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Complications Associated with Type 2 Diabetes Mellitus in Pediatric Patients

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Introduction

T2DM in pediatric patients is a serious public health problem that requires the attention of stakeholders at different levels. It is associated with immediate health and metabolic problems and it constitutes an important risk factor for early morbidity and mortality. In this second article, I want to define pediatric T2DM and do a small but representative inventory of the causes that could explain its development and discuss briefly its short and long term consequences. In addition, I aim to make uniform these important concepts to ensure that all stakeholders are on an equal step. Obviously, in this special issue, there will be often links made to pediatric obesity as it is the main cause of pediatric T2DM.

Definition

Diabetes mellitus (DM) consist of a heterogeneous group of disorders characterized by intolerance to glucose to eventually develop in hyperglycemia. In clinical practice, Type 1 Diabetes Mellitus (T1DM) contains about 96% of all affected children, and is characterized by an absolute insulin deficiency due to autoimmune destruction of insulin producing β-cells of the pancreas. Unfortunately, affected children will die unless insulin therapy is instituted [1-2].

In contrast, T2DM occurs when insulin secretion is insufficient to meet the increased insulin needs caused by tissue insulin resistance [1-2]. T2DM is frequently associated with obesity, dyslipidaemia, hypertension (HTN), albuminuria, ovarian hyperandrogenism, non-alcoholic fatty liver disease (NAFLD), and obstructive sleep apnoea [1-2]. T2DM is also associated with component of systemic inflammation as estimated by elevated C-reactive protein, inflammatory cytokines and white blood cell counts [1-2].

As explained earlier, the natural history of pediatric T2DM starts with fasting hyperinsulinaemia, exacerbated by obesity [1-3]. This is followed by postprandial hyperglycaemia, when the pancreatic β-cells are unable to maintain high enough circulating insulin levels to respond to a glucose load as demonstrated by an impaired glucose tolerance (IGT) on an oral glucose tolerance test (OGTT) [3-4]. Due to the combination of both lipid and glucose toxicity on âcells, increasing tissue insulin resistance and hepatic glucose output, fasting hyperglycaemia follows [1-4] and then T2DM develops.

Genetics of type 2 diabetes mellitus

Several genome wide association studies (GWAS) have been helpful to help highlight the genetic basis of T2DM and several single nucleotide polymorphisms (SNPs) have been discovered to be associated with T2DM. The majority of these SNPs are in non-coding regions or nearby a gene and few are missense mutations (such as the rs1801282 in the PPAR-γ characterized by a C-to-G substitution encoding a proline to alanine substitution at codon 12) [5].

These GWAS studies have demonstrated that the majority of gene variants associated with T2DM are in genes expressed in the β-cells [5]. While the majority of these studies have been conducted in large cohorts of adults, information about these associations in children and adolescent is limited but there is no reason to believe that these observations could be different from those in adults. Dabble et al. genotyped the rs12255372 and rs7903146 variants in or near the *TCF7L2* gene in a multiethnic cohort with 1239 (240 cases and 999 controls) children and adolescents enrolled in the SEARCH study; they observed that in African Americans the rs7903146 variant was associated with almost two folds increased odds of T2DM occurrence [6].

Barker et al. genotyped 16 SNPs, found to be associated with diabetes by GWAS studies, in a population of over 6000 children and adolescent, and investigated whether they may be additionally associated with fasting glucose levels [7]. Baker et al. observed that 9 loci were associated with the fasting plasma glucose levels. In particular, they confirmed 5 previously discovered SNPs and discovered 4 more loci associated with fasting plasma glucose. The strongest associations were with the *G6PC2* rs560887, *MTNR1B* rs10830963, and *GCK* rs4607517, and the effect size of the confirmed loci was similar to that observed in adults. The latter observation confirms that the effect of certain gene variants is constant over time and may not be influenced by changes in insulin secretion and sensitivity occurring with age [7]. Again, the discovery of this SNPs and Loci may represent a great advent for the treatment of T2DM in a sense that children having specific gene may have different glucose level target, different medication and/or different dosage of the same medication and less risk of developing adverse drug reactions. This interesting topic will be further discussed in the article number 7 of this special issue.

Many studies have demonstrated that the co-occurrence of more risk alleles does not improve the ability to predict the development of T2DM when compared to the clinical risk factors, such as BMI or family history of diabetes and other risk factors [5]. More recently, a significant association between the co-occurrence of risk alleles and T2DM has been observed by the investigators of the CARDIA study [8]. They followed young adults into middle adulthood and observed that the co-occurrence of 38 gene variants predicted the incidence of T2DM over 24 years follow up. In addition, it has been shown that the genetic predisposition to T2DM may be stronger in the pediatric population [8]. In fact, Vassy JL et al. have demonstrated that the co-occurrence of five common variants in or near the genes modulating insulin secretion are associated with a higher risk of developing pre-diabetes and T2DM in children and adolescents. Vassy JL, et al. asked whether the co-occurrence of risk alleles in or near the 5 genes discovered by GWAS studies (*TCF7L2* rs7903146, *IGF2BP2* rs4402960, *CDKAL1* rs7754840, the *HHEX* rs1111875, and *HNF1A* rs1169288) might be associated with a higher risk of IGT or T2DM in obese children and adolescents [8]. With a higher number of risk alleles, there is a higher chance of progression from NGT to IGT or T2DM. For those who were IGT at baseline, a higher number of risk alleles were associated with lower odds to revert back to NGT [8].

Despite the strength of these associations, the portion of heritability explained by the identified loci is estimated to be less than 10%. Although the sample size of GWAS studies continues to increase revealing new associations, each newly associated variant has an incrementally smaller effect size to the cumulative variation of the phenotype. GWAS may be reaching the limits of its ability to reveal genetic variations underlying complex traits associated with T2DM [5].

Risk Factors

Risk factors for the development of T2DM in children include the following [9-22]; 1). history of T2DM in a first- or second-degree relative; 2). being a member of a high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent); 3). obesity; 4). IGT; 5). PCOS; 6). exposure to diabetes in utero; 7). acanthosis nigricans; 8). HTN and dyslipidemia; 9). NAFLD; 10). atypical antipsychotic medications and 11). neuropsychiatric disorders. In the following paragraphs I will only discussed some of these risks factors. However, while you perform the medical history of a new pediatric patient with T2DM all of the above should be considered.

Family factors

An important risk factor in the increase risk of developing T2DM in youth is the genetic influence [23] as discussed above. A strong family history of diabetes is present in 45% to 80% of children with T2DM. Having parents with T2DM is a risk factor for the development of T2DM among pre-pubertal youth. Children born to mothers with T2DM are particularly at increased risk for T2DM when compared to children and adolescents whose fathers had T2DM. The risk is higher for boys than for girls for a ratio of 2 for 1. More females than males are diagnosed with T2DM during puberty; however, among adults, more males than females are diagnosed with T2DM according to the data from the Public Health Agency of Canada [23].

Insulin resistance

Insulin resistance associated with T2DM means an impaired response to the physiological actions of insulin on glucose, lipid and protein metabolism and on endothelial function [1-3]. The main tissues affected by insulin resistance are the liver, muscle and fat. In the liver this impaired insulin-related action leads to an increased hepatic glucose output which exacerbates hyperglycaemia. In muscle, insulin resistance leads to reduced transport of glucose into muscle combined with lipid deposition in muscle cells which results in impaired exercise ability and reduced the threshold for fatigue in response to physical activity. In fat tissue, there is impaired insulin mediated reduction of hormone-dependent lipase, with breakdown of lipids to free fatty acids and glycerol, contributing to dyslipidaemia [1-3].

Insulin resistance is a key factor in the development of T2DM in both adults and pediatric patients [1-3]. While insulin resistance is most commonly associated with obesity, it is not all obese children that have insulin resistance and conversely insulin resistance is seen also in non-obese children. As briefly discussed above, several genes linked to beta cell function and insulin sensitivity have been demonstrated to be associated with T2DM in different population. For Instance, the T2DM protective variant Pro12Ala in PPAR-ϒ is associated with higher insulin sensitivity in Caucasian children [5] which suggest that this variant can be considered as a possible molecule for the treatment of T2DM in pediatric patients (See article # 7).

Overweight and Obesity

Obesity is the major contributor to the rising prevalence of T2DM in children [1-3]. Globally, overweight and obesity are extremely common in T2DM, affecting about 90% of children and adolescent and 92% have two or more cardiovascular (CVD) risk factors at the time of diagnosis of T2DM [24]. For instance, HTN affects approximately 23% of children and adolescent with T2DM and lipid abnormalities about 33% of them. Clearly, youth who are overweight or obese have a higher risk for early T2DM development. Weight loss and/or weight maintenance is effective in preventing T2DM in at-risk children and adolescent. As expected, youth with T2DM tend to be less active, less physically fit, and more sedentary when compared with aged matched non-diabetic children and adolescent which emphasis our role in putting in place public health measures to keep our youth active. Risk prediction models estimated that by 2035, up to 100,000 excess cases of CVD could be attributable to increased obesity in children and adolescent. This is likely to get worst by the earlier age of onset of T2DM [24]. In Canada, currently almost 1 in 7 children and youth are obese. Rates vary based on sociodemographic factors such as age, sex, socioeconomic status and place of residence. But the good news is that overall; the rates of excess weight have been relatively stable over the past decade [25].

T2DM is associated with a twofold excess risk for a wide range of CVD, including coronary heart disease, stroke, and vascular deaths, after adjusting for age, sex, smoking status, BMI, and systolic blood pressure [24]. The causes for this increased risk for CVD

complications and mortality in T2DM compared with T1DM are not well understood. Certainly, obesity and a greater degree of insulin resistance in obese youth with T2DM compared with obese peers with normoglycemia and compared with youth with T1DM may be the underlying factors for this higher CVD risk, with an added effect related to chronic exposure to hyperglycemia. According to Bacha F and Gidding SS, hyperglycemia and insulin resistance are associated with increased oxidative stress and increased advanced glycation end-products, which have been implicated in microvascular and macrovascular complications [24].

Puberty

Puberty is a period of dynamic physiologic change, including activation of the reproductive axis and subsequent secretion of sex steroids hormones, acceleration in growth, and accumulation of both lean and fat mass. There is also a well-known physiologic decrease in insulin sensitivity during puberty. The presence of relative insulin resistance in puberty was first described by Amiel et al. in 1986 in a study designed to explore reasons for deterioration of glycemic control in pubertal children with T1DM (26). The authors found that pubertal children, both with and without diabetes, had lower insulin sensitivity than prepubertal children and adults [26]. This transient pubertal reduction in insulin sensitivity has been confirmed in multiple cross-sectional and longitudinal studies [26-27].

Puberty is also a period of change in other cardiometabolic risk factors, such as lipids, blood pressure, and adipokines. This has significant implications for obese children and adolescents. In fact, there is evidence that puberty is one of the greatest risk factors for transition from metabolically healthy to unhealthy obesity [28]. Furthermore, the incidence of youth-onset T2DM is tightly linked with puberty as mentioned before. For these reasons, it is critical to understand the normal physiology of metabolic changes during puberty and the additional impact of obesity on these changes. In healthy youth, this decline in insulin sensitivity discussed above is accompanied by compensatory insulin secretion that recovers after puberty is completed. In contrary, there is evidence that obese youth do not recover baseline insulin sensitivity at the end of puberty [27].

Antipsychotic Medications

Children and adolescent receiving treatment with antipsychotic medication are particularly susceptible to weight gain, T2DM and its associated metabolic disorders [29]. The risk of T2DM is 2 to 3 fold that of the general population, it starts early in the course of treatment, and reflects the effects of weight gain in conjunction with the direct effects of antipsychotics on the hypothalamus, the pancreatic β-cells and the insulin-sensitive peripheral tissues. Regular monitoring with early intervention through lifestyle intervention is essential with the use of this medication, Switching for antipsychotics with less deleterious metabolic effects and adjunctive treatment with metformin are modalities available to mitigate weight gain and improve cardiometabolic health in these patients [29].

Comorbidities

Short-term complications in pediatric patients with T2DM include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS). Around 10% of Canadian children and adolescent with T2DM present DKA at the time of diagnosis of T2DM (23, 30-31). Up to 37 % of mortality rates have been reported in youth presenting with combined DKA and HHS at the onset of T2DM. Evidence suggests that early-onset of T2DM is often associated with severe and early-onset of microvascular complications, including retinopathy, neuropathy and nephropathy [23, 30-31]. Micro- or macroalbuminuria has been observed frequently in children and adolescent at the time of diagnosis of T2DM [23, 30-31]. For the purpose of this article, it is impossible to discuss all the co-morbidities associated with T2DM in details. Therefore, my discussion will be limited to the most common one.

Cardiovascular complications

One reason for the possible future of CVD is that the high density lipoprotein (HDL) size shifts to smaller particles in children and adolescent with T2DM [24, 31]. A major cause to explain this shift is the insulin resistance. The changes that occur in T2DM patients are influenced by the changes observed in obesity. For example, carotid intima-media thickness (CIMT) has been noted to be thicker and stiffer among obese adolescents with T2DM than among non-obese adolescents without T2DM [32]. Regardless of the causative factor, these vascular changes can predispose obese adolescents with T2DM to stroke and myocardial infarction later in life [32].

Unfortunately, many of the lifestyle behaviors associated with these risk factors in adults, such as physical inactivity (sedentary lifestyle), poor eating habits, smoking and others, origin in childhood and adolescence, and the risk factors for both CVD and T2DM that can be tracked from childhood into adulthood increase the likelihood of adverse health outcomes in adulthood [33]. Therefore, it is evident that early screening for these risk factors in children and adolescents and early interventions to address these unhealthy lifestyle behaviors will help prevent the development of these diseases in later years [33]. Given the unfortunate rise in both of these diseases in pediatric populations, it is increasingly important to begin prevention efforts in childhood or even prenatally (this will be further discussed in the following article of the current issue).

Vascular Health in Children and Adolescent with Obesity and T2DM

Results from autopsy studies of individuals dying from non-cardiac causes demonstrated a strong association between obesity and the extent and severity of early coronary atherosclerosis in adolescents and young men [32]. In large population-based cohort studies, a strong linear association was found between BMI in childhood and adolescent and risk for coronary artery disease (CAD) in adulthood [24, 32]. These studies clearly indicated a clear relationship between obesity in the childhood years and subsequent CVD in adulthood [24, 32-33]. This has led to an effort to better understand the pathophysiology of vascular injury in children and adolescent using surrogate measures of subclinical vascular disease to help in risk prediction. These methods include the peripheral endothelial function measures (PEFM), the brachial artery reactivity measurement (BARM), the carotid intima-media thickness (CIMT), aortic pulse wave velocity (a-PWV), and peripheral arterial tonometry (PAT)

measurements among others. PWV is a marker of arterial stiffness and is associated with CVD and predictive CV mortality in adults. CIMT is a marker of atherosclerosis and is predictive of CV morbidity and mortality in adults.

Using these methods, it was found that the BARM was adversely affected by overweight/obesity and hyperinsulinemia in children suggesting that these patients has less brachial artery distensibility compared to normal subjects [24]. Children and adolescent with T2DM and with obesity were found to have elevated a-PWV compared with normal weight controls suggesting a higher risk for arterial stiffness in this population. Youth with T2DM had higher CIMT compared with lean and obese normoglycemic controls indicating a higher risk for atherosclerosis. Finally, an association was found between CIMT and glycemia, as reflected by the HbA1c, whereas vascular stiffness measure by the a-PWV was mainly related to insulin resistance and inflammation.

These findings suggest that different aspects of the vasculature are differentially affected by different metabolic disturbances associated with childhood obesity and T2DM. These findings also demonstrate that the presence of early coronary artery calcification in these obese youth. These calcifications were mainly related to total body fat and abdominal adiposity measures independent of the traditional CVD risk factors of blood pressure and dyslipidemia [24]. Globally, these studies of surrogate markers of vascular health indicate premature aging of the vascular system in children with obesity and T2DM and a higher propensity for early-onset CVD events in young adulthood.

Retinopathy and nephropathy

In addition to macrovascular changes, T2DM can also present with major microvascular induced complications such as retinopathy, microalbuminuria, neuropathy and nephropathy [34-35]. According to the authors, one of the reasons for the increase in diabetic microvascular complications among adolescents with T2DM is due to the increased in blood hypercoagulability secondary to an elevation in D-dimer and in the total serum cholesterol levels [34-35].

However, even though retinal abnormalities i.e., retinal venular dilation occur very early in the course of T2DM, the clinical picture may remain occult during childhood and adolescence. For example, most diabetic retinopathy during childhood and adolescence remains only as background retinopathy. Therefore, glycemic control during childhood and adolescence is essential in order to delay or to prevent the development of diabetic retinopathy later in life [34-35].

Non-Alcoholic Fatty Liver Disease (NAFLD)

The deposition of fat in the liver is commonly associated with T2DM, with approximately 25% of children having NAFLD at the time of diagnosis of T2DM [5]. NAFLD is determined by an elevated serum liver enzyme levels because of infiltration and accumulation of large triglyceride droplets within the hepatocytes [5]. Adolescents with T2DM have nearly three times as much hepatic triglyceride as adolescents of a comparable weight but without T2DM (36-37). As a consequence of this elevated tryglyceride levels, NAFLD occurs and it is the most common cause of childhood liver disease and is common in pediatric patients with T2DM, dyslipidemia, and abdominal obesity. Approximately 3% to 10% of children in the general population and 40% to 70% of obese children have NAFLD [5].

Recent studies in obese children and adolescents have demonstrated the effect of hepatic steatosis on insulin sensitivity. In a multiethnic group of 118 obese adolescents, it was observed that independent of obesity, that the severity of fatty liver disease was associated with the presence of pre-diabetes i.e., IGT with and without IFG [36]. In parallel to the severity of hepatic steatosis, there was a significant decrease in insulin sensitivity and impairment in beta-cell function in these obese adolescents. Moreover, it was observed with the increasing severity of fatty liver disease, that there was a significant rise in the prevalence of the metabolic syndrome, suggesting that hepatic steatosis may be a strong predictive factor of metabolic syndrome in obese children and adolescents [36].

In recent studies, the role of hepatic fat content in modulating insulin sensitivity was shown [37-39). The authors studied two groups of adolescents, one group with hepatic steatosis and the other group without this disorder. The two groups had similar visceral fat and intramyocellular lipid (IMCL) contents [37]. The obese subjects with hepatic steatosis showed an increased in muscular and hepatic insulin resistance; although not statistically significant, and a trend towards increased adipose tissue insulin resistance was also noted [37]. In a recent longitudinal study it was shown that the baseline hepatic fat content correlates with the 2-hour glucose, insulin sensitivity, and the insulin secretion at follow-up. These data indicate that the deleterious effect of intra-hepatic fat accumulation influences the insulin sensitivity at a multi-organ level, playing a bigger role than the other ectopic compartments [38].

Hepatic steatosis is only the first step of a more complex disease known as NAFLD, which has become the most common cause of liver disease in obese pediatrics patients [38-39]. NAFLD is defined by the presence of macrovescicular steatosis in more than 5% of the hepatocytes in the absence of drug consumption, alcohol abuse and other determinants that may result in fatty liver (38-39). NAFLD encompasses a range of disease severity, from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis [39].

Therefore, the screening for NAFLD should be recommended to overweight and obese children (40) and also in children and adolescents with T2DM. Although liver histology is the gold standard for diagnosing NAFLD, performing biopsies in regular clinical practice to determine disease prevalence is not always possible. Children with NAFLD typically have elevated liver enzyme values [aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] in absence of other causes of steatosis. Therefore, elevated serum levels of liver enzymes, even though they often misrepresent the entity of intrahepatic damage, are used as a non-invasive test to screen for pediatric NAFLD along with liver ultrasound (US), that can detect the disease when steatosis involves >30% of hepatocytes. Although it does not represent the imaging gold standard, performing liver US has several advantages as a screening tool including it's: 1) relative low cost; 2) large diffusion in medical community, and 3) feasibility in the pediatric population (41). However, a diagnosis based upon elevated

liver enzymes is not necessarily sufficient to diagnose NAFLD. If ALT levels are elevated three times the upper limit of normal for more than six months, an abdominal examination using liver US should be performed to rule out the possibility of viral hepatitis. Liver biopsy is required for accurate diagnosis and staging of the NAFLD [40].

Computed tomography (CT) scan is not recommended in pediatric setting to screen for NAFLD because of the unjustified radiation exposure involved in the process (41). Magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) have been demonstrated to be the best methods to assess and quantify the amount of lipids present in the liver, but these techniques are too expensive to be used in clinical practice [38].

NAFLD, as well as reduced insulin sensitivity, may be reversible by application of even a short-term diet and exercise program that induces weight loss [3]. If left untreated, however, NAFLD is progressive and may ultimately lead to cirrhosis later in either childhood or adulthood. Other complications associated with NAFLD include a possible progression to hepatocarcinoma, liver-related death in adulthood, and the development of CVD.

Dyslipidemia

Pediatric patients with T2DM have an increased prevalence of dyslipidemia, with ~ 45% of children reported to have dyslipidemia at the time of diagnosis. There is recommended to, screen for dyslipidemia at diagnosis of T2DM and every 1 to 3 years as clinically indicated thereafter [30].

In pediatric patients, dyslipidemia is significantly worse among those with T2DM when compared to those who are obese but without T2DM. Even with tight glycemic control, the dyslipidemia may persist [31-32]. Nevertheless, data on dyslipidemia in pediatric patients with T2DM remain limited. The problem is complicated by the differences among ethnic groups. For example, Canadian Aboriginal children with T2DM were less likely to present with dyslipidemia than White children with T2DM [23, 30]. The control of elevated triglycerides is important in preventing the development of CVD as dyslipidemia including elevated levels of triglycerides are also risk factors for the development of CVD and atherosclerosis in patients with T2DM [23, 30, 43-44].

These risk factors are highly prevalent in children and adolescents with T2DM early in the presentation of the disease. Moreover, youth with T2DM appear to be at higher risk for these complications when compared with children and adolescents with T1DM. In the SEARCH for Diabetes in Youth study, youth with T2DM exhibited a more atherogenic lipid profile compared with youth with T1DM, with higher fasting total cholesterol, higher LDL-C, and triglycerides and lower HDL-C, for a similar degree of HbA1c elevation [45].

The first step in the treatment of dyslipidemia should be weight loss through diet and exercise, as both of which are known to have a significant impact on cholesterol levels (discussed in article number 4). If the use of drug is not needed or if other options are available they should first be used. If the cholesterol levels continue to increase with age and if other signs of CVD are discovered perhaps statins would be something that needs to be considered. However, statin is not approved to be used in children and it's not worth risking the side effects associated with statins when long term effects are unknown. Statins should only be use if the benefits outweigh the risks and there are no alternatives [30].

In children with familial dyslipidemia and a positive family history of early CVD events, a statin should be started if the LDL-C level remains >4.1 mmol/L after a 3- to 6 months of unsuccessful life style interventions (LSI). The goals of the therapy are to maintain LDL-C below 2.6 mmol/L, triglycerides below 1.7 mmol/L, and HDL-C above 0.9 mmol/L. Statins are the first line of therapy in these patients. However, long term effects have not yet been determined and they are known for have mild side effect of headache, GI distress, and myalgia [42-43].

Hypertension (HTN)

HTN (BP ≥ 95th percentile for age, sex, and height and confirmed on two visits is present in 20–30% at initial diagnosis of T2DM. Blood Pressure (BP) should be checked at diagnosis and with every clinical visit afterwards [30]. When HTN is associated with proteinuria, it can progress to end-stage renal disease (ESRD) and requires aggressive treatment [46]. HTN may be responsible for 35–75% of micro- and macrovascular problems in T2DM. HTN is uncommon in the general pediatric population. However, HTN is more common among children with T2DM than children with T1DM. Among children with T2DM, rates for HTN range from 12% to 36% [46].

As for dyslipidemia, the development of HTN also varies according to ethnicity and the family history of HTN. Minimal weight loss and LSI is most of the time sufficient to correct HTN in obese pediatric patients with T2DM. However, if the HTN is not corrected after 3–6 months of LSI, treatment using angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) might be considered (Further detail will be provided in the article number 4).

Pancreatic complications

β–cells function in overweight and obese adolescents is impaired relative to the reduction in insulin sensitivity in pediatric patients with T2DM [46]. This is due to the fact that β–cells function is rapidly declining, even without significant changes occurring concurrently, with peripheral or hepatic insulin sensitivity. At the time of diagnosis of T2DM, adolescents already present with β–cells dysfunction that is comparable to that observed in their adult counterparts. In response to β–cells dysfunction, it is recommended to use the HbA1c as a screening tool to investigate the progression and even the reversal of T2DM risk in such adolescents [47].

Polycystic Ovary Syndrome (PCOS)

PCOS is seen in obese and T2DM women, including adolescents [48-50]. The diagnosis criteria are not fully defined in teens because several features of PCOS are only seen during the course of normal puberty. However, emphasis on using more rigorous criteria for teen PCOS diagnosis has gained more support, including the recently revised Rotterdam criteria; these involve having oligo- or anovulation or primary amenorrhea at 16 years of age, clinical and biochemical hyperandrogenism, and ovarian volume of ≥ 10 cm^3 on ultrasound

(need 3 of 3) [51]. Patients with PCOS require an OGTT as there is a higher rate of dysglycemia associated with the diagnosis of PCOS. Some of the features of PCOS result from excess insulin actions including increasing ovarian testosterone production and reducing hepatic sex hormone-binding globulin production [51].

The treatment of PCOS involves LSI; in addition, combined oral contraceptive pills, antiandrogens (e.g., spironolactone), and insulin sensitizers including metformin all play a role in different patients [47]. For more information on the management of PCOS in pediatric obese patients, please consult the book of Dr. Plourde on the management of pediatric obesity, especially on chapter 7 of this book and in the learning module for the BMJ [49-50].

Proteinuria

Microalbuminuria (≥2.5 mg/mmol) or macroalbuminuria is far more common in T2DM when compared to T1DM. Microalbuminuria was present in 22.2% of T2DM versus 9.2% in T1DM patients [34-35, 46, 52]. It was observed in Canada that 14.2% of T2DM subjects had proteinuria (30). The rate of progression of microalbuminuria is also faster in T2DM. Screening for proteinuria should start at diagnosis and annually afterwards. It should be confirmed on 2-3 samples [30].

Screening can be done initially with a random or early morning albumin: creatinine ratio (ACR), and, if the result is abnormal, this should be confirmed with another early morning ACR 4 weeks later. If the two results are abnormal, a timed overnight urine collection for ACR should be done. The diagnosis is made by repeated samples over 3-4 months, and, if persistent over 6–12 months, then a referral to nephrology specialist for further evaluation is warranted. A patient with T2DM should be tested several times a year for protein in the urine [30, 52].

This is a sign that there is diabetes related kidney damage as the kidney is allowing protein to escape the body without being absorbed. An extremely high amount of protein may be a sign of kidney disease [34, 52]. Kidney malfunctions and diabetes are related as kidneys are one of the organs that respond to the body's glucose intolerance [34, 52].

Renal injury

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) can begin in childhood, particularly in children who are obese and have T2DM (35). In fact, diabetic kidney disease (DKD) remains a leading cause of morbidity and mortality in people with T2DM. The 2011 US Renal Data System reported that DKD accounted for 44.5 % of all cases of ESRD. In 2009, overall Medicare expenditure for people with CKD and diabetes accounted for $18 billion [53]. The prevalence of DKD has remained relatively stable over the last 20 years, despite increasing prevalence of T2DM, likely related to improved glycemic control, blood pressure, and weight control, since evidence-based therapies directly targeting DKD are rather rare. However, children and adolescents with T2DM are at higher risk for developing primary renal disease (*e.g.,* IgA nephropathy, membrano-proliferative glomerulonephritis) and a four-fold increased risk for developing renal failure. As such, children and adolescent diagnosed with T2DM should be screened with regards to glomerular filtration rate (GFR), blood pressure, and urinary albumin excretion rate [30, 52, 54-55]. The detection of microalbuminuria is the earliest possible marker for renal disease; it is also an independent predictor for future CVD morbidity and mortality [35, 52, 54-55]. However, renal disease cannot be reliably determined only by clinical and laboratory findings. Renal biopsy is needed to provide accurate diagnosis of renal disease. T2DM and HTN are the 2 leading causes of ESRD. The risks for developing diabetic nephropathy are further increased by the presence of the co-existing risk factors of hyperlipidemia and/or obesity [34]. The risk factors for DKD in T2DM include female sex, obesity, triglycerides, hyperglycemia, CVD, insulin resistance, and elevated uric acid (39). Children and adolescent with T2DM have increased risk for earlier onset and accelerated progression of albuminuria when compared with both their T1DM counterparts and adults with T2DM of similar duration [54-55]. Furthermore, children and adolescent with T2DM have an extended lifetime exposure to these risk factors [34].

As discussed earlier, β–cells failure may have a negative impact on nephropathy progression [26-27, 34]. In addition, worsening of glycemic control among teens and young adults with T2DM is responsible for both earlier and increased cumulative microvascular complications [54-55]. Longitudinal data from the T2DM in Adolescents and Youth (TODAY) study predict that children and adolescents diagnosed with T2DM may have a much more aggressive course of disease with an increased risk for early HTN and nephropathy when compared with adolescents with T1DM. [56] A higher prevalence of hyperlipidemia, NAFLD, and inflammatory markers further contributes to the concern for cumulative lifetime nephropathy risk in children and adolescents with T2DM [57-61].

Sustained motivation of youth with T2DM to adhere to LSI is often difficult. Also, the compliance with medical therapy and LSI recommendations is often hampered by a multitude of contributing psychosocial, medical, and physiologic factors [49-50]. Effectively addressing the underlying factors that contribute to deteriorating glycemic control, HTN, and obesity in adolescent is critical to reducing renovascular disease risk in T2DM pediatric patients [5]. This very important issue will be discussed in depth in the article number 4. In the previous book and learning module from Dr Plourde, the use of motivational interviewing clearly explain how to proceed to help manage the issue of non-compliance and lack of motivation in pediatric patients having chronic diseases such as obesity [49-50].

Conclusion

To date, a huge number of complications have been identified regarding T2DM in children and adolescents including cardiovascular (coronary heart disease, macrovascular and microvascular changes, HTN), metabolic (dyslipidemia), hepatic (NAFLD), pancreatic (β–cells dysfunction), pulmonary (altered peak oxygen intake, sleep disorders), and renal (CKD, ESRD). Considering, the high number of complications associated with T2DM, it is, therefore, essential that major effort be put in place at the prevention level to ensure that this number will not further increase. Efforts should also be put in place to rapidly diagnose and treat these patients. Which further increase the need of rending available to the HCP, and to other stakeholders

relevant information on the prevention and on the management of T2DM in pediatric patients?

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