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# DIABETES AND ITS COMPLICATIONS

# Diabetes complications in childhood and adolescent onset type 2 diabetes—a review



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# 1. Introduction

Globally there is a rapid increase in the prevalence of adult type 2 diabetes (T2DM). Unfortunately there is also a parallel increase of T2DM among children and adolescents (Urakami et al., 2007). The main driver of this epidemic is the increasing rates of obesity among children, consequent to sedentary lifestyle, and this increase largely rises in those with a parental history of T2DM (Kitagawa, Owada, Urakami, & Yamauchi, 1998; Likitmaskul et al., 2003; Mohan, Jaydip, & Deepa, 2007; Ramachandran, Snehalatha, Satyavani, Sivasankari, & Vijay, 2003; Urakami et al., 2005). The shift in age at diagnosis of T2DM in children and adolescents has serious implications, as it not only affects the health of the youth, but it also has the potential to pose a huge socio economic burden on the society at large as they grow into adults. Developing T2DM during childhood or adolescence places them at markedly increased risk for developing diabetes complications and mortality in early adulthood. An extensive list of studies was summarized in the long term outcomes in youth with diabetes especially in type 1 diabetes (White, 2015), whereas only limited

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#### ABSTRACT

Diabetes mellitus is one of the most common endocrine disorders in children. Earlier, diabetes in children was almost exclusively type 1 diabetes. Recently, the scenario has changed and increasing numbers of children and adolescent T2DM are being diagnosed. As the epidemic of T2DM shifts to children and adolescents, there is an increased risk of development of micro and macrovascular complications. This could potentially affect the economy of the nation apart from posing a large burden to the individual and his or her family. Prevention and treatment are especially important, given the fact that onset at an early age increases the risk of developing micro and macrovascular complications due to increased duration of exposure to hyperglycemia and other metabolic abnormalities. Diagnosing children and adolescents with T2DM early and instituting good control of all risk factors could yield good results in the prevention of long term complications of diabetes. This review focuses on the prevalence of complications of diabetes among children and adolescents with T2DM.

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follow up studies are available with respect to complications in children and adolescents with T2DM. The purpose of the article was to review studies on the micro and macrovascular complications in childhood and adolescent onset T2DM.

# 2. Methods

Due to limited published articles related to our topic, we did an extensive literature search on studies done in children and adolescents with T2DM. The types of studies were not restricted owing to the rarity of the topic. Mostly they were all clinic based cohort studies on diabetes complications like diabetic retinopathy, diabetic nephropathy, diabetic neuropathy etc., especially on children and adolescents with age onset of T2DM at or below 19 years. The online search engines used were Google scholar, PubMed (MEDLINE), EBSCO, Ovid, Science direct, Web of science, Proquest and IDF Diabetes Atlas for articles in English using subject headings and key words like "childhood onset T2DM", "children with T2DM and complications", "adolescent onset T2DM with complications", "youth onset T2DM with complications", "young onset T2DM", "microvascular complications", "diabetic retinopathy", "diabetic nephropathy" and "diabetic neuropathy" which were published in the previous years.

The inclusion criteria used were as follows:

1. Studies on children and adolescents with onset of T2DM at or below 20 years.

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- 2. If any one of the diabetes complications like diabetic retinopathy, diabetic nephropathy (micro or macroalbuminuria) and diabetic neuropathy was assessed, those studies were included.
- 3. Only articles published in English language were included.

#### 3. Microvascular complications

# 3.1. Diabetic retinopathy (DR)

DR is the most common microvascular complication of diabetes posing a serious threat to vision in T2DM. DR is the affection of the small vessels on the retina due to prolonged uncontrolled hyperglycemia leading to appearance of microanuerysms and/or hemorrhages and/or exudates and/or abnormal vessels on the retina. This condition may occur with or without other systematic complications of diabetes, and its prevalence increases with the duration of diabetes. Even though the severity of hyperglycemia may be greater in T1DM, among adolescents with T2DM as the disorder may be for several years the risk for retinopathy may be higher and indeed DR may even be present at two of diagnoses of T2DM. Hence there is a need for screening for retinopathy even at the time of diagnosis of adolescents with T2DM (Eppens et al., 2006).

Prevalence rates of DR among T1DM and T2DM vary widely in different studies due to various reasons including case mix. In a clinic based study from Australia, DR was significantly more frequent in individuals with T1DM than in those with T2DM (20 vs. 4%, p = 0.04) (Eppens et al., 2006). Similarly Scott et al. (2006) also reported that 10 vs. 4% of those with T1DM and T2DM respectively had background retinopathy. In both these studies, the duration of diabetes among T2DM was shorter than in T1DM. The SEARCH study (Mayer-Davis et al., 2012) reported a prevalence of 42% with DR among those who had more than 5 years duration of diabetes and with a mean age of 21 years. The TODAY study (TODAY Study Group, 2013b), reported the prevalence of DR to be 13.7% with a mean duration of 4.9 years but none of them had macular edema, or proliferative diabetic retinopathy. These prevalence rates are higher than previously reported among Pima Indians, in whom DR was detected only after 20 years of age (Krakoff et al., 2003).

There are very few studies on the prevalence of retinopathy in childhood diabetes. In 1990, a study from Kerala diagnosed eight patients with T2DM (then called as non insulin dependent diabetes) who had the onset of diabetes at below 20 years. Among them, two (25%) had diabetic retinopathy with duration of diabetes between 6 and 30 years (Abraham & Geevarghese, 1990). From Chennai, at a tertiary diabetes specialty center (Amutha, Datta, Unnikrishnan, Anjana, & Mohan, 2012) reported that the prevalence of DR increased from 4.2% among those with diabetes duration of  $\leq 5$  years to 81.5% in those with duration of diabetes >15 years and two patients had DR at the time of diagnosis of diabetes. In one of our recent studies on youth onset diabetes (Rajalakshmi et al., 2014), the age and gender adjusted prevalence of retinopathy in T1DM-Y and T2DM-Y was 62.5 and 65.8% respectively. Among the T2DM-Y, 22.7% of them were adolescents with T2DM (age at onset 10–19 years) and the prevalence of overall DR was found to be 32.4% (Fig. 1).

# 3.2. Diabetes nephropathy

Diabetic nephropathy is the leading cause of chronic renal failure and end stage renal disease (ESRD) (Ayodele, Alebiosu, & Salako, 2004). This is due to the increasing prevalence of T2DM, longer lifespan of diabetic patients and improved therapeutic options which allow the patients to live long enough to develop chronic complications including nephropathy. Less than 20% develop ESRD as most of the T2DM patients succumb earlier to coronary artery disease. Diabetic nephropathy is characterized clinically by urinary albumin excretion, progressing through various stages of albuminuria and finally to ESRD. Microalbuminuria (MIC) is defined as an albumin excretion rate of 30–299 µg/mg of creatinine, which is currently the earliest detectable stage of nephropathy at which appropriate interventions can delay, or retard, the progression. Overt diabetic nephropathy is clinically defined as presence of persistent proteinuria of  $\geq$ 500 mg/day or if MIC is  $\geq$ 300 µg/mg of creatinine usually along with diabetic retinopathy and accompanying hypertension, and in the absence of any other renal disorder.

Screening for microalbuminuria should be done at the time of diagnosis of diabetes and at yearly intervals thereafter (American Diabetes Association, 2014). Persistent microalbuminuria is seen in approximately 10% of children and adolescents (Pinhas-Hamiel & Zeitler, 2007) which later progresses to overt nephropathy. Nephropathy occurs at all the age groups and it is not related to age at diagnosis of diabetes (Krakoff et al., 2003). In a clinic based study, we found that the prevalence of microalbuminuria increased from 8.7 to 29.5% when the diabetes duration increased from  $\leq 5$  to >15 years, while the prevalence of overt nephropathy increased from 9 to 34.4%, respectively (Amutha et al., 2012). The development of diabetic microalbuminuria and nephropathy at younger age is preventable which predisposes these individuals to a higher risk for cardiovascular complications which in turn could lead to a reduction in life expectancy. Longitudinal studies on the progression of microalbuminuria, risk factors, mechanisms and treatment options of nephropathy in youth onset T2DM are urgently needed to reduce this complication potentially especially in high risk populations (Afkarian, 2015; Solis-Herrera, Triplitt, & Lynch, 2014).

# 3.3. Diabetic neuropathy

Neuropathy is one of the commonest complications of diabetes (Vinik, Park, Stansberry, & Pittenger, 2000). Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunctions after exclusion of other causes. It is a heterogeneous condition that encompasses a wide range of peripheral nerve dysfunction whose development might be attributed to diabetes per se or to factors associated with the disease. It can be assessed non invasively by several tests varying from simple assessment of pin-prick perception to more detailed assessment using several different modalities including clinical signs and symptoms, sensory tests or electro diagnostic tests (Bhadada, Sahay, Jyotsna, & Agrawal, 2001). It is one of the most common and is referred to as the 'painful complication' of diabetes

Clinical neuropathy in adolescence is rare, although subclinical neuropathy demonstrated by abnormalities of vibration perception threshold or nerve conduction studies have been reported in 20 to 57% of adolescents with diabetes. The prevalence of neuropathy increased from 3 to 49.2% in those with diabetes duration of  $\leq$  5 and >15 years duration respectively in a clinic based study (Amutha et al., 2012). Some studies suggest that there is no difference among the rates of diabetic neuropathy in T1DM and T2DM, although, it tends to develop at a more rapid rate among T2DM adolescents (Eppens et al., 2006; Karabouta, Barnett, Shield, Ryan, & Crowne, 2008).

The prevalence of microvascular complications in children and adolescent onset T2DM in various published studies is summarized in Table 1.

# 4. Macrovascular complications

#### 4.1. Cardiovascular disease (CVD) and mortality

Cardiovascular disease (CVD) is the major cause of death among patients with T2DM (Moss, Klein, & Klein, 1991; Stamler, Vaccaro,



Fig. 1. Prevalence of diabetic retinopathy (DR) in children and adolescent onset T2DM subjects (Rajalakshmi et al., 2014).

Neaton, & Wentworth, 1993). Although myocardial infarction and cerebrovascular accident are rare until later decades of life, the process of atherosclerosis begins in childhood. Data on CVD in youth with T2DM are limited. Berenson et al. demonstrated that an increased number of CVD risk factors increase the severity of asymptomatic coronary and aortic atherosclerosis in youth (Berenson et al., 1998). In individuals with diabetes, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study demonstrated a highly significant increase in the prevalence of advanced American Heart Association (AHA) grade atherosclerotic lesions at ages as young as 15–19 years of age (Zieske, Malcom, & Strong, 2002).

A significant increase in the prevalence of CVD, ischemic heart disease and any macrovascular disease ascertained clinically by medical records was found in YT2DM (Wong, Constantino, & Yue, 2015). The deteriorating atherogenic characteristics observed in the TODAY study over time, even after aggressive intervention, suggest that significant CVD could be detected in the earlier decades of life in adolescents with T2DM (TODAY Study Group, 2013a). Also identifying obese children at risk for T2DM is most important to prevent its progression to diabetes related cardiovascular complications in this young age (D'Adamo & Caprio, 2011). Furthermore, psychosocial barriers could be challenges to deliver effective interventions to this age group (Anderson et al., 2011). More studies are needed in this vulnerable population with more intensive interventions, both behavioral and pharmacological, to lower their CVD risk.

A recent meta-analysis, compared interventions with conventional treatment to improve glycemic control among T1DM and T2DM and found that improved glycemic control reduces cardiac and peripheral vascular events in T1DM substantially, whereas the effect was modest and limited to peripheral vascular disease and stroke among T2DM (Stettler et al., 2006). This suggests that role of glycemic control in the development of CVD may differ between T1DM and T2DM subjects.

Mortality data for children and adolescents with T2DM are very limited. A Canadian study reported that seven had died among 51 subjects who developed T2DM before age 17, and who were surveyed later as young adults between the ages of 18 and 33 years (Dean & Flett, 2002). Another study from Sweden reported diabetes as one of the underlying causes of death in 32% of incident cases of young adults with T2DM in the 15–34 year age group, after an average follow-up of 8.5 years (Waernbaum et al., 2006). A cohort of 354 patients with T2DM and 470 patients with T1DM with similar age of onset between 15 and 30 years were compared to study the clinical and mortality outcomes in Australia (Constantino et al., 2013). It was found that there was a markedly higher prevalence of macrovascular disease among T2DM, with a significantly higher prevalence of ischemic heart disease (T2DM 12.6 vs. T1DM 2.5%), stroke (4.3 vs. 0.7%), and any macrovascular disease (14.4 vs. 5.7%).They also reported a significantly increased risk of death for T2DM, which was associated with diastolic BP and albuminuria.

Despite the increasing prevalence of T2DM among children and adolescents worldwide, the incidence and prevalence rates of complications given above have some limitations and drawbacks. Moreover, the reported rates of the complications in pediatric and adolescent onset T2DM are still diagnosed later in adulthood and not at the time of diagnosis (Jordan & Jordan, 2012). Firstly, some of the studies have reported rates of complications in different age categories. Some of the studies could not be included as they include people with differing ages at onset e.g. 25, 30, 40 and 45 years and the age and age at onset of diabetes studied also varied significantly (Amutha et al., 2011; Hillier & Pedula, 2003; Okudaira, Yokoyama, Otani, Uchigata, & Iwamoto, 2000; Song, 2015). Differences in methodology make direct comparisons difficult, e.g. for retinopathy screening some authors have used direct ophthalmoscopy while others have used fundus photography. Finally, the studies reported are mostly diagnosed cases of T2DM and many asymptomatic children are not screened for diabetes or its complications as screening for diabetes is not currently recommended for children. Hence the prevalence rates will expand on the stage at which these children were diagnosed due to symptoms of diabetes.

# 5. Metabolic risk factors

#### 5.1. Hypertension

Hypertension is one of the independent risk factors for the development of albuminuria, retinopathy and cardiovascular disease

# Table 1

Microvascular complications in children and adolescent onset T2DM.

Author, year	Country	Year or period of study	Age at diagnosis (years)	Duration of diabetes (years)	Retinopathy n (%)	Nephropathy n (%)	Neuropathy n (%)
Abraham and Geevarghese (1990)	India	1990	≤20	6 to15	1/4 (25.0)	-	-
			≤20	16 to 30	1/1 (100.0)	-	-
Amutha et al. (2012)		2012	<20	≥15	44/54 (81.5)	21/61 (34.4)	30/61 (49.2)
Dart et al. (2014)	Canada	1986-2007	<18	-	40/342 (11.7)	30/342 (8.9)	26/342 (7.6)
					$[7.4 \pm 5.9]$	$[7.5 \pm 5.7]$	$[6.5 \pm 5.6]$
Amed et al. (2012)		2006-2008	<18	-	_	32/221 (14.5%)	_
Sellers et al. (2009)		2003	10 to 17	0.4 to 5.0	-	14/90 (16%)	-
Sellers et al. (2016)		2010-2012	<18	21 days	-	50/976 (5.1%)	-
Fagot-Campagna, Knowler, and Pettitt (1998)	USA	1998	15 to19	5 to 10	-	6/36 (17%)	-
Krakoff et al. (2003)		2003	<20	15 to 20	9 cases	10 cases	-
Ettinger, Freeman, DiMartino-Nardi, and Flynn (2005)		2005	10 to18	3.0	-	10/25 (40.0)	-
Farah et al. (2006)		2006	_	-	1/40 (2.5)	9/33 (27.3)	-
Pavkov et al. (2006)		2006	<20	Decades of age	-	ESRD-25 cases/1000 person	-
. ,				, in the second s		years	
Kim et al. (2010)		1982-2007	<20	1.3 (0-2.1)	-	3/103 (2.9)	-
SEARCH study (Mayer-Davis et al. (2012), Maahs et al. (2007), Jaiswal et al. (2013)		2001-2007	<20	-	18/43 (42.0) [7.2 yrs]	83/374 (22.2) [1.9 (0.4–3.2) years]	18/70 (25.7) [7.6 + 1.8 years]
TODAY study group (2013b, 2013c)		2004-2009	10–17	4.9	71/517 (13.7)	MIC-44/699 (6.3)-baseline 116/699 (16.6)-end of study	_
Karabouta et al. (2008)	UK	2008	<18	0.5 to 3.0		-	4/7 (57.0)
McGrath, Parker, and Dawson (1999)	New Zealand	1998	19.4	10.1	9/26 (35.0)	7/26 (27.0)	-
Hotu, Carter, Watson, Cutfield, and Cundy (2004)		1997-2001	11–19	At diagnosis	-	2/12 (16.7)	-
Eppens et al. (2006)	Australia	1996-2005	≤18	0.6 to 3.1	1/25 (4.0)	MIC-10/36 (28.0)	5/24 (21.0)
Yoo, Choi, and Kim (2004)	Korea	2004	$12.8 \pm 1.5$	$5.5 \pm 3.9$	-	1/22 (4.5)	-
Yokoyama et al. (2000)	Japan	2000	10-19	~10 to 15	_	12.44/1000 person years <sup>a</sup>	-
Okudaira et al. (2000)	~ 1	1980-1989	22.6	5-10	88/322 (27.3)	_	-

Data in [] square brackets denotes duration of diabetes. MIC-microalbuminuria, ESRD-end stage renal disease.

<sup>a</sup> Incidence density.

in T2DM. Hypertension is an important factor in the early appearance of atheroscelerotic lesions in children and adolescents (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). An earlier study reported that raised blood pressure is eight times more in T2DM adolescents than in young T1DM at the time of diagnosis (Zdravkovic, Daneman, & Hamilton, 2004). In the SEARCH study, 39% of the youth had hypertension (Rodriguez et al., 2010). Findings from the TODAY study, reported that hypertension was present in 11.6% of the population at baseline and increased to 33.8% by the end of the study (TODAY Study Group, 2013c; Tryggestad & Willi, 2015).

In our study, raised blood pressure was seen among 27.2% of boys and 21.4% of girls (Amutha et al., 2012). In one study we found that increased systolic and diastolic blood pressure, regardless of the type of young onset diabetes, increased the risk for retinopathy, while diastolic blood pressure was an independent predictor for DR in T2DM patients (Rajalakshmi et al., 2014). The ABCD (Appropriate Blood pressure control in Diabetes) trial found that lowering the diastolic pressure, slowed the progression of diabetic retinopathy and nephropathy while also lowering the incidence of stroke (Schrier, Estacio, Esler, & Mehler, 2002).

# 5.2. Dyslipidemia

Increased serum triglycerides and reduced high density lipoprotein cholesterol (HDL) are the hallmarks of T2DM dyslipidemia and these not only contribute to significant cardiovascular morbidity but also increase the severity of retinopathy (Miljanovic, Glynn, Nathan, Manson, & Schaumberg, 2004). The characteristic lipid abnormality in patients with T2DM is atherogenic dyslipidemia, i.e. raised levels of both triglycerides, LDL cholesterol and a low level of HDL cholesterol. Dyslipidemia is common among young T2DM aged <18 years with raised cholesterol and triglyceride concentrations in 33–60% of them (Bell et al., 2009; Fong et al., 2004; Upchurch et al., 2003; Zdravkovic et al., 2004). These rates are found to be higher than in non-diabetic obese individuals, suggesting that the presence of diabetes has an added impact on dyslipidemia. We found that 40.3% boys and 36.2% girls have hypertriglyceridemia, while 61.1 and 69.2% respectively have low HDL cholesterol (Amutha et al., 2012).

In the TODAY study (TODAY Study Group, 2013a), many participants had reduced HDL cholesterol levels. Similarly, the SEARCH study (Rodriguez et al., 2006) also reported a substantial proportion of young-onset diabetes individuals aged <20 years had elevated triglycerides (30%) and low HDL-cholesterol (24%). These observations are of particular concern, due to the potential increased risk of developing cardiovascular disease at an early age.

#### 5.3. Arterial stiffness and carotid intimal medial thickness

Arterial stiffness occurs as a consequence of age and arteriosclerosis. Arterial stiffness is associated with an increased risk of cardiovascular events. Studies on arterial stiffness and carotid intimal medial thickness (CIMT) among youth are scarce. A comparative study of 20 T2DM patients compared with obese and healthy-weight controls over the age of 15 years, showed increased arterial stiffness among T2DM subjects (Gungor, Thomposon, Sutton-Tyrrell, Janosky, & Arslanian, 2005b). Young T2DM individuals have abnormal vascular stiffness as measured by aortic pulse wave velocity (Gungor, Hannon, Libman, Bacha, & Arslanian, 2005a).

Wadwa et al. (2010) assessed the effect of risk factors on arterial stiffness and showed that those with T2DM had worse arterial stiffness than those with T1DM. The authors concluded that the

increased central adiposity and hypertension associated with T2DM were the primary factors contributing to the difference in arterial stiffness. They also report that these changes may occur before the development of clinically significant T2DM (Wadwa et al., 2010). There is a need for longitudinal studies to determine whether arterial stiffness is one of the signs of future progression to cardiovascular disease in young diabetes.

Early changes of atherosclerosis can be detected by assessment of carotid intima-media thickness (IMT) (Davis, Dawson, Riley, & Lauer, 2001). Carotid intima media thickness (CIMT) has been shown to be a predictive marker of stroke and myocardial infarction in adults (Chambless et al., 1997; Hodis et al., 1998). CIMT has also been a useful technique for following progression of cardiovascular disease and the impact of lipid and hypertensive treatments (Furberg et al., 1994; Pitt et al., 2000; Salonen et al., 1995). In adolescents with T2DM, every percent increase in HbA1c level or duration of diabetes increased the odds of finding greater carotid IMT by 30% (Shah et al., 2009). Raitakari et al. (2003) sought to study the relationship between CVD risk factors and CIMT in patients examined in adolescence (age 3-18) and again 21 years later. In this study, adolescents with multiple risk factors for atherosclerosis after the age of 12, had higher measured CIMT as adults compared with those that did not

# 6. Recommendations by American Diabetes Association (ADA) for Monitoring Complications and Risk Factors (American Diabetes Association, 2014)

# 6.1. Retinopathy

In T2DM, the initial examination should be done shortly after diagnosis or at the time of diagnosis itself. Annual routine follow-up is generally recommended. Diabetic individuals should be made to meet professionals with expertise in diabetic retinopathy. The risk of retinopathy and awareness about the early prevention/intervention should be counseled to the patient and family members.

# 6.2. Nephropathy

Annual screening for urinary albumin excretion levels should be considered at diagnosis. If MIC levels are persistently higher in two to three visits, it should be treated with an ACE inhibitor and this should if possible be titrated to normalization of albumin excretion levels.

#### 6.3. Neuropathy

Annual foot examinations are recommended as they are inexpensive and painless, and provide an opportunity for education about foot care and its importance among children and adolescents. All individuals at diagnosis of T2DM and 5 years after the diagnosis of T1DM, should be screened for distal symmetric polyneuropathy (DPN) and annually thereafter.

# 6.4. Lipid profile

All T1DM and T2DM children should be assessed for their lipid profile at diagnosis. If they are less than 10 years, it should be assessed once the glucose profile is under control. If necessary, treatment should be started according to guidelines (McCrindle, Urbina, Dennison, et al., 2007).

# 6.5. Blood pressure

Blood pressure must be routinely assessed at each visit and those who have raised blood pressure, it should be confirmed on a separate day. ACE inhibitors are considered for the treatment of hypertension in children. Normal blood pressure levels for age, sex, and height, appropriate methods for measurement, and treatment recommendations are available at the website: http://www.nhlbi.nih.gov/ health-pro/guidelines/current/hypertension-pediatric-jnc-4 (The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, 2004)

# 6.6. Cardiovascular disease

In 2011, an NHLBI Expert panel created guidelines for CVD risk reduction in children and adolescents. The recommendations included a CVD health schedule, in which clinicians should review family history of early cardiovascular disease, tobacco exposure, nutrition, BMI, lipids, blood pressure, physical activity, and diabetes. The recommendations included universal lipid screening starting at age 9 in the absence of significant family history of early cardiovascular disease. Overall, the recommendations reflect a more aggressive approach to treating non-HDL cholesterol with both lifestyle modifications and statins. In addition, T2DM has been recognized as a condition associated with accelerated atherosclerosis and early CVD and patients with the condition should be included in the high-risk category for risk stratification (Expert panel guidelines) (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011).

Apart from the above recommendations from ADA and other Expert groups, Consensus Guidelines were also released by ISPAD Clinical Practice 2014 especially on Type 2 diabetes in the child and adolescent and Microvascular and macrovascular complications in children and adolescents (Donaghue et al., 2014; Zeitler et al., 2014).

# 7. Summary of our learnings from childhood and adolescent onset T2DM

Based on a large series of childhood onset and adolescent T2DM treated at our center we would like to offer some of our learning's.

- Although screening of all childhood and adolescents for T2DM is clearly not justified, screening of high risk groups e.g. belonging to high risk groups, those with obesity, acanthosis nigricans or family history of diabetes may be justified as we find up to 12% of such high risk group to have dysglycemia i.e. either prediabetes or diabetes.
- Routine screening of all childhood onset and adolescent T2DM for complications should start right from the time of diagnosis of diabetes.
- All efforts should be made to screen for other co morbidities e.g. hypertension, dyslipidemia etc.
- Aggressive treatment of hyperglycemia, blood pressure and lipids can potentially help prevent micro and macrovascular complications of diabetes.

# 8. Conclusion

T2DM is rapidly emerging as a common disorder in children and adolescents, following the same pattern as in adults. This rapid rise in the prevalence of T2DM is due to unhealthy lifestyle practices by individuals at risk of developing the disorder. Luckily, physical inactivity and unhealthy diet are eminently modifiable risk factors which can help to prevent not only for T2DM, but also cardiovascular diseases. The life-time risk of developing diabetes complications can be expected to be higher in children with diabetes due to the long disease duration and greater duration of glycemic exposure. Hence it is important that appropriate screening measures be implemented to diagnose younger onset T2DM at an early stage in those at high risk e.g. family history of diabetes plus obesity and also to prevent them from progressing to the stage of complications of diabetes.

# References

- Abraham, A., & Geevarghese, P. J. (1990). Young-onset diabetes in central Kerala–A preliminary report. *International Journal of Diabetes in Developing Countries*, 10, 17–20.
- Afkarian, M. (2015). Diabetic kidney disease in children and adolescents. Pediatric Nephrology, 30, 65–74.
- Amed, S., Hamilton, J. K., Sellers, E. A., Panagiotopoulos, C., Hadjiyannakis, S., Shah, B. R., ... Dean, H. (2012). Differing clinical features in Aboriginal vs. non-Aboriginal children presenting with type 2 diabetes. *Pediatric Diabetes*, 13(6), 470–475.
- American Diabetes Association (2014). Standards of medical care in diabetes–2014. Diabetes Care, 37(Suppl. 1), S14–S80. http://dx.doi.org/10.2337/dc14-S014 (PMID: 24357209).
- Amutha, A., Datta, M., Unnikrishnan, R., Anjana, R. M., & Mohan, V. (2012). Clinical profile and complications of childhood- and adolescent-onset type 2 diabetes seen at a diabetes center in south India. *Diabetes Technology & Therapeutics*, 14, 497–504. http://dx.doi.org/10.1089/dia.2011.0283 (PMID: 22551567).
- Amutha, A., Datta, M., Unnikrishnan, I. R., Anjana, R. M., Rema, M., Narayan, K. M., & Mohan, V. (2011). Clinical profile of diabetes in the young seen between 1992 and 2009 at a specialist diabetes centre in south India. *Primary Care Diabetes*, 5, 223–229.
- Anderson, B. J., Edelstein, S., Abramson, N. W., Katz, L. E., Yasuda, P. M., Lavietes, S. J., ... Casey, T. L., ... Marcus, M. D. (2011). Depressive symptoms and quality of life in adolescents with type 2 diabetes: Baseline data from the TODAY study. *Diabetes Care*, 34(10), 2205–2207. http://dx.doi.org/10.2337/dc11-0431 (PMID: 21836107).
- Ayodele, O. E., Alebiosu, C. O., & Salako, B. L. (2004). Diabetic nephropathy: A review of the natural history, burden, risk factors and treatment. *Journal of the National Medical Association*, 96, 1445–1454 (PMID: 15586648).
- Bell, R. A., Mayer-Davis, E. J., Beyer, J. W., D'Agostino, R. B., Jr., Lawrence, J. M., Linder, B., ... SEARCH for Diabetes in Youth Study Group (2009). Diabetes in non-Hispanic white youth: Prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. *Diabetes Care*, 32, S102–S111. http://dx.doi.org/10.2337/ dc09-S202 (PMID: 19246575).
- Berenson, G. S., Srinivasan, S. R., Bao, W., Newman, W. P., III, Tracy, R. E., & Wattigney, W. A. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *The New England Journal of Medicine*, 338, 1650–1656. http://dx.doi.org/10.1056/ NEJM199806043382302 (PMID: 9614255).
- Bhadada, S. K., Sahay, R. K., Jyotsna, V. P., & Agrawal, J. K. (2001). Diabetic neuropathy: Current concepts. Journal, Indian Academy of Clinical Medicine, 2, 305–318 (PMID: 11310392).
- Chambless, L. É., Heiss, G., Folsom, A. R., Rosamond, W., Szklo, M., Sharrett, A. R., & Clegg, L. X. (1997). Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. American Journal of Epidemiology, 146(6), 483–494 (PMID:9290509).
- Constantino, M. I., Molyneaux, L., Limacher-Gisler, F., Al-Saeed, A., Luo, C., Wu, T., ... Wong, J. (2013). Long-term complications and mortality in young-onset diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care*, 36(12), 3863–3869. http://dx.doi.org/10.2337/dc12-2455 (PMID: 23846814).
- D'Adamo, E., & Caprio, S. (2011). Type 2 diabetes in youth: Epidemiology and pathophysiology. *Diabetes Care*, 34(Suppl. 2), S161–S165. http://dx.doi.org/10. 2337/dc11-s212.
- Dart, A. B., Martens, P. J., Rigatto, C., Brownell, M. D., Dean, H. J., & Sellers, E. A. (2014). Earlier onset of complications in youth with type 2 diabetes. *Diabetes Care*, 37, 436–443. http://dx.doi.org/10.2337/dc13-0954 (PMID:24130346).
- Davis, P. H., Dawson, J. D., Riley, W. A., & Lauer, R. M. (2001). Carotid intimal medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation*, 104(23), 2815–2819. http://dx.doi. org/10.1161/hc4601.099486 (PMID:11733400).
- Dean, H., & Flett, B. (2002). Natural history of type 2 diabetes diagnosed in childhood: Long term follow-up in young adult years. *Diabetes*, 51(Suppl. 1), A24.
- Donaghue, K. C., Wadwa, R. P., Dimeglio, L. A., Wong, T. Y., Chiarelli, F., Marcovecchio, M. L., ... Craig, M. E. (2014). International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Microvascular and macrovascular complications in children and adolescents. *Pediatric Diabetes*, 15(Suppl. 20), 257–269.
- Eppens, M. C., Craig, M. E., Cusumano, J., Hing, S., Chan, A. K., Howard, N. J., ... Donaghue, K. C. (2006). Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care*, 29, 1300–1306. http://dx.doi.org/10. 2337/dc05-2470 (PMID: 16732012).
- Ettinger, L. M., Freeman, K., DiMartino-Nardi, J. R., & Flynn, J. T. (2005). Microalbuminuria and abnormal ambulatory blood pressure in adolescents with type 2 diabetes mellitus. *The Journal of Pediatrics*, 147, 67–73. http://dx.doi.org/10.1016/j.jpeds. 2005.02.003 (PMID:16027698).
- Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute (2011). Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. *Pediatrics*, 128(Suppl. 5), S213–S256. http://dx.doi.org/10.1542/peds.2009-2107C (PMID:22084329).
- Fagot-Campagna, A., Knowler, W. C., & Pettitt, D. J. (1998). Type 2 diabetes in Pima Indian children: Cardiovascular risk factors at diagnosis and 10 years later. *Diabetes*, 47(Suppl. 1), A155.
- Farah, S. E., Wals, K. T., Friedman, I. B., Pisacano, M. A., & DiMartino-Nardi, J. (2006). Prevalence of retinopathy and microalbuminuria in pediatric type 2 diabetes

mellitus. Journal of Pediatric Endocrinology & Metabolism, 19, 937–942. http://dx. doi.org/10.1515/JPEM.2006.19.7.937 (PMID:16995574).

- Fong, D. S., Aiello, L., Gardner, T. W., King, G. L., Blankenship, G., Cavallerano, J. D., & Klein, R. (2004). Retinopathy in diabetes. *Diabetes Care*, 27(Suppl. 1), S84–S87. http://dx.doi.org/10.2337/diacare.27.2007.S84 (PMID: 14693935).
- Furberg, C. D., Adams, H. P., Jr., Applegate, W. B., Byington, R. P., Espeland, M. A., Hartwell, T., ... Young, B. (1994). Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation*, 90(4), 1679–1687. http://dx.doi.org/10. 1161/01.CIR.90.4.1679 (PMID: 7734010).
- Gungor, N., Hannon, T., Libman, I., Bacha, F., & Arslanian, S. (2005a). Type 2 diabetes mellitus in youth: The complete picture to date. *Pediatric Clinics of North America*, 52(6), 1579–1609. http://dx.doi.org/10.1016/j.pcl.2005.07.009 (PMID: 16301084).
- Gungor, N., Thomposon, T., Sutton-Tyrrell, K., Janosky, J., & Arslanian, S. (2005b). Early signs of cardiovascular disese in youth with obesity and type 2 diabetes. *Diabetes Care*, 28(5), 1219–1221. http://dx.doi.org/10.2337/diacare.28.5.1219 (PMID: 15855596).
- Hillier, T. A., & Pedula, K. L. (2003 Novv). Complications in young adults with earlyonset type 2 diabetes: Losing the relative protection of youth. *Diabetes Care*, 26(11), 2999–3005.
- Hodis, H. N., Mack, W. J., LaBree, L., Selzer, R. H., Liu, C. R., Liu, C. H., & Azen, S. P. (1998). The role of carotid arterial intima-media thickness in predicting clinical coronary events. Annals of Internal Medicine, 128, 262–269. http://dx.doi.org/10.7326/0003-4819-128-4-199802150-00002 (PMID: 9471928).
- Hotu, S., Carter, B., Watson, P. D., Cutfield, W. S., & Cundy, T. (2004 Aprr). Increasing prevalence of type 2 diabetes in adolescents. *Journal of Paediatrics and Child Health*, 40(4), 201–204.
- Jaiswal, M., Lauer, A., Martin, C. L., Bell, R. A., Divers, J., Dabelea, D., ... SEARCH for Diabetes in Youth Study Group (2013). Peripheral neuropathy in dolescents and young adults with type 1 and type 2 diabetes from the SEARCH for Diabetes in Youth follow-up cohort: A pilot study. *Diabetes Care*, 36, 3903–3908. http://dx.doi. org/10.2337/dc13-1213 (PMID: 24144652).
- Jordan, D. N., & Jordan, J. L. (2012). Pediatric type 2 diabetes mellitus complications: A systematic review of the literature. Journal of Diabetes Research and Clinical Metabolism, 1, 24.
- Karabouta, Z., Barnett, S., Shield, J. P., Ryan, F. J., & Crowne, E. C. (2008). Peripheral neuropathy is an early complication of type 2 diabetes in adolescence. *Pediatric Diabetes*, 9, 110–114. http://dx.doi.org/10.1111/j.1399-5448.2007.00339.x (PMID: 18221439).
- Kim, N. H., Pavkov, M. E., Knowler, W. C., Hanson, R. L., Weil, E. J., Curtis, J. M., ... Nelson, R. G. (2010). Predictive value of albuminuria in American Indian youth with or without type 2 diabetes. *Pediatrics*, 125(4), e844–e851.
- Kitagawa, T., Owada, M., Urakami, T., & Yamauchi, K. (1998). Increased incidence of non-insulin dependent diabetes mellitus in Japanese school children correlates with an increased intake of animal protein and fat. *Clinical Pediatrics*, 37, 111–115. http://dx.doi.org/10.1177/000992289803700208 (PMID: 9492119).
- Krakoff, J., Lindsay, R. S., Looker, H. C., Nelson, R. G., Hanson, R. L., & Knowler, W. C. (2003). Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. *Diabetes Care*, 26, 76–81. http://dx.doi.org/10.2337/ diacare.26.1.76 (PMID: 12502661).
- Likitmaskul, S., Kiattisathavee, P., Chaichanwatanakul, K., Punnakanta, L., Angsusingha, K., & Tuchinda, C. (2003). Increasing prevalence of type 2 diabetes mellitus in Thai children and adolescents associated with increasing prevalence of obesity. *Journal* of *Pediatric Endocrinology & Metabolism*, 16, 71–77. http://dx.doi.org/10.1515/JPEM. 2003.16.1.71 (PMID: 12585343).
- Maahs, D. M., Snively, B. M., Bell, R. A., Dolan, L., Hirsch, I., Imperatore, G., ... Dabelea, D. (2007). Higher prevalence of elevated albumin excretion in youth with type 2 than type 1diabetes: The SEARCH for Diabetes in Youth study. *Diabetes Care*, 30, 2593–2598. http://dx.doi.org/10.2337/dc07-0450 (PMID: 17630264).
- Mayer-Davis, E. J., Davis, C., Saadine, J., D'Agostino, R. B., Jr., Dabelea, D., Dolan, L., & SEARCH for Diabetes in Youth Study Group (2012). Diabetic retinopathy in the SEARCH for Diabetes in Youth Cohort: A pilot study. *Diabetic Medicine*, 29(9), 1148–1152. http:// dx.doi.org/10.1111/j.1464-5491.2012.03591.x (PMID: 22269205).
- McCrindle, B. W., Urbina, E. M., Dennison, B. A., et al. (2007). Drug therapy of high-risk lipid abnormalities in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council on Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation*, 115, 1948–1967.
- McGrath, N. M., Parker, G. N., & Dawson, P. (1999). Early presentation of type 2 diabetes mellitus in young New Zealand Maori. *Diabetes Research and Clinical Practice*, 43(3), 205–209. http://dx.doi.org/10.1016/S0168-8227(99)00003-0 (PMID: 10369431).
- Miljanovic, B., Glynn, R. J., Nathan, D. M., Manson, J. E., & Schaumberg, D. A. (2004). A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes*, 53(11), 2883–2892. http://dx.doi.org/10.2337/diabetes.53.11. 2883 (PMID: 15504969).
- Mohan, V., Jaydip, R., & Deepa, R. (2007). Type 2 diabetes in Asian Indian youth. *Pediatric Diabetes*, 8(Suppl. 9), 28–34. http://dx.doi.org/10.1111/j.1399-5448.2007.00328.x. Review (PMID: 17991130).
- Moss, S. E., Klein, R., & Klein, B. E. (1991). Cause-specific mortality in a population-based study of diabetes. *American Journal of Public Health*, 81, 1158–1162. http://dx.doi. org/10.2105/AJPH.81.9.1158 (PMID: 1951827).
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*, 114(2 Suppl. 4th Report), 555–576.

- Okudaira, M., Yokoyama, H., Otani, T., Uchigata, Y., & Iwamoto, Y. (2000). Slightly elevated blood pressure as well as poor metabolic control are risk factors for the progression of retinopathy in early-onset Japanese type 2 diabetes. *Journal of Diabetes and its Complications*, 14(5), 281–287.
- Pavkov, M. E., Bennett, P. H., Knowler, W. C., Krakoff, J., Sievers, M. L., & Nelson, R. G. (2006). Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA*, 296, 421–426. http://dx.doi.org/10.1001/jama.296.4.421 (PMID: 16868300).
- Pinhas-Hamiel, O., & Zeitler, P. (2007). Acute and chronic complications of type 2 diabetes mellitus in children and adolescents. *Lancet*, 369(9575), 1823–1831. http://dx.doi.org/10.1016/S0140-6736(07)60821-6 (PMID:17531891).
- Pitt, B., Byington, R. P., Furberg, C. D., Hunninghake, D. B., Mancini, G. B., Miller, M. E., & Riley, W. (2000). Prevent Investigators. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation*, *102*, 1503–1510. http://dx.doi.org/10.1161/01.CIR.102.13.1503 (PMID: 11004140).
- Raitakari, O. T., Juonala, M., Kähönen, M., Taittonen, L., Laitinen, T., Mäki-Torkko, N., ... Viikari, J. S. (2003). Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns Study. JAMA, 290(17), 2277–2283. http://dx.doi.org/10.1001/jama.290.17.2277 (PMID: 14600186).
- Rajalakshmi, R., Amutha, A., Ranjani, H., Ali, M. K., Unnikrishnan, R., Anjana, R. M., ... Mohan, V. (2014). Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. *Journal of Diabetes and its Complications*, 28, 291–297. http://dx.doi.org/10.1016/j.jdiacomp.013.12.008 (PMID:24512748).
- Ramachandran, A., Snehalatha, C., Satyavani, K., Sivasankari, S., & Vijay, V. (2003). Type 2 diabetes in Asian-Indian urban children. *Diabetes Care*, 26, 1022–1025. http://dx. doi.org/10.2337/diacare.26.4.1022 (PMID: 12663567).
- Rodriguez, B. L., Dabelea, D., Liese, A. D., Fujimoto, W., Waitzfelder, B., Liu, L., ... SEARCH Study Group (2010). Prevalence and correlates of elevated blood pressure in youth with diabetes mellitus: The SEARCH for diabetes in youth study. *The Journal of Pediatrics*, 157(2), 245–251.e1. http://dx.doi.org/10.1016/j.jpeds.2010.02.021 (PMID: 20394942).
- Rodriguez, B. L., Fujimoto, W. Y., Mayer-Davis, E. J., Imperatore, G., Williams, D. E., Bell, R. A., ... Linder, B. (2006). Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: The SEARCH for diabetes in youth study. *Diabetes Care*, 29(8), 1891–1896. http://dx.doi.org/10.2337/dc06-0310 (PMID: 16873798).
- Salonen, R., Nyyssonen, K., Porkkala, E., Rummukainen, J., Belder, R., Park, J. S., & Salonen, J. T. (1995). Kuopio Atherosclerosis Prevention Study (KAPS): A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation*, 92, 1758–1764. http://dx.doi.org/10.1161/01.CIR.92.7.1758 (PMID: 7671358).
- Schrier, R. W., Estacio, R. O., Esler, A., & Mehler, P. (2002). Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney International*, 61(3), 1086–1097. http://dx.doi. org/10.1046/j.1523-1755.2002.00213.x (PMID: 11849464).
- Scott, A., Toomath, R., Bouchier, D., Bruce, R., Crook, N., Carroll, D., ... Wu, D. (2006). First national audit of the outcomes of care in young people with diabetes in New Zealand: High prevalence of nephropathy in Maori and Pacific Islanders. *The New Zealand Medical Journal*, 119(1235), U2015 (PMID: 16751833).
- Sellers, E. A., Blydt-Hansen, T. D., Dean, H. J., Gibson, I. W., Birk, P. E., & Ogborn, M. (2009 Mayy). Macroalbuminuria and renal pathology in First Nation youth with type 2 diabetes. *Diabetes Care*, 32(5), 786–790.
- Sellers, E. A., Hadjiyannakis, S., Amed, S., Dart, A. B., Dyck, R. F., Hamilton, J., ... Dean, H. J. (2016). Persistent albuminuria in children with type 2 diabetes: A Canadian paediatric surveillance program study. *The Journal of Pediatrics*, 168, 112–117.
- Shah, A. S., Dolan, L. M., Kimball, T. R., Gao, Z., Khoury, P. R., Daniels, S. R., & Urbina, E. M. (2009). Influence of duration of diabetes, glycemic control, and traditional cardiovascular risk factors on early atherosclerotic vascular changes in adolescents and young adults with type 2 diabetes mellitus. *The Journal of Clinical Endocrinology and Metabolism*, 94(10), 3740–3745. http://dx.doi.org/10.1210/jc.2008-2039 (PMID: 19723759).
- Solis-Herrera, C., Triplitt, C. L., & Lynch, J. L. (2014). Nephropathy in youth and young adults with type 2 diabetes. *Current Diabetes Reports*, 14(2), 456.
- Song, S. H. (2015). Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. BMJ Open Diabetes Research & Care, 3, e000044.

- Stamler, J., Vaccaro, O., Neaton, J. D., & Wentworth, D. (1993). Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*, *16*, 434–444. http://dx.doi.org/10.2337/ diacare.16.2.434 (PMID: 8432214).
- Stettler, C., Allemann, S., Jüni, P., Cull, C. A., Holman, R. R., Egger, M., ... Diem, P. (2006). Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *American Heart Journal*, 152(1), 27–38. http:// dx.doi.org/10.1016/j.ahj.2005.09.015 (PMID: 16824829).
- TODAY Study Group (2013a). Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: The TODAY clinical trial. *Diabetes Care*, 36, 1758–1764. http://dx.doi.org/10.2337/dc12-2388 (PMID: 23704675).
- TODAY Study Group (2013b). Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. *Diabetes Care*, 36(6), 1772–1774. http://dx.doi.org/10. 2337/dc12-2387 (PMID: 23704677).
- TODAY Study Group (2013c). Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: The TODAY clinical trial. *Diabetes Care*, 36, 1735–1741. http:// dx.doi.org/10.2337/dc12-2420 (PMID: 23704672).
- Tryggestad, J. B., & Willi, S. M. (2015). Complications and comorbidities of T2DM in adolescents: Findings from the TODAY clinical trial. *Journal of Diabetes and its Complications*, 29, 307–312. http://dx.doi.org/10.1016/j.jdiacomp.2014.10.009.
- Upchurch, S. L., Brosnan, C. A., Meininger, J. C., Wright, D. E., Campbell, J. A., McKay, S. V., & Schreiner, B. (2003). Characteristics of 98 children and adolescents diagnosed with type 2 diabetes by their health care provider at initial presentation. *Diabetes Care*, 26(7), 2209. http://dx.doi.org/10.2337/diacare.26.7.2209 (PMID: 12832339).
- Urakami, T., Kubota, S., Nitadori, Y., Harada, K., Owada, M., & Kitagawa, T. (2005). Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. *Diabetes Care*, 28, 1876–1881. http://dx.doi.org/10.2337/diacare.28.8.1876 (PMID: 16043726).
- Urakami, T., Morimoto, S., Nitadori, Y., Harada, K., Owada, M., & Kitagawa, T. (2007). Recent change in the annual incidence of childhood type 2 diabetes in the Tokyo metropolitan area. *Clinical Pediatric Endocrinology*, 16, 53–58. http://dx.doi.org/10. 1297/cpe.16.53 (PMID: 24790345).
- Vinik, A. I., Park, T. S., Stansberry, K. B., & Pittenger, G. L. (2000). Diabetic neuropathies. Diabetologia, 43, 957–973. http://dx.doi.org/10.1007/s001250051477 (PMID: 10990072).
- Wadwa, R. P., Urbina, E. M., Anderson, A. M., Hamman, R. F., Dolan, L. M., Rodriguez, B. L., ... SEARCH Study Group (2010). Measures of arterial stiffness in youth with type 1 and type 2 diabetes: The SEARCH for diabetes in youth study. *Diabetes Care*, 33(4), 881–886. http://dx.doi.org/10.2337/dc09-0747 (PMID: 20067960).
- Waernbaum, I., Blohmé, G., Ostman, J., Sundkvist, G., Eriksson, J. W., Arnqvist, H. J., ... Nyström, L. (2006). Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: A population-based study (DISS) in Sweden. *Diabetologia*, 49(4), 653–659. http://dx.doi.org/10.1007/s00125-005-0135-x (PMID: 16447054).
- White, N. H. (2015). Long-term outcomes in youths with diabetes mellitus. Pediatric Clinics of North America, 62, 889–909.
- Wong, J., Constantino, M., & Yue, D. K. (2015). Morbidity and mortality in young-onset type 2 diabetes in comparison to type 1 diabetes: Where are we now? *Current Diabetes Reports*, 15, 566.
- Yokoyama, H., Okudaira, M., Otani, T., Sato, A., Miura, J., Takaike, H., ... Iwamoto, Y. (2000). Higher incidence of diabetic nephropathy in type 2 than in type 1 diabetes in early-onset diabetes in Japan. *Kidney International*, 58(1), 302–311. http://dx.doi. org/10.1046/j.1523-1755.2000.00166.x (PMID: 10886575).
- Yoo, E. G., Choi, I. K., & Kim, D. H. (2004). Prevalence of microalbuminuria in young patients with type 1 and type 2 diabetes mellitus. *Journal of Pediatric Endocrinology* & Metabolism, 17(10), 1423–1427. http://dx.doi.org/10.1515/JPEM.2004.17.10. 1423 (PMID: 15526721).
- Zdravkovic, V., Daneman, D., & Hamilton, J. (2004). Presentation and course of type 2 diabetes in youth in a large multi-ethnic city. *Diabetic Medicine*, *21*, 1144–1148. http://dx.doi.org/10.1111/j.1464-5491.2004.01297.x (PMID: 15384964).
- Zeitler, P., Fu, J., Tandon, N., Nadeau, K., Urakami, T., Barrett, T., ... International Society for Pediatric and Adolescent Diabetes (2014). ISPAD Clinical Practice Consensus Guidelines 2014. Type 2 diabetes in the child and adolescent. *Pediatric Diabetes*, 15(Suppl. 20), 26–46.
- Zieske, A. W., Malcom, G. T., & Strong, J. P. (2002). Natural history and risk factors of atherosclerosis in children and youth: The PDAY study. *Pediatric Pathology & Molecular Medicine*, 21, 213–237. http://dx.doi.org/10.1080/pdp.21.2.213.237 (PMID: 11942537).