, but the individual reasons for lack of adherence should be addressed. Shaming would likely decrease perceptions of self-efficacy, which has been shown to be associated with worse health outcomes. Given that the disease progresses rapidly in youths, if glycemic control cannot be accomplished in the first few months of treatment, surgical options should be considered in those that are eligible. While surgery is an intensive treatment and may seem extreme in pediatric patients, the success surgery has shown in limiting the progression of T2DM should make it a viable option in improving glycemic control and reducing diabetic complications.

Future efforts to reduce the prevalence of youth-onset T2DM are going to require a greater understanding of T2DM. T2DM is a well-characterized and well-understood disease, but there are still significant gaps in our understanding of how the disease arises and the complex interactions of genetics and environment that influence the progression of the disease. A key area of importance would be understanding the role that pubertal rise in insulin resistance plays in the development of T2DM in youths. It appears likely that it plays a role in the progression of youth-onset T2DM since puberty appears to coincide with the emergence of T2DM in youths. Additionally, understanding how differences in fat distribution occur and how to specifically target visceral adiposity seems key to understanding the underlying T2DM pathogenesis. While the link between obesity and T2DM is well documented, there is still debate in the mechanism of the interaction and improving our understanding of the link between obesity and T2DM will help better direct future research in the management of T2DM. The increasing prevalence of T2DM in youthful populations is a relatively new phenomenon and it is imperative to increase our knowledge of the causes of the trend in order to enhance our ability to delay this growing epidemic.

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