MEDWIN PUBLISHERS
Committed to create value for Researchers

Open Access Journal of Endocrinology

Is there an Escalation of Type 2 Diabetes Mellitus in Children and Adolescents: Therapeutics and Preventive Approach

Kulvinder Kochar Kaur[1]*, Allahbadia G[2] and Mandeep Singh [3]

[1]Scientific Director, Kulvinder Kaur Centre for Human Reproduction, Punjab, India

[2]Scientific Director, Rotunda-A Centre for Human Reproduction, Mumbai, India

[3]Consultant Neurologist, Swami Satyanand Hospital, Jalandhar, Punjab, India

Review Article

Volume 2 Issue 1

Received Date: October 25, 2017

Published Date: January 18, 2018

***Corresponding author:** Kulvinder Kochar Kaur, scientific Director, Kulvinder Kaur Centre For Human Reproduction, 721,G.T.B. Nagar, Jalandhar-144001, Punjab, India, Tel: 91-181-9501358180; Email: Kulvinder.Dr@Gmail.Com

Abstract

There is an increasing prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents from all over the world from various ethnicities, although the incidence of obesity is not increasing any more. Most of the young people having T2DM were found in specific ethnic subgroups such as African-American, Asian/Pacific Islanders, Hispanic and American Indians.T2DM in childhood presents with more frequent mild/asymptomatic manifestations. Hence one needs to screen in high risk group like obesity, relatives with T2DM, those with clinical features of insulin resistance (hypertension, dyslipidemia, PCOS, Acanthosis Nigerians). New drugs like dipeptidyl peptidase inhibitors or glucagon like peptide 1 mimetics are going to be soon available for treatment of youth having T2DM.But there is a high dropout of the medical care system of adolescents with T2DM, which suggests that management of children and adolescents with T2DM needs some changes in current health practices.

Keywords: Type 2 Diabetes Mellitus; Children; Adolescents; Obese; Ethnicities; PCOS; Acanthosis Nigrans; GLP1 mimetics; DPP inhibitors

Introduction

Type 2 diabetes mellitus (T2DM) was thought to be a rare occurrence in children and adolescents over 30years back. Yet in mid 1990's investigators began to observe an increasing incidence of T2DM worldwide [1]. This has especially been the core case in US, but has also been reported in other countries like Japan, Canada, Austria, UK &Germany [2-6]. In some areas of US, T2DM is as frequent as T1DM in adolescents. This classification followed a striking increase in both prevalence and degree of obesity of children and adolescents in many populations [2,4,7]. Overweight is at present the most common health problem facing children in the developed countries and the developing countries [8]. Though obesity is not increasing any more in the USA and some countries like USA and some countries in Europe the prevalence has been increasing threefold [9,10]. This has been attributed to the fact, that although the prevalence of obesity is not increasing, the degree of obesity in affected children and adolescents are on the rise [10]. T2DM is a serious and costly disease. Chronic complications of T2DM include increased development of cardiovascular disease. End stage renal disease, loss of visual acuity, limb amputations.

Since both the incidence and prevalence of T2DM in children are increasing and if this incidence cannot be reversed our society will face major challenges. That is the burden of DM and its complications will affect many more individuals than anticipated at present and the cost of DM to our society will cause us to consume enormous resources.

Pathology of T2DM in Children and Adolescents

T2DM is a complex metabolic disorder of varied etiology along with social behavior and environmental risk factors in masking the effects of genetic susceptibility [11]. There is a strong hereditary (likely mulitigenic) components of the disease with the role of genetic determinants illustrated when difference in the prevalence of T2DM in various racial groups is considered [12]. Though there is great work in the field of genetic basis of T2DM, these work represent just a small proportion of the genetic variation underlying the chance of getting this disorder. Recent increases in DM incidence are occurring at very rapid pace to explain it as a result of raised gene frequency and altered gene pool, gives the importance of environmental factors.

Glucose homeostasis depends on the balance between insulin secretion by the pancreatic β cells and insulin action. It is seen that insulin resistance to insulin stimulated glucose uptake is characteristic finding in patients with T2DM and impaired glucose metabolism. The evolution from normal to impaired glucose tolerance (IGT) is associated with a worsening of IR. Impaired glucose tolerance is an intermediate stage in natural history of T2DMand is a predictor of the risk of developing DM and cardiovascular disease [13-16]. However there is high spontaneous conversion rate from IGT to normal glucose tolerance in the next 3-5yearsin children and adolescents with impaired glucose tolerance [17,18]. This normalization has been attributed to changes in IR at end of puberty.

Puberty appears to take a major part in the development of T2DM in children [15]. Increased resistance occurs to the action of insulin during puberty=>hyperinsulinemia. After puberty basal and stimulated insulin response decreases hyperinsulinemic-euglycemic clamp studies demonstrated that insulin mediated glucose disposal is on an average 30% lower in adolescents between Tanner stage II-IV compared with prepubertal children and young adults. Increased growth hormone secretion in puberty is discussed to be responsible for the IR during puberty [19]. Given this information it is not surprising that the peak age at presentation of T2DM children coincides with the usual age of midpuberty [2,15]. For DM to developer alone is not sufficient and inadequate β cell insulin secretion is necessary insulin action and insulin secretory failure are both present. It has been proposed that hyperglycemia may worsen both IR and insulin secretory abnormalities, thus enhancing the transition from impaired glucose tolerance to DM [12,14-16].

The adverse effects of obesity on glucose metabolism is evident early in childhood. Obese children are hyperinsulinemic, have approximately 40%lower insulin stimulated glucose metabolism compared with nonobese children [20]. Furthermore the inverse relationship between insulin sensitivity and abdominal fat is stronger for visceral than for subcutaneous fat [20,21]. It is seen that adipose tissue expanding in the obese state synthesizes and secretes metabolites and signaling proteins like leptin, adiponectin and tumor necrosis factor alpha. These factors are known to alter insulin secretion, sensitivity and even cause IR under experimental and clinical conditions [1-3,7].

Racial differences in insulin sensitivity are also seen in childhood. African-American 7-14 yr old children have significantly>insulin levels than age related white children [21]. These data suggest that particular ethnic groups may have a genetic predisposition to IR which may increase their risk for T2DM. Similarly obese Swedish children have higher fasting glucose levels as compared to obese German children [22].

Epidemiology of T2DM in Childhood and Adolescents

The prevalence of type 2 DM in children and adolescents in USA is approximately 12:100000, although it is still rare in Europe 2.5:100000 [10,16,23-25]. Most of young people diagnosed with T2DM were found in specific ethnic subgroups such as African American, Hispanic, Asian/Pacific islanders and American Indians 22.3/1000 in 10-14 yr old children [26]. The greater majority of children were obese. Screening studies in obese adolescents have reported a prevalence of 0.4%upto 1% of T2DM in obese children>=12yrs [8,27,28] Within whole pediatric population the overall incidence of DM remained low as compared to T1DM. This has lead some to question the claims of an epidemic of pediatric T2DM, although most agree that T2DM in youth is appearing as a serious clinical issue [29-31].

Clinical Features of T2DM in Children/Adolescents

Most children with T2DM are obese or extremely obese at diagnosis and present with glucosuria without ketonuria, absent or mild polyuria and polydipsia and little or no weight loss [2,14]. Right now children with T2DM are usually diagnosed over the age of 10yrs and are in the middle to late puberty [2,14,15].

In the mildest form of T2DM diagnosis is made in an asymptomatic child during a routine medical checkup by detection of hyperglycemia or glycosuria [14]. 1/3rd of patients are diagnosed by urinanalysis during routine physical examination [14,15]. In its severest form the child presents with polyuria, polydipsia, weight loss. Upto 33% in particular ethnic groups have ketonuria at diagnosis. 5-25%ketoacidosis at presentation very rare, manifest with a hyperglycaemic hyperosmolar coma [1,13-15]. With these clinical features, often the seperation from T1DM is not possible until mths later, when insulin requirements decline and a noninsulin dependent course develops without dependence on insulin for survival .Children with T2DM usually have a family history of T2DM, those of non European ancestry (Americans or African proportionately represented. Of the pts 74-100% have a 1st or 2nd degree relative with T1DM [14]. Important is that diagnosis in parents or other relatives might not be required till the child is diagnosed. Acanthosis nigrans and PCOS disorders associated with insulin resistance and obesity are common in youth with T2DM [14]. Acanthosis is a cutaneous finding characterized by velvety hyper pigmentation patches most prominent in intertrigous areas. It is present in upto50 to 90% children with T2DM. It seems more frequently in darker skinned obese individuals. PCOS is characterized by hyperandrogenism and chronic an ovulation. Lipid disorders and hypertension also occur more frequently in children with T2DM. Most of the Caucasian childhood, adolescents with T2DM were asymptomatic at diagnosis in contrast to other clinicians. The minority populations demonstrated at manifestation of DM>symptoms with higher insulin and C peptide levels [9].

Some syndromes like Klinefelters syndrome, Barder-Biedel Syndrome, Prader Willi Syndrome and Alstrom syndrome are associated with T2DM. They are all associated with mental retardation and frequently with extreme obesity.

Differential Diagnosis of T2DM

Individuals with T2DM may have clinical presentations indistinguishable from patients with other types of DM [14]. This is relevant as the number of children with T2DM increases it becomes increasingly important classifying their DM correctly, so that appropriate therapy may be instituted.

Typically children with T1DM are more overweight and have recent weight loss, polydipsia, and polyuria .They have a short symptom and frequency duration, have ketoacidosis at presentation [12,14,32]. After metabolic stabilization, they may have an initial period of diminished insulin requirement after which they require insulin for survival.

Increased prevalence of T2DM within whole population means that many individuals with T1DM are now more likely to have a family history of T2DM. Similarly T1DM also presents in overweight /obese individuals and indeed the prevalence of weight related problems in T1DM appears to be significant [33]. Even if T2DM is defined by the absence of β cell autoantibodies some studies reported nearly 30% β cell auto antibodies in european children and adolescents clinicly appearing as T2DM [9,12,15,16,24]. These children have noninsulin dependent children over a period of >1yr. The possibility that positive β cell antibodies in these non insulin requiring diabetic children and adolescents represent a form of Early onset latent autoimmune DM, similar to that described In adults (LADA: latent autoimmune DM of the adult) need to be considered. Worldwide studies have identified 10-20% of diabetic pts with β cell autoantibodies in non insulin requiring adult D [34-36]. Patient with LADA share IR with T2DM patients but display a more severe defect in β cell capacity [37]. Following the terminology latent autoimmune DM in adulthood "the noninsulin dependent diabetic children and adolescents with β cellautoantibodies could be named latent autoimmune DM in youth (LADY). Double DM or type 1.5 DM or other proposed names for this entity.

The accelerator hypothesis poshdated a shared basis for both T1 & T2DM. Besides individual predisposition and autoimmunity IR is discussed to=>βcell insufficiency [38,39]. In the prediabetic period of an immune mediated destruction of β cells increasing IR can =>clinical DM [33]. Obesity and puberty are important factors for developing IR in childhood and adolescents [21]. Apart from β cell is autoantibodies in children classified as T2DM, negative autoantibodies children with T1DM with acute onset of DM, severe metabolic impairment and insulin requirement only in the early stage of disease are reported [13,30]. Thus T1DM & T2DM are not completely distinctive and can overlap considerably. Therefore serology can't completely distinguish these types of DM. Maturity onset of DM of the young (MODY) is another rare

form of DM in children which includes various disorders caused by monogenic defects in β cells function MODY2 (defect in glucokinase) and MODY3 (defect in HNF1α) are the most frequent types of MODY [40]. Patients with MODY have a dominant genetic trait, usually are non obese and have low fasting insulin levels. Recent studies suggest that the clinical presentation of MODY is broad, ranging from asymptimatic hyperglycemia to severe acute presentation. MODY has been presented in allrace/ethnicities. These gene abnormalities are thought to be rare and need molecular diagnostic testing.

Diagnostic Criteria of T2DM in Children/Adolescents

These are symptoms of DM like polydipsia, polyuria and unexplained weight loss plus Fasting glucose>=126mg/dl (7mmol/l in venous or capillary plasma or 2hr glucose during OGTT>200mg/dl (11.1mmol/l in venous plasma or capillary whole blood sample. Recently revised ADA criteria allow utilization of Haemoglobin HbA1c>=6.5%for diagnosis of DM [16,41]. In case of asymptomatic manifestation, fasting glucose, HbA1cor OGTT has to be repeated on another day for diagnosis. In most patients with DM, classification can be made on the basis of clinical presentation and course [12,14,16]. In the usual circumstances that requires a specific classification to be made, other tests may be necessary, like fasting insulin or C peptide determination and occasionally β cell autoantibodies measurements to achieve a high degree of sensitivity, a combination of tests is required which greatly increases the cost of classification.

C peptide levels are elevated in individuals with T2DM in contrast to patients with T1DM or MODY patients. Specific autoantibodies to insulin, to GAD 11 or tyrosine phosphatases insulin antibodies (IA2) and IA2b are found in presentation in 85-98% of individuals with immune mediated T1DM [1,32]. T1DM has a strong HLA Association, however HLA typing is not a useful diagnostic tool.

Screening for Type 2DM in Children and Adolescents

Most of the European, Caucasian children and adolescents with T2DM and 1/3RD of the American children were asymptomatic at diagnosis. According to this the prevalence in screening studies in Europe of obese children was much higher than the prevalence rate reported in the standardized documentation system of DM for e.g in Germany [28,42]. Therefore it is likely that with adults undiagnosed T2DM is a common condition in childhood [43]. Thus screening of T2DM seems necessary since unrecognized hyperglycaemia would undoubtedly contribute to both microvascular and macrovascular risk in later life [15]. But at present time <general screening for T2DM in youths is unlikely to be cost effective. Therefore a targeted screening seems to be necessary consistent with the recommendations for screening in adults, only children at substantial risk for the presence or the development of T2DM should be tested. Screening in high risk population demonstrated T2DM in approximately 1%of obese Caucasian children in Germany and in 4%of screened obese adolescents in particular ethnic groups in the USA [42,44,45]. The ADA recommends a screening in overweight children and adolescents at onset of puberty in high risk patients. Fasting glucose should be performed every 2yrs starting at the age of 10yr or puberty if it occurs in a younger age by fasting glucose or OGTT [6].

However these screening recommendations have some pitfalls. Requirements for testing an asymptomatic group include the availability of a test that is sensitive (few false negatives) and accurate and acceptable specificity (minimal number of false positive). Since Fasting blood glucose failed to diagnose in the European cohort OGTT seems to be a better screening tool even if fasting glucose is preferred because of its lower costs and greater convenience. However the lower reproducibility of an OGTT has to be kept in mind [2,46].

Using the criteria1) T2DM in the 1st or 2nd degree relatives 2) onset of puberty and 3) extreme obesity allows to identify the great majority of overweight European children which should be reasoned by OGTT when 2 of 3 criteria are fulfilled. Studies using HbA1C screening tools were disappointing since 1/3rd of the asymptomatic children with T2DM had normal values [42]. The standardadization process of the HbA1c has been included in the ADA recommendations for the diagnosis of DM [16,42]. But studies testing the usefulness of HbA1c after the standardization process as screening tool are missing.

Complications of T2DM in Children/Adolescents

The chronic complication of DM in adults include macrovascular disease like accelerated development of cardiovascular disease =>stroke and myocardial infarction and microvascular diseases like retinopathy ,nephropathy and neuropathy =>end stage renal disease ,loss of visual acuity and limb amputations. One notable outcome of the UK Prospective DM Study (UKPDS) analysis was the observation that the accrual of endpoints was a time dependent process [26]. Therefore children and adolescents with T2DM have a>risk for complications

as compared to adults with DM, Accordingly, developing T2DM at a younger age is also associated with a very much >risk of long term cardiovascular disease than those who developT2DM in middle age [21]. Young people with T2DM appear to be at much higher risk of developing early DM associated complications than those with T1DM. This higher level of risk does not appear to be related to overall levels of glycemic control or duration of disease but to occurrence of hypertension and dyslipidemia [44]. These CVS risk factors are more frequent in adolescents suffering from T2DM as compared to T1DM [32]. In the TODAY study 14% of adolescents with T2DM suffered from hypertension, 80% demonstrated low HDL concentrations &10%had hypertriglyceridemia [32]. In the SEARCH study 92%of the adolescents with T2DM fulfilled the definition of metabolic syndrome [7]. These prevalence are similar to CVS risk factors in European adolescents with T2DM [3,45].

Little is known regarding the onset and progress of macrovascular disease in children and adolescent with T2DM. Arteriosclerosis is a time dependent phenomenon and the absolute time from diagnosis to developing pathological CVS lesions may be many years –in that sense these children may be protected by age since they do not have preexisting age related CVS disease .However already adolescents with T2DM demonstrated an increased intima media thickness which is predicting for heart attack and stroke [47-49].

Microvascular disease is the hallmark of hyperglycemia diagnosed at a young age. Data from Japanese, Pima Indian children show the presence of microvascular diabetic complications already at diagnosis and follow up [1]. In Japanese children, incipient relationship was detected in 36% of the cases at the time of diagnosis, in 39% of the cases at 2yrs follow up, while micoalbuminuria was observed in 39%at 2yrs follow-up [50]. Among pima Indian children 22%had microalbuminuria and at follow-up between 20-and 29yrs of age between 60%had microalbuminurea and 17%had already macroalbuminurea [45]. In the SEARCH study 4%of the adolescents with T2DM demonstrated retinopathy and 28% microalbuminuria [7]. While in reverse in European adolescents with T2DM, no retinopthy and microalbuminurea was reported, suggesting genetic differences [3,48].

Treatment of T2DM in Childhood and Adolescents

American Academy of Paediatricians very recently published management guideline which show to treat children and adolescents with T2DM Ideal goals of treatment is normalization of blood glucosevalues and HbA1c [14, 30].

Successful control of the associated comorbidities, such as hypertension and dyslipdemia is also important [14]. Ultimate goal of treatment is to decrease the risk of acute and chronic complications associated with DM.

Most of the recommended guidelines for treatment in children with T2DM are extrapolated from experience got from treating adults [6,14,30]. Despite of severe manifestations, initial management of obese children and adults with T2DM should consist of behavior modification strategies for lifestyles changes such as decreasing high calorie high fat food choice and sedentary behavior, while increasing physical activity [51]. Weight control is important for reaching treatment goals and are effective for getting treatment of T2DMin adolescents [52]. However lifestyle changes imposition is not easy and self motivation is required [53,54]. Also one needs to refer to a dietician having experience in nutritional management of children with DM [53]. These dietary recommendations need to be culturally appropriate and sensitive to family resources and provided to all caregivers. It is essential to encourage healthy eating habits by the whole family [51,53]. All children with T2DM should receive comprehensive self management education [15,21]. Self management education should include teaching self monitoring of blood glucose (SMBG). SMBG should be performed as required during periods of acute illness or when symptoms of hyper or hypoglycemia occur. Patients on insulin should be monitored periodically for asymptomatic hypoglycemia. Routine blood glucose monitoring should be tailored to individual needs but should probably include a combination of fasting and postprandial glucose measurements.HbA1c should be assayed to monitor glycaemic control.

Only a few of youths with T2DM can be treated with diet and exercise alone [55]. Hence pharmacological intervention is usually required for getting a normoglycaemic state.

Pharmacological Treatment of T2DM in Children /Adolescents

If the treatment goal (HbA1c<7%) with nutrition education and exercise is not met pharmacotherapy is indicated [14,30]. Many drugs are available for individuals with T2DM although only metformin and insulin are currently licensed for the use of under 18 yr old [14]. Most paediatric diabetologists use oral agents for children with T2DM.Advantages of oral agents include potentially greater compliance and convenience for the patient. Cinical features suggesting initial treatment with

insulin include dehydration, presence of ketosis and acidosis.

Metformin, a biguanide, is the most appropriate starting point for pharmacological treatment in children and adolescents with T2DM.The effectiveness has been proven in adolescents in a RCT [51]. Metformin decreases hepatic glucose output and increases mainly hepatic along with muscle insulin sensitivity without a direct effect on βcell function. Metformin has the advantage of weight reduction, reduction in lipids without the risk of hypoglycaemia. Due to lactic acidosis concerns, metformin is contraindicated in patients with impaired renal function and needs to be discontinued with the administration of radio contrast material or hypo caloric diet. Metformin should not be used in patients with known hypoxaemic conditions, severe infection, hepatic disease, or alcohol abuse. The most common side effects of metformin are gastrointestinal disturbances. The dose of metformin should be increased upto 2g in split doses, unless there are gastrointestinal side effects. Metformin has a good safety record, but should not be given if there is any doubt at all about the nature of diagnosis.

If monotherapy with metformin is not successful over a reasonable period of time (3-6months), various alternatives can be considered. Other drugs which are not approved for children and adole scents, have been less frequently used in children. No oral agents should be used like rosiglitazone during pregnancy. The use of rosiglitazone has been studied in a randomized trial in adolescents as compared to lifestyle interventions and metformin in the TODAY study [56]. Monotherapy with metformin was associated with durable glycaemic control in roughly half of children and adolescents with T2DM. The addition of rosiglitazone, but not an intensive lifestyle intervention, was superior to metformin alone. However rosiglitazone has been withdrawn from the market due to the side effects and is not available any more.

Insulin treatment will often be the only feasible way on controlling hyperglycaemia. There is no specific contraindication in children. Insulin regimens should be carefully tailored to lifestyle (bedtime insulin alone, twice day insulin or multidose insulin regimens).

In those extremely obese adolescents where lifestyle changes and pharmacotherapy have been unsuccessful, bariatric surgery may be considered [57].

Monitoring and treatment of complications of T2DM in Children/Adolescent,

A microvascular complications of T2DM like retinopathy and nephropathy already occur in children, dilated eye examination should be performed [1,53]. Screening for microalbuminurea should also be performed yearly [1,6]. Angiotensin converting enzyme (ACE) inhibitors are the agents of choice in children with microalbuminuria [1,6]. It is not clear whether foot examination is essential in children [17]. Control of hypertension is a must in children with T2 DM [1,6]. If normotension is not achieved with ACE inhibitors alpha blockers, calcium antagonists, or low dose diuretics may be considered. Testing for and treating lipid abnormalities are essential to avoid macrovascular disease [1,6].

Psychosocial Aspects

Adolescents with T2DM rate lower quality of life scores act their peers with T1DM and the burden of neuropsychiatric disorders in young people with T2DM is high, with as many as one in 5 experiencing either psychiatric illness or neurodevelopmental /behavioral problems [53,58]. Coupled with this, young people with T2DM are often from lower socioeconomic backgrounds where social networks are less well developed to cater for the psychosocial needs of the individual [59,60]. This is important as psychosocial factors represent a significant barrier to optimum self management in adolescents with T2DM, often leading to a vicious circle of spiraling poor self management and increasing psychosocial problems [60,61].

Interestingly evidence from adult studies also suggests that daily negative mood has a negative effect on fasting glucose concentration on the following day, which suggests that poor psychosocial health may also be physiologically related to poorer glycaemic control [59,61]. Therefore psychologists should core components of care of children and adolescents with T2DM [53].

Prevention

Because this emerging epidemic has financial and societal consequences a lot of urgent public health response is demanded. Prevention of T2DM in childhood means preventing obesity in childhood. Effect of weight loss on comorbid conditions and importantly T2DMhasbeen unequivocally proven [51,55]. As prevention should start very early in life, even before birth, a population and community approach for prevention of obesity in childhood and thus T2DM in children and adolescents seems to be very promising, and reasonable strategy available currently.

However, primary prevention has proven to be difficult or impossible in most societies [62]. A multidisciplinary approach is required and needs development and secure preventive strategies. Good nutrition, modest exercise for

pregnant women along with monitoring intrauterine growth of the foetus are mandatory..Avoid rapid weight gain after birth and teach principles of good nutrition and physical activity at allages. Strongly recommend breast feeding. Children's food choice can be influenced by early intervention and guidance. Teacher training, modification of school meals and physical education are effective in reducing risk factors for obesity [11].

Cost effectiveness of group and mixed family based treatment for childhood obesity has been tested and proven for motivated families [59]. Therefore, family based, behavioral treatment for obesity is also effective in preventing T2DMalong with being cost effective. But in unmotivated families treatment remains difficult and frustrating for the pts and his family along with the multidisciplinary team taking care of the obese child.

To prevent the development of DM and its life threatening squeal early detection of impaired glucose regulation may represent an appropriate strategy for prevention of T2DM, as subjects with impaired GTT are at increased risk of developing this disease [63]. Recent intervention studies have shown that adopting a healthy lifestyle, eating habit, regular physical activity and subsequent modest weight loss can prevent the progression of impaired GTT to clinical DM [64]. However use of metformin was not effective in preventing T2DM in obese adolescent's with impaired GTT [65]. This might be due to the fact that impaired GTT normalized physiologically at the end of puberty even without any intervention [20].

Conclusions

Although T2DM still remains a rare disorder in children and adolescents, but recent reports show an increasing prevalence around the world. This seems to be secondary to the increasing obesity prevalence in children and adolescents. This is mainly in USA, but also in countries like Asia and Europe. It has become clear that obese children and adolescents with clinical signs of IR (Acanthosis nigricans, Dyslipidemia, hypertension, PCOS or relatives of T2DM)or special ethnic populations like American-Indians, African-Americans, Hispanic) above the age of 10years should be screened.

Vertia RA found that copy number losses in the subtelomeric region on chromosome 4p16.3 were detected in early onset Japanese T2DM patients (onset at<35yr) at a high frequency. They additionally found 2 novel copy number losses with in the subtelomeric regions on chromosome 16q24.2-3&16q13.31-33, which have significant associations with early onset Japanese T2DM.

They found simultaneously copy number losses in all 3 subtelomeric regions in 11of their 100T2DM subjects while none of 100 non diabetic cohort showed the CN losses in all three regions. This suggested that the mechanism underlying induction of CNV's is involved in the pathogenesis of early onset T2DM.Thus they suggested copy number losses within multiple subtelomeric regions are strongly associated with early onset T2DM and examination of simultaneous CNV'S in these three regions may lead to the development of an accurate and selective procedure for detecting genetic susceptibility to T2DM [66].

To prevent retinopathy and DME (diabetic macular edema), Hammes, et al. reported hypertension, HbA1c.8%, Macroalbuminurea, BMI>35KG/M^2 and male sex were significantly associated with retinopathy while HbA1cand micro and macroalbuminurea increased the risk for DME by 177%. Metabolic control and BP are relative factors amenable to treatment [67]. Najafi, et al. did not find it cost effective to routinely screen for T2DM [68]. Still increasing public awareness remains an important target and prevention of childhood obesity right from antenatal stage to prevent this in getting to an epidemic stage.

References

1. Arslanian S (2002) Type2 diabetes in children: clinical aspects and risk factors. Horm Res 57(1): 19-28.

2. Reinehr T (2005) Clinical presentation of type 2 dibetes mellitus in children and adolescents. Int J Obes (Lond) 2: S105-S110.

3. Awa WL, Boehm BO, Rosinger S, Achenbach P, Ziegler AG, et al. (2013) HLA typing, clinical and immunological characterization of youth with type2 diabetes mellitus phenotype from the German/Austrian DPV database. Pediatr Diabetes 14(8): 562-574.

4. Schober E, Waldhoer T, Rami B, Holer S (2009) Incidence and time trend of type1and type2 diabetes in Austrian children 1999-2007. J Pediatr 155(2): 190-193e1.

5. Drake AJ, Smith A, Betts PR, Crowne EC, Shield JP (2002) Type 2 diabetes in obese white children. Arch Dis Child 86(3): 207-208.

6. American Diabetes Association (2000) Type 2 Diabetes in children and Adolescents. Diabetes Care 23: 381-389.

7. Rodriguez BL, Fujimoto WY, Mayer-Davis EJ, Imperatore G, Williams DE, et al. (2006) Prevalence of cardiovascular disease risk factors in US children and adolescents with diabetes: the SEARCH for diabetes in youth study. Diabetes Care 29(8): 1891-1896.

8. Han JC, Lawlor DA, Kimm SY (2010) Childhood obesity. The Lancet 375(9727): 1737-1748.

9. Moss A, Klenk J, Simon K, Thaiss H, Reineher T, et al. (2012) Declining prevalence rates for overweight and obesity in German children starting school. Eur J Pediatr 171(2): 289-299.

10. May AL, Kuklina EV, Yoon PW (2012) Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. Paediatrics 129(6): 1035-1041.

11. Kiess W, Bottner A, Raile K, Kapellen T, Muller G, et al. (2003) Type2 diabetes mellitus in children and adolescents :a review from a European perspective. Horm Res 59(1): 77-84.

12. Florez JC (2008) Clinical review: the genetics of type 2diabetes: a realistic appraisal in 2008. J Clin Endocrinol Metab 93(12): 4633-4642.

13. Lobstein T, Frelut ML (2003) Prevalence of overweight among children in Europe. Obes Rev 4(4): 195-200.

14. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ (2008) ISPAD Clinical Practice Consensus Guidelines2006-2007. Type2 diabetes mellitus in the child and adolescent. Paediatr Diabetes 9(5): 512-526.

15. Arslanian SA (2000) Type 2 diabetes mellitus in children pathophysiology and risk factors. J Pediatr Endocrinol Metab 13(6): 1385-1394.

16. American Diabetes Association (2013) Diagnosis and classification of diabetes mellitus. Diabetes Care 36(1): S67-S74.

17. Kleber M, Lass N, Papcke S, Wabitsch M, Reinehr T (2010) One year follow-up of untreated obese white children and adolescents with impaired glucose tolerance: high conversion rate to normal glucose tolerance. Diabet Med 27(5): 516-521.

18. Kleber M, deSousa G, Papcke S, Wabitsch M, Reinehr T (2011) Impaired glucose tolerance in obese white children and adolescents: three to five years follow-up in untreated patients. Exp Clin Endocrinol Diabetes 119(3): 172-176.

19. Pinhas-Hamiel O, Lerner–Geva L, Copperman NM, Jacobson MS (2007) Lipid and insulin levels in obese children: changes with age and puberty. Obesity (Silver Spring) 15(11): 2825-2831.

20. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, et al. (2004) Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 350(23): 2362-2374.

21. Taskali SE, Caprio S, Dziura J, Dufour S, Cali AM, et al. (2008) High visceral fat and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 57(2): 367-371.

22. Hagman F, Reinehr T, Kowalaski J, Ekbom A, Marcus C, et al. (2013) Impaired fasting glucose prevalence in two nationwide chohorts of obese children and adolescents. Int J Obes (Lond) 38(1): 40-45.

23. Dabelea D, Bell RA, D'Agostino RB, Imperatore G, Johansen JM, et al. (2007) Incidence of diabetes in youth in the Unites States. JAMA 297(24): 2716-2724.

24. Liese AD, D'Agostino RB, Hammam RF, Kilgo PD, Lawrence JM, et al. (2006) The burden of diabetes mellitus among US youth: Prevalence estimates from the SEARCH for diabetes in youth study. Pediatrics 118(4): 1510-1518.

25. Rotteveel J, Belksina EJ, Renders CM, Hirasing RA, Delemarre-vander Waal HA (2007) Type2 diabetes in children in the Netherlands: the need for diagnostic protocols. Eur J Endocrinol 157(2): 175-180.

26. Fagot Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, et al. (2000) Type2 diabetes among North American children and adolescents: an epidemiological review and a public health perspective. J Pediatr 136(5): 664-672.

27. Sinha R, Frisch G, Teague B, Tamborlane WV, Banyas B, et al. (2002) Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 346(11): 802-810.

28. Wabitsch M, Hauner H, Hetrampf M, Muche R, Hay B, et al. (2004) Type 2 diabetes mellitus and impaired glucose regulation in Caucasian children and

adolescents with obesity living in Germany. Int J Obese Relat Metab Disord 28(2): 307-313.

29. Goran MI, Davis J, Kelly L, Shaibi G, Spruiit–Metz D, et al. (2008) Low prevalence of pediatric type 2diabetes: wheres' the epidemic?. J Pediatr 152(6): 753-755.

30. Springer SC, Silverstein J, Copeland K, Moore KR, Prazar GE, et al. (2013) Management of type2 diabetes mellitus in children and adolescents. Pediatrics 131(2): e648-e664.

31. Diabelea D (2009) The accelerating epidemic of childhood diabetes. Lancet 373(9680): 1999-2000.

32. Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, et al. (2011) Characterisation of adolescents and youth with recent onset type2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 96(1): 159-167.

33. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DL, et al. (2010) Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for diabetes in youth study. Paediatr Diabetes 11(1): 4-11.

34. Pozilli P, Di MarioU (2001) Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult): definition, characterization and potential prevention. Diabetes Care 24(8): 1460-1467.

35. Niskanen LK, Tuomi T, Kajalinen J, Groop LC, UUsitupa MI (1995) GAD antibodies in NIDDM. Ten year follow-up from the diagnosis. Diabetes Care 18(12): 1557-1565.

36. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okobo M, et al. (1993) Immunogenetic and clinical characterization of slowly progressive IDDM. Diabetes Care 16(5): 780-788.

37. Carlsson A, Sundvist G, Group L, Tuomi T (2000) Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). J Clin Endocrinol Metab 85(1): 76-80.

38. Knerr J, Wolf J, Rejnehr T, Stachow R, Grabert M, et al. (2005) The accelerator hypothesis 'relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9248German and Austrian children with type1 diabetes mellitus. Diabetologia 48(12): 2501-2504.

39. Wilkin TJ (2006) The accelerator hypothesis: a unifying explanation for type1 & type2 diabetes. Nestle Nutr Workshop Ser Clin Perform Programme 11: 139-150.

40. Schober E, Rami B, Grabert M, Thon A, Kapellen A, et al. (2009) Phenotypical aspects of maturity onset diabetes of the young (MODY Diabetes) in comparison with type 2 diabetes mellitus in children and adolescents: experience from a large multicentre database. Diabet Med 26(5): 466-473.

41. Kapadia CR (2013) Are the ADA haemoglobin A1c criteria relevant for the diagnosis of type 2 diabetes mellitus in the youth?. Curr Diab Rep 13(1): 51-55.

42. Reinehr T, Andler W, Kapellen T, Kiess W, Richter-Unruth A, et al. (2005) Clinical characteristics of type2 diabetes mellitus in overweight European Caucsean adolescents. Exp Clin Endocrinol Diabetes 113(3): 167-170.

43. Lobstein T, Leach R (2004) Diabetes may be undetected in many children in the UK. BMJ 328(7450): 1261-1262.

44. Eppens MC, Craig ME, Cusumano J, Hing S, Chan AK, et al. (2006) Prevalence of diabetes complications in adolescents with type2 compared with type1 diabetes. Diabetes Care 29(6): 1300-1306.

45. Hillier TA, Pedula KI (2003) Complications in young adults with early onset type2 diabetes: losing the relative protection of youth. Diabetes Care 26(11): 2999-3005.

46. Libman JM, Barinas-MitchellE, Bartucci A, Robertson R, Arslanian S (2008) Reproducibility of the oral glucose tolerance test in overweight children. J Clin Endocrinol Metab 93(11): 4231-4237.

47. Reinehr T, Schoeber E, Wiegand S, Thon A, Holl R, et al. (2006) Beta cell autoantibodies in children with type2 diabetes mellitus: subgroup or misclassification?. Arch Dis Child 91(6): 473-477.

48. Reinehr T, Kiess W, Kapellen T, Wiegand S, Holl RW (2010) Children with diabetes mellitus type2 in Europe: an underserved population. Arh Dis Child 95(11): 954.

49. Hurwitz-Eller N, Netterstrom B (2001) The intima media thickness and coronary risk factors. Int Angiol 20(2): 118-125.

50. Owada M, Hanaoka Y, Tanimoto Y, Kitagawa T (1990) Descriptive epidemiology of non-insulin dependent diabetes mellitus detected by urine glucose screening

in school children in Japan. Acta Paediatr Jpn 32(6): 716-724.

51. Reinehr T (2013) Lifestyle interventions in childhood obesity: changes and challenges. Nat Rev Endocrinol 9(10): 607-614.

52. Reinehr T, Kiess W, Kapellen T, Andler W (2004) Insulin sensitivity among obese children and adolescents according to degree of weight loss. Pediatrics 114(6): 1569-1573.

53. Sabin MA (2013) Type 2 diabetes in children. Clinical Obesity 3(3-4): 112-116.

54. Reinehr T, Schoeber E, Roth CL, Wiegand S, Holl R (2008) Type 2 diabetes in children and adolescents in a 2 year follow-up: insufficient adherence to diabetes centres. Horm Res 69(2): 107-113.

55. Skaff MM, Mullan JT, Almeida DM, Hoffman I, Masharani U, et al. (2009) Daily negative mood affects fasting glucose in type2 diabetes mellitus. Health Psychol 28(3): 266-272.

56. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ (2002) Effects of metformin in pediatric patients with type2 diabetes: a randomized controlled trial. Diabetes Care 25(1): 89-94.

57. Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, et al. (2012) A clinical trial to maintain glycaemic control in youth with type 2 diabetes. N Engl J Med 366(24): 2247-2256.

58. Levitt-Katz LE, Swami S, Abrahm M, Murphy KM, Jawad AF, et al. (2005) Neuropsychiatric disorders at the presentation of type2 diabetes mellitus in children. Pediatr Diabetes 6(2): 84-89.

59. Grinstein G, Muzumdar R, Aponte L, Vuguin P, Saenger P, et al. (2003) Presentation and 5 year follow-up of type2 diabetes mellitus in African-Americans and Caribbean-Hispanic adolescents. Horm Res 60(3): 121-126.

60. Inge TH, Miyano G, Bean J, Helmrath M, Courcoulas A, et al. (2009) Reversal of type2 diabetes mellitus and improvements in cardiovascular risk factors after surgical weight loss in adolescents. Pediatrics 123(1): 214-222.

61. Mulvaney SA ,Mudasiri E, Schlundt DG, Baughman CL, Fleming M, et al. (2008) Self management in type2 diabetes mellitus, the adolescent perspective. Diabetes Educ 34(4): 674-682.

62. Campbell K, Waters E, O'Meara S, Summerbell C (2001) Interventions for preventing obesity in childhood and adolescents. A systematic review. Obes Rev 2: 149-157.

63. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis of diagnostic criteria in Europe (1999) Lancet 354(9179): 617-621.

64. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, et al. (2001) Prevention of type2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344(18): 1343-1350.

65. Wiegand S, I'Allemand D, Hubel H, Krude H, Burmann M, et al. (2010) Metformin and placebo therapy both improve weight management and fasting insulin in obese insulin resistant adolescents: a prospective, placebo controlled ,randomized study. Eur J Endocrinol 163(4): 585-592.

66. Veitia RA (2014) Simultaneous copy number losses within multiple subtelomeric regions in early-onset type2 Diabetes Mellitus. PLoS One 9(4): e88602.

67. Hammes HP, Welp R, Kempe HP, Wagner C, Siegler E, et al. (2015) Risk factors for retinopathy and DME in Type2 Diabetes-Results from the German /Austrian DPV Database. PLoS One 10(7): e0132492.

68. Najafi B, Farshadfar F, Ghaderi H, Hadian M (2015) Cost effectiveness of type2 diabetes screening: A systematic review. Med J Islam Repub Iran 30: 326.