

Childhood Type II Diabetes: Risks and Complications

Danielle Kapke

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Deanna Britt, Ph.D.  
Thesis Chair

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Dana Woody, MSN  
Committee Member

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Lew Weider, Ph.D.  
Committee Member

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Marilyn Gadowski, Ph.D.  
Assistant Honors Director

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Date

## Abstract

Type II Diabetes Mellitus is an endocrine disorder that affects people of all ages. Type II Diabetes was once considered adult-onset diabetes, as it was nearly exclusively diagnosed in adults. Over the last three decades, the number of children diagnosed with Type II Diabetes has greatly increased. This rapid increase in childhood Type II Diabetes has prompted researchers to investigate why the epidemic exists and what its life-long ramifications may be for those diagnosed. Childhood Type II Diabetes is a heterogeneous disorder, meaning it is caused by both genetic and environmental factors. The incidence of childhood Type II Diabetes can only be reduced by an alteration in environmental factors, which are called modifiable risk factors. These include obesity, exercise, diet, and breastfeeding in infancy. Due to the chronic nature of Type II Diabetes, individuals with the disorder are at significant risk for developing additional medical conditions, or co-morbidities. These include cardiac diseases, renal failure, and vision impairment. Due to the early onset of childhood Type II Diabetes, these co-morbidities are often pronounced and debilitating once the child has reached middle adulthood. To reduce lifelong complications, screening for Type II Diabetes should be initiated early in at-risk children.

### Childhood Type II Diabetes: Risks and Complications

Diabetes Mellitus is considered an epidemic in the United States. Over 29.1 million Americans, or 9.3% of the population, have been diagnosed with the disease as of 2012 (National Diabetes Statistics Report, 2014). While the incidence of diabetes is quickly growing, the gravity of the disease's risks and complications are often not realized. Yet, according to the American Diabetes Association (ADA), diabetes currently ranks as the 7<sup>th</sup> leading cause of death in the United States (National Diabetes Statistics Report, 2014). At this time, diabetes is considered a treatable yet incurable disease, magnifying the complications associated with its diagnosis (Taylor, 2013). Diabetes is a metabolic disease characterized by the body's inability to properly utilize glucose. There are two distinct categories of diabetes: Type I and Type II. Type II Diabetes Mellitus (DMII) is similar to Type I Diabetes (DMI) in many ways. However, recognizing the differences between the two disease processes is vital to understanding the risks, treating the disease, and preventing complications. Both DMI and DMII can be diagnosed in childhood. The diagnosis of DMII in childhood is predicated by several risk factors and wrought with lifelong complications.

#### **Pathophysiology of Childhood DMII**

Diabetes is a metabolic disease in which a person has abnormally high blood glucose levels. Under normal physiological conditions, blood glucose levels will be controlled between 70 and 125 mg/dL, despite wide fluctuations in the supply of glucose and demand for insulin. A high blood glucose level is referred to as hyperglycemia. Hyperglycemia is the result of impaired insulin release due to a dysfunction of the pancreatic beta cells and diminished insulin efficacy due to insulin resistance by the

body's tissues (Ozougwu, Obimba, Belonwu, & Unakalamba, 2013). Insulin, a peptide hormone produced by the pancreas, is the body's means of controlling blood sugar levels by withholding and releasing glucose as it is needed for appropriate body function. The primary difference between DMI and DMII is how the body produces and utilizes insulin. Type I Diabetes leaves individuals dependent on insulin supplements due to the pancreas' inability to produce insulin. Individuals with DMII may still produce insulin, but their bodies are unable to utilize it effectively (Copeland et al., 2013). The body's inability to effectively utilize insulin is called insulin resistance. Insulin resistance in DMII is generally due to one of three issues. Insulin resistance may be the result of a signaling defect. In such a case, the pancreas is not signaled to release insulin when the body needs it, resulting in inadequate insulin release and hyperglycemia. Insulin resistance may be due to a glucose transporter defect. This means that the pancreas is producing enough insulin, but it is not being transported effectively to control blood glucose. Insulin resistance may be caused by lipotoxicity (Taylor, 2013). Lipotoxicity is an accumulation of toxic lipid metabolites in the body's tissues, including the liver and arteries. This buildup acts as a barrier and prevents proper insulin use by the affected tissues. Lipotoxicity, which is essentially excess tissue fat, is driven by obesity (DeFronzo, 2010).

Depending on the type and severity of insulin resistance associated with DMII, the treatment varies. Some individuals may be able to initially manage their DMII with diet and lifestyle changes alone. If this is not enough, oral medications will be used to promote insulin utilization. However, if insulin production is impaired or deficient, the individual will require insulin therapy to manage his or her DMII and resulting hyperglycemia.

### **Prevalence of Childhood DMII**

Type II Diabetes was long considered a disease of adulthood until the 1980s when children and adolescents were increasingly diagnosed with the endocrine disease. In 2001, DMII accounted for three percent of diabetes diagnoses in children, while DMI accounted for 97%. As of 2011, DMII accounted for 45% of the childhood diabetes diagnoses (D'Adamo & Caprio, 2011). Thus, in only one decade, the prevalence of DMII in children increased from three percent to 45% of diabetic cases. The prevalence of DMII is 1.7 per 1000 children and adolescents in the United States (Center for Disease Control and Prevention [CDC], 2013). The CDC (2013) suggested that the rate of childhood DMII could increase four times over the next 40 years. The average age of onset of childhood DMII coincides with the physiological insulin resistance of puberty. While children are most commonly diagnosed between the ages of 11-14, children as young as 5 years old are increasingly being diagnosed with DMII (D'Adamo & Caprio, 2011). Although childhood DMII was once a rare diagnosis, it has become an epidemic in the United States (CDC, 2013).

### **Risk Factors of Childhood DMII**

The etiology of DMII is heterogenous in that both genetics and environment contribute to the disease ("Type 2 Diabetes", 2010). Genetic causes are often called non-modifiable risk factors. These factors are those that cannot be modified or altered; thus, they are permanent and irreversible risk factors for developing DMII. Environmental factors are often called modifiable risk factors. These factors, such as diet and lifestyle, can be modified to prevent the development of DMII.

**Non-modifiable Risk Factors**

Non-modifiable risk factors cannot be prevented or reversed. There are three primary non-modifiable risk factors that have been identified in the etiology of DMII: intrauterine exposure, family history, and ethnicity (Kommoju & Reddy, 2011). While these factors all contribute to the development of DMII, they do not necessarily explain the current epidemic of childhood DMII.

**Intrauterine exposure.** One factor strongly associated with the diagnosis of DMII in children is their intrauterine exposure to maternal diabetes. Maternal diabetes diagnoses can include DMI, DMII, and gestational diabetes. It is proposed that neonates' intrauterine exposure to diabetes is largely the result of maternal hyperglycemia and an unstable insulin-glucose balance throughout gestation. However, studies have shown that fetal intrauterine exposure to diabetes is still a risk factor, despite excellent maternal control of blood glucose levels throughout the pregnancy. Intrauterine exposure to maternal diabetes predisposes children to developing DMII in several respects, including hyperglycemia, macrosomia, and impaired endocrine development.

**Hyperglycemia.** Children of mothers with diabetes are exposed to a hyperglycemic intrauterine environment throughout the pregnancy. The maternal hyperglycemia leads to increased glucose transfer to the fetus via the umbilical cord. This forces the fetus to increase insulin secretion to prevent fetal hyperglycemia. When these infants are born, their bodies continue to expect high levels of blood glucose. If the high levels of blood glucose are not achieved through the infant's nutrients, the infant's pancreas will naturally produce less insulin to maintain the expected hyperglycemic state. Additionally, the elevated insulin production required by the infant in-utero leads to

inefficient insulin use and premature insulin resistance in childhood. This is a precursor for the development of DMII (Ruchat, Hivert, & Bouchard, 2013). Essentially, intrauterine exposure to maternal hyperglycemia results in impaired endocrine control in the infant. Depending on the severity and longevity of the hyperglycemic exposure, the infant may experience lifelong metabolic complications as a result. In addition to maternal hyperglycemia, the infant's birth weight is important.

***Macrosomia.*** Macrosomia is the term to describe an infant with an excessive birth weight. An infant's weight at birth is influenced by the mother's metabolic and endocrine function. Even diabetic mothers with excellent glucose control throughout pregnancy may give birth to macrosomic infants. It is important to note that while the infants are macrosomic, it is specifically an excess of fat mass rather than lean body mass. Research indicates that an increase in infants' fat mass persists even when their birth weight is appropriate for gestational age. This indicates that maternal diabetes causes increased buildup of fat tissue in neonates, even when blood glucose is controlled. Ultimately, the intrauterine metabolic environment affects the infant's adipose growth, predisposing the child to endocrine dysfunction (Catalano & Hauguel-De Mouzon, 2011).

***Impaired endocrine development.*** Exposure to maternal diabetes can also lead to impaired endocrine development in neonates. When infants are exposed to intrauterine hyperglycemia, they are forced to produce excess insulin, this is known as hyperinsulinism. When hyperinsulinism occurs during the first trimester, which is a critical period of brain development, it can lead to impaired development and permanent maladaptation of the hypothalamic center that regulates endocrine function. This maladaptation results in lifelong endocrine complications for the infant, including early

development of DMII. Several studies have followed the endocrine development of children who were exposed to intrauterine hyperglycemia, revealing the correlation between the exposure and lifelong endocrine maladaptation (Ruchat et al., 2013). The growth patterns and risk of DMII in children exposed to diabetes in-utero are influenced by unique gene-environment interactions. Consequently, children exposed to DMII and hyperglycemia while in-utero have a higher risk for obesity, insulin resistance, and the development of DMII in childhood (Mendelson et al., 2011).

**Family History of DMII.** Children are at a higher risk of developing DMII if they have an immediate family member also diagnosed with diabetes, whether DMI or DMII. There appears to be a strong connection between family history and childhood diagnosis of DMII. The risk of developing DMII is 40% for individuals who have one parent with the disease and 70% if both parents are affected (Ahlqvist, Ahluwalia, & Groop, 2011). This is due, in part, to the genetic prevalence of obesity and its role in the diagnosis of DMII. However, several studies and genome mapping suggests that there is a genetic factor related to the body's glucose control and ability to effectively utilize insulin (Santoro et al., 2013). Current research indicates a strong connection between the TCF7L2 and MTNR1B genes and DMII (Ahlqvist et al., 2011). It is important for children of parents with diabetes to be screened starting in elementary school to ensure early diagnosis of DMII.

***Excess glucose production.*** Glucose production is affected by genetics. Genetic mapping allows one to identify specific genes that increase susceptibility to a disease or influence a physiological characteristic. Several genes have been identified as influential in the development of DMII. Transcription factor 7-like 2 (TCF7L2) is a protein that has

been identified as a genetic factor leading to increased rate of hepatic glucose production. Several studies have confirmed the association between DMII and several single-nucleotide polymorphisms (SNPs) in the TCF7L2 gene (Ahlqvist et al., 2011). These studies were performed in several ethnic groups, all confirming the association between the TCF7L2 gene, excess hepatic glucose production, and the development of DMII.

***Decreased insulin production.*** Insulin production is also affected by genetics. Another important gene involved in the development of DMII is melatonin receptor 1B (MTNR1B). Melatonin receptor 1B is associated with elevated fasting blood glucose and the development of DMII due to its influence in the production of insulin. Melatonin, often referred to as the sleep hormone, works primarily to adjust the body's biological clock. There are melatonin receptors located in the pancreas that contribute to the nocturnal lowering of insulin levels to maintain fasting blood glucose throughout the night. However, a mutation in the MTNR1B gene is associated with altered melatonin signaling at the pancreas. Initially, this mutation causes mild overproduction of insulin, which often goes unnoticed. However, genetic studies suggest that over time the pancreas will become maladapted to the MTNR1B mutation, resulting in diminished insulin production, hyperglycemia, and ultimately the development of DMII (Ahlqvist et al., 2011). Research is ongoing to determine the genetic factors associated with DMII.

**Ethnicity.** Another genetic factor that predisposes children to DMII is ethnicity. Certain ethnicities, specifically African Americans, Native Americans, Asian Americans, and Hispanics have higher rates of childhood DMII (Agency for Healthcare Research and Quality, 2013). Compared to these ethnicities, Caucasian children have a lower prevalence of DMII and are less likely to be diagnosed with the disease. It has been

suggested that obesity, rather than ethnicity, is the cause of higher incidence of DMII in certain ethnic groups. However, recent ethnicity studies have shown that, regardless of weight, ethnicity is a factor in the development of DMII. In 2010, the National Institute of Health (NIH) conducted a study that examined the prevalence of DMII in children of five different ethnicities. The five ethnicities included in the study are Non-Hispanic whites, Hispanics, African Americans, Navajo Indians, and Asian Americans. Several factors including blood pressure, cholesterol, and obesity were studied. The study ranked the prevalence (per 1000) of DMII in children from highest to lowest: Navajo Indians (1.45), African Americans (1.06), Asian Americans (0.52), Hispanics (0.46), and Non-Hispanic whites (0.18). The study also ranked the percentage of children diagnosed with DMII who are also obese from highest to lowest: African Americans (94), Non-Hispanic whites (92), Asian Americans (90), Navajo Indians (85), and Hispanics (83). It is interesting to note that while Navajo Indians have the highest prevalence of childhood DMII, they also claim the second lowest obesity rate. In the same respect, Non-Hispanic whites have the lowest prevalence of DMII by a significant margin, yet claim a close second in obesity rates (Brown & Rother, 2010). This study does not deny the influence of obesity in the diagnosis of childhood DMII, but it illustrates the relevance of ethnicity in the development of the endocrine disease. As such, children of African American, Native American, and Hispanic ethnicity are considered high-risk for developing DMII (Bobo, Shantz, Kaufman, & Kollipara, 2009).

### **Modifiable Risk Factors**

Modifiable risk factors are those that can be avoided or reversed in children to prevent the onset of DMII. Modifiable risk factors include obesity, exercise, diet, and

breastfeeding in infancy. The majority of modifiable risk factors, however, are largely out of the child's control, this includes lifestyle. Factors such as diet and breastfeeding in infancy are two factors that are controlled by the parents rather than the child. These pose a unique risk to childhood DMII and necessitate early intervention.

**Obesity.** Obesity is the most significant risk factor for developing childhood DMII. Children who are overweight or obese are at a significantly greater risk for developing DMII than children of healthy weight. In the US, overweight and obese are defined as the 85<sup>th</sup> and 95<sup>th</sup> percentiles for weight, respectively. There is an increase in the prevalence of childhood DMII from 2.4% for children of normal weight to 14.2% for children who are obese. Because body mass index (BMI) changes so rapidly in children, it is generally not considered reliable in defining overweight and obese. A 2011 report indicates that 15-17% of children, ages 6-17, are considered obese in the US. The increasing rates of childhood DMII are closely paralleled with increasing rates of childhood obesity (Rabbitt & Coyne, 2012).

The risk for DMII is associated with obesity's affect on insulin sensitivity and glucose utilization. Children who are overweight or obese experience impaired glucose tolerance (IGT), characterized by significant peripheral insulin resistance and subsequent beta-cell failure. In normal weight children, a balance between the pancreas' beta-cell insulin secretion and insulin sensitivity of the peripheral tissues maintains glucose metabolism. The peripheral tissues include muscle, liver, and adipose tissue. In overweight or obese children, impaired beta-cell function caused by excess visceral fat and decreased insulin sensitivity by the peripheral tissues due to peripheral fat are the two

primary components in the development of DMII. Insulin resistance is the major link between obesity and DMII (Yaturu, 2011).

Insulin resistance can be caused by numerous factors, however an excess of free fatty acids (FFA) plays a leading role. Visceral fat causes an increase in the release of FFA, as a result of accelerated lipolytic activity. Current research suggests that an oversupply of lipid to skeletal muscle, as is found in overweight and obesity, contributes to diminished insulin sensitivity. Increased FFA also results in the development of triglyceride buildup in both muscle and the liver, inhibiting the efficacy of insulin. The FFA buildup causes insulin resistance as the result of several physiologic changes. First, FFAs inhibit insulin-stimulated glucose uptake at the level of glucose transport. This means that while the body is producing adequate insulin, the FFAs prevent it from being used to effectively maintain blood glucose levels. Second, FFAs impede insulin-stimulated glycogen synthesis. In a normal physiologic process, insulin will assist in the conversion of glucose to glycogen for storage purposes. However, in the presence of excess FFAs, insulin cannot efficiently or effectively synthesize the blood glucose into glycogen. In addition to provoking impaired insulin sensitivity, excess FFAs also contribute to overstimulation and increased production of hepatic glucose. This is due to suppression of glycogenolysis and gluconogenesis. Without these factors, hepatic glucose production becomes unchecked. Elevated FFAs play a direct role in the overproduction of hepatic glucose. Consequently, overweight and obese children have a significantly greater likelihood of developing DMII. It is also important to note that children have a decreased tolerance to unstable blood glucose levels as compared to adults. This means that when children experience FFA induced hyperglycemia and insulin sensitivity, it

quickly progresses to DMII (Yaturu, 2011). There is a narrow window for intervention once FFAs have taken their toll, indicating the need for early screening.

**Physical inactivity.** Physical inactivity is an important risk factor and one of the most easily modified factors in the prevention of childhood DMII. The effect of physical activity on insulin resistance and susceptibility to DMII in children is immense. Physical activity is proven to improve body composition, lower the resting heart rate, and lower blood pressure in children. High-risk DMII children experience additional benefits of exercise, including improved insulin sensitivity and balanced glucose uptake in the periphery. As a result, adequate physical activity has the potential to drastically reduce insulin resistance and the incidence of childhood DMII (Tompkins, Soros, Sothern, & Vargas, 2009). Research conducted over the last decade has demonstrated a positive association between physical activity and insulin utilization, showing that increased activity leads to balanced fasting glucose levels and improved insulin sensitivity.

There are two key ways that physical activity improves insulin sensitivity, thus lowering the risk of developing DMII. First, physical activity improves insulin sensitivity by increasing glucose transport to muscle cells and encouraging the production of muscle glycogen to maintain blood glucose levels. Second, physical activity has long-term implications for insulin sensitivity and blood glucose maintenance. By increasing the fat-free muscle mass, exercise increases the volume of muscle into which blood glucose can be transported. The expansion of muscle volume lowers the demand for insulin while simultaneously promoting better utilization of blood glucose (Lumb, 2014). Dr. Connie Tompkins and associates (2009) reported a study on the effects of aerobic exercise on insulin sensitivity in overweight and obese 9-15 year olds. The study found that, after 12

weeks of aerobic training, insulin sensitivity increased without any significant changes in body weight or fat mass. Furthermore, the study discovered that lower limb fat-free mass increased by an average of 6.2%. This change in fat-free mass, as addressed earlier, is significantly associated with improved insulin sensitivity and blood glucose control. A reduction in peripheral fat allows for better utilization of insulin in the peripheral tissues.

It is important to note that, in most cases, obesity and physical inactivity are coexisting factors. The two factors tend to work in a cyclic pattern, since obesity impairs physical mobility and inactivity promotes obesity. As such, the two factors are often addressed simultaneously by encouraging physical activity in early childhood and throughout development. An important aspect of exercise is the different types of physical activity. The U.S. Government Physical Activity Guidelines for American Children and Adolescents includes both aerobic and resistance, or strength, training as elements to prevent the development of DMII. According to these guidelines, the best option for children is combination exercise, which includes both aerobic and weight lifting exercises (“Youth Physical Activity”, 2014). Aerobic activity recommendations include swimming, playing tag, and organized sports such as soccer. Strength training recommendations include climbing trees, martial arts, and swinging on monkey bars. The recommendation for high-risk children is 40-60 minutes/day of moderate to vigorous aerobic/resistance combination exercise, five days a week. After four consecutive months of this regimen, insulin sensitivity will improve and the child’s risk of developing DMII will decrease (Tompkins et al., 2009).

**Diet.** Diet plays a significant role in the development of childhood DMII. The foods that children eat directly impact the body’s ability to utilize insulin effectively.

Because insulin is necessary for proper glucose storage, transfer, and use, the relationship between diet and DMII is critical (Dabelea & Harrod, 2013). Extensive research been conducted in the last five years to better understand the dynamic between diet and childhood DMII. The ADA reported a study from the UK, led by Dr. Angela Donin (2014), which looked at several dietary factors in relation to childhood DMII. The study examined the correlation between total energy intake, energy density, dietary nutrient intakes, and risk markers for DMII in a large, cross-sectional, multiethnic population of 9–10-year-old children. The study procured a structured 24-hour diet recall from the 2,569 participants. The energy and nutrient intakes were calculated using the Medical Research Council Human Nutrient Research Center's standards for childhood nutrition needs. By using an estimate of basal metabolic rate (BMR), the study was able to identify several dietary risk markers for DMII.

For many years, it was believed that the greatest dietary risk factor associated with DMII was fat intake. However, current research disproves this theory (Donin et al., 2014). In fact, of all the dietary factors identified in the ADA study, including energy intake, energy density, glycemic markers, and fat mass index, there was only a positive association between total energy intake and insulin resistance. Total energy intake is essentially caloric intake. Other factors, such as energy density or macronutrients, showed little to no association with insulin resistance and the development of DMII in childhood. This means that the total caloric intake is a more significant risk marker for DMII than specific nutrient intake. The study further investigates dietary intake of the participants. While overall caloric, or energy, intake is what is most closely associated with DMII, the balance of carbohydrate and protein intake is also influential.

Carbohydrates, specifically simple carbohydrates, such as donuts, bread, and sugary cereal, provide empty calories for children. These foods are high in calories and low in nutrients, which causes the child to consume more calories to feel satisfied. Conversely, lean protein, such as chicken, beans, and tuna, promote ideal nutrient intake while maintaining appropriate caloric intake. Thus, high carbohydrate and low protein diets are strongly correlated with insulin resistance and the development of DMII. Excessive carbohydrate intake is a primary risk factor in the development of childhood DMII (Donin et al., 2014).

**Breastfeeding in infancy.** Breastfeeding during infancy plays a critical role in the child's long-term health, specifically in regards to weight and metabolic syndromes. Studies indicate that breastfeeding is associated with a 22-24% lower subsequent risk of childhood obesity and lower risk for DMII (Gunderson, 2010). The CDC growth charts indicate the healthy weight of children from birth through adolescence. Exclusively breastfed infants consistently gain weight more rapidly in the first three months of life compared to bottle-fed infants. However, after the first three months of life, exclusively breastfed infants have lower, healthier weight-for-age compared to bottle-fed infants. Several studies have been conducted in the last decade to examine the long-term weight and metabolic implications of children who were exclusively breastfed as infants. A meta-analysis of 17 studies indicates the duration of breastfeeding is directly associated with reduced risk of obesity and DMII in childhood. One of these studies, a population-based survey of over 15,000 American children between the ages of nine and 14, found that the children who were breastfed for longer than seven months were less likely to be obese or experience subsequent metabolic disorders (Bartz & Freemark, 2011).

While much of the current data focuses on obesity and metabolic disorders in general, several studies have been done specifically to find the association between breastfeeding and childhood DMII. A reverse study, which identified obese teens with DMII and normal weight teens without DMII, found that the teens with DMII were 40% less likely to have been breastfed in infancy compared to the teens that did not have DMII. Research continues to determine the precise mechanism of defense against DMII provided by breastfeeding, as the association is not entirely clear. However, current research suggests that breastfed infants are less likely to be overfed since the physiological association between the infant's needs and mother's milk production is somewhat synchronized. It is suggested that bottle-fed infants are more likely to be overfed because bottle feedings normally occur on a fixed schedule. Consequently, bottle fed infants are trained to expect food at fixed intervals, whereas breastfed infants expect food when hungry. This expectation then stays with the child throughout childhood and adolescence (Bartz & Freemark, 2011). While this risk factor is modifiable, many parents often realize too late that breastfeeding is a way to prevent childhood medical disorders such as DMII (Shaw, 2007). Thus, early intervention is essential to provide parents with accurate information regarding the benefits of breastfeeding and its association with decreased obesity and DMII in childhood.

### **Long-term Complications of Childhood DMII**

Childhood DMII has tremendous and long-lasting effects. Not only are the ramifications seen throughout childhood, as the young patient learns to cope with diabetes, but childhood DMII predisposes an individual to additional significant medical conditions later in life. Although additional medical conditions may not develop

immediately, most individuals will experience complications within 30 years of diagnosis (Michel, 2011). This is especially detrimental for children diagnosed with DMII because they will experience the complications at a much younger age than will adults diagnosed with DMII. If an adult is diagnosed with DMII at the age of 40, he or she will likely experience several comorbid medical conditions by the age of 70. If a child is diagnosed with DMII at the age of 10, he or she will likely experience several comorbid medical conditions by the age of 40. Thus, by middle age, these DMII children will face numerous obstacles that their peers will not face for decades, including significant cardiac complications, renal failure, and vision impairment.

### **Cardiac Complications**

Cardiac complications are the most common and often the most dangerous complication associated with DMII. Nearly 70% of diabetes-related deaths are linked directly to cardiac complications, with type II diabetics facing a two- to four-fold higher death rate due to heart disease compared to non-diabetics. Type II Diabetes adversely affects several aspects of cardiac function, including cardiomyocyte metabolism, cardiac insulin signaling and calcium control, and the stimulation of vascular and cardiac fibrosis (Gardner, Murray, & Wold, 2013). These abnormalities all contribute to cardiac dysfunction in patients with DMII.

Alterations in several molecular signaling pathways have been identified in the development of cardiac complications due to DMII. Research suggests that impaired insulin signaling – the result of hyperinsulinism, hyperglycemia, and insulin resistance – likely forms the foundation for imbalances in diabetic cardiac complications. Following the initial insulin signaling impairment, diabetics experience subsequent changes in

coronary and renal blood vessels as a result of impaired nitric oxide regulation and decreased vascular permeability. This causes constriction of the coronary and renal blood vessels and over-activation of the Renin-Angiotensin-Aldosterone System (RAAS). Finally, increased FFAs and poorly regulated lipid signaling results in the buildup of FFAs, called atherosclerosis, and lipotoxicity in the heart and blood vessels. The progression of diabetic cardiac complications results in fibrotic buildup throughout the cardiac system and progressive overworking of the cardiac muscle (Manadavia, Aroor, DeMarco, & Sowers, 2013). Individuals with DMII must be closely monitored for levels of High-Density Lipoproteins (HDL) cholesterol, Low-Density Lipoproteins (LDL) cholesterol, blood pressure, and triglycerides to determine each individual's cardiovascular risk. Children with DMII consistently display lower levels of HDL and higher levels of LDL cholesterol, pre-hypertension or hypertension, and elevated triglycerides when compared to their non-diabetic counterparts. This is due in part to diet, but also to the nature of DMII and its impact on the body and cardiac function. Many cardiovascular risks cannot be controlled once DMII has been diagnosed (Rodriguez, 2006). Common comorbid cardiac diagnoses associated with DMII include hypertension, coronary artery disease, hyperlipidemia, and diabetic cardiomyopathy.

**Hypertension.** In the US, hypertension occurs in 70% of all individuals with DMII. The American Diabetes Association performed a study in 2013 that found that 34% of children with DMII between the ages of 8-17 also had hypertension (Pyle, 2013). Hypertension is the most commonly occurring comorbid disease process associated with DMII (Cheung & Li, 2012). This is in part due to the several risk factors the two diseases share, including obesity, hyperlipidemia, and atherosclerosis. Hypertension is caused by

plaque build-up in the arteries and veins, which is called atherosclerosis. As atherosclerosis worsens, the blood vessels become obstructed or blocked, thus less blood is transported to the body tissues. Additionally, plaque is made up of a firm shell containing soft fat, cholesterol, calcium, fibrous tissue, and other substances in the blood. As blood hits the plaque during each heartbeat, the plaque weakens and eventually cracks open to expose the soft cholesterol. This newly exposed cholesterol promotes abnormal blood clotting, which further impairs necessary blood flow to the body by creating additional structural barriers that blood flow must work against (Matfin, 2009). Diagnosis of hypertension prior to adulthood presents the individual with additional medical complications and comorbid factors. Children who are diagnosed with DMII have a significant risk of developing hypertension during their childhood or adolescent years.

**Coronary Artery Disease.** Coronary Artery Disease (CAD), also known as coronary heart disease, is the leading cause of mortality among patients with DMII (“Cardiovascular Disease”, 2014). Cardiologists Nima Alipour, Nathan Wong, and Shaista Malik (2012) suggest that 50% of DMII patients have or will develop CAD during their lifetime. Coronary artery disease occurs when the arteries that supply blood to the heart, called the coronary arteries, become hard and narrow. As with hypertension, this is caused in part by atherosclerosis and plaque buildup along the lining of the vessels. Coronary artery disease is particularly dangerous for two reasons. First, the coronary arteries are fairly small, which means even minimal atherosclerotic buildup can prevent adequate blood flow. Second, the coronary arteries supply blood directly to the cardiac muscle. If the heart is not supplied with adequate blood flow via the coronary arteries, the entire body is affected. Over time, less blood is able to flow through the coronary arteries

to supply the heart with essential blood and oxygen. Diminished blood flow to the heart can lead to angina or heart attack. Coronary artery disease also contributes to weakening the cardiac muscle and the development of heart failure and arrhythmias (Alipour et al., 2012). Children with DMII should be screened for CAD, as early diagnosis allows for more diverse treatment options (Upchurch, 2012).

**Hyperlipidemia.** Hyperlipidemia is excess lipids, or fats, in the bloodstream, including cholesterol and triglycerides. Triglycerides are the most abundant type of fat in the body. According to the American Heart Association, healthy triglyceride levels should be below 150mg/dl. Forty percent of individuals with DMII have triglyceride levels greater than 200mg/dl (“What Your Cholesterol Levels Mean”, 2015). The most common dyslipidemic pattern in DMII, diabetic hyperlipidemia, is characterized by elevation in triglycerides, low HDL cholesterol, and an increase in small dense LDL particles. This particular lipid disturbance pattern is associated with insulin resistance in DMII. The insulin resistance is related to the impaired pancreatic and beta cell signaling, which leads to decreased insulin sensitivity and excess free glucose in the blood stream. An elevation in small dense LDL particles can be detrimental in the presence of pre-existing cardiac disease. The small LDL particles contribute to atherosclerosis, as they are highly susceptible to oxidative modification and increased buildup along the arterial wall. Once triglyceride levels reach 132 mg/dl or higher, small LDL particles begin to accumulate along arterial walls. This diabetic hyperlipidemia contributes to and exacerbates hypertension (Solano & Goldberg, 2006). Children who are diagnosed with DMII must have their HDL, triglycerides, and small LDL particles monitored to prevent exacerbation of cardiac complications.

**Diabetic Cardiomyopathy.** Diabetic cardiomyopathy is cardiac disease that is characteristically independent of other vascular complications during diabetes. While comorbid cardiac conditions may exist, they are not the cause of the diabetic cardiomyopathy. The number of cases of diabetic cardiomyopathy each year is growing parallel to the number of cases of DMII. Diabetic cardiomyopathy is essentially a heart failure syndrome that is characterized by hypertrophy of the left ventricle and decreased diastolic function, with or without concurrent systolic dysfunction. Decreased diastolic function results in prolonged diastolic relaxation with each heartbeat. This dysfunction frequently leads to subsequent progressive fibrosis and impaired serum calcium utilization. Cardiac fibrosis and imbalanced serum calcium result in contractility dysfunction, cardiac autonomic neuropathy, and excess stress on the heart muscle (Mandavia et al., 2013). Typically, diabetic cardiomyopathy is diagnosed in the absence of hypertension or CAD. If both hypertension and CAD are present, the diagnosis will be congestive heart failure (CHF) rather than diabetic cardiomyopathy. This is because diabetic cardiomyopathy, by definition, is heart failure that is not caused by underlying cardiac conditions (Isfort, Stevens, Schaffer, Jong, & Wold, 2013). Diabetic cardiomyopathy is a progressive disease. Screening for diabetic cardiomyopathy is an important component of the management of DMII in children. Because diabetic cardiomyopathy does not have underlying cardiac causes, such as hypertension or CAD, it is sometimes unnoticed until the disease has progressed to the point of physiological impairment.

**Renal Failure**

Diabetic nephropathy, a condition caused by poor blood flow to the kidneys, is the leading cause of chronic kidney disease (CKD) and end stage renal disease (ESRD) in the US (Porth, 2009). Physiologically, diabetic nephropathy causes several dysfunctions in the renal system. Dr. Thinzar Min and associates (2012) examined two cross-sectional studies to determine the prevalence of diabetic nephropathy in patients with DMII. The analysis concludes that, on average, 26% of DMII patients are also diagnosed with diabetic nephropathy. These dysfunctions include glomerulosclerosis, chronic vascular damage, and increased susceptibility to glomerular diseases related to the glomerulosclerosis. Diabetic nephropathy can be diagnosed using several different factors. The earliest biochemical marker of diabetic nephropathy is the presence of albuminuria, which is excessive albumin protein in the urine. The rate of renal decline is directly related to the severity of the albuminuria. Albuminuria is the most sensitive indication of CKD. Microalbuminuria is defined as urine albumin levels that are above normal, but below the level detectable by dipstick testing. For most patients, microalbuminuria marks the beginning of renal impairment, though no outward physiological changes may have yet occurred. If microalbuminuria persists, over time it will progress to macroalbuminuria. On average, 20% of DMII patients will progress to macroalbuminuria levels within five years. Albuminuria causes deterioration in renal function. Studies suggest that albumin that would normally be filtered out by the glomerulus causes injury to the tubular cells, which leads to tubular fibrosis, or stiffening. The etiology, or cause, of diabetic nephropathy is primarily hyperglycemia. Because high blood glucose levels and insulin resistance characterize DMII, the renal tissues are

overexposed to hyperglycemia. The mesangial cells, which are the cells that make up the capillaries within the renal system, are exceptionally sensitive to hyperglycemia. The mesangial cells are damaged by hyperglycemia, which impairs their ability to filter properly. Thus, albumin builds up in the urine leading to albuminuria (Min, Stephens, Kumar, & Chudleigh, 2012). While not all individuals with DMII will develop diabetic nephropathy, it is a debilitating complication of DMII. Children who are diagnosed with DMII should undergo screening for microalbuminuria to promote early detection of the disease.

### **Vision Impairment**

Vision impairment due to diabetic retinopathy is a complication of diabetes. Retinopathy is a result of microvascular damage to the retina as a result of chronic hyperglycemia and hypertension (Carroll, Scott, & Curtis, 2009). In the US, diabetic retinopathy is the leading cause of preventable blindness in working-age adults. It is estimated that 40% of people with DMII have retinopathy, with eight percent experiencing blindness as a result of the disease process. Historically, retinopathy has a more significant and debilitating effect on individuals with DMI than those with DMII. Research indicates that this is due to the historically later onset of DMII rather than the physiological processes of the different types of diabetes. Children who are diagnosed with DMII prior to puberty have a 30% greater chance of developing diabetic retinopathy than those who are diagnosed after puberty. The physiological changes of puberty, including hormones, insulin sensitivity alterations, and adipose redistribution, trigger retinopathy. The primary cause of retinopathy is chronic exposure to hyperglycemia. As with the renal capillaries, retinal vessels tend to be more sensitive to the toxic effects of

chronic hyperglycemia. Hyperglycemia, as well as chronic hypertension, initiates a cascade of physiological changes that result in microvascular damage and retinal impairment. Several biochemical factors are involved in the cascade, including accumulation of sorbitol, oxidative stress resulting in tissue damage, protein kinase C activation, and dysfunction of the RAAS. Inflammation is also a key component in the destruction of retinal vessels and the development of retinopathy (Cheung, Mitchell, & Wong, 2010). The ADA recommends that children who are diagnosed with DMII prior to puberty undergo screening for retinopathy within three years of diagnosis. For children diagnosed after puberty, screening should take place with annual ophthalmologist visits (“Diabetic Retinopathy”, 2007).

### **Conclusion**

Over the last three decades, the number of children diagnosed with DMII has greatly increased. This rapid increase in childhood DMII has prompted numerous studies and extensive research to investigate why the epidemic exists and what its life-long ramifications may be for children. Since DMII is a heterogeneous disease with both genetic and environmental risk factors, it is imperative that the environmental, or modifiable, risk factors be addressed. These include obesity, exercise, diet, and breastfeeding in infancy. Due to the chronic nature of DMII, children with the disorder are at significant risk for developing additional medical conditions, or co-morbidities. These include cardiac complications, renal failure, and vision impairment. Due to the early onset of childhood DMII, these co-morbidities are often pronounced and debilitating once the child has reached middle adulthood. Childhood DMII is an

epidemic. Aggressive effort including the screening for and understanding of the disease is imperative to reduce the risks and complications associated with childhood DMII.

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