TYPE 2 DIABETES IN YOUNG PEOPLE – ETIOPATHOGENESIS, DIAGNOSIS

Ileana Puiu, Maria Mota, Rodica Elena Stefanescu, Ioana Felicia Opritoiu

UMF Craiova

Abstract

The worldwide prevalence of diabetes mellitus type 2 in young people has increased dramatically in recent decades, in parallel to the increasing prevalence of obesity. Diagnosis of type 2 diabetes mellitus (T2DM) in young people is often difficult, there are problems in differentiating between T1DM and T2DM.

T2DM is characterized by insulin resistance with progressive alteration of pancreatic beta cell function and progressive loss of insulin secretion capacity.

The screening performed in high-risk groups may be useful in early diagnosis of T2DM in young people and may prevent complications.

Although the diagnosis of T2DM in adolescents was initially regarded with skepticism, most of the cases being reported in certain ethnic groups, but nowadays, more and more cases are reported even in European populations, with a prevalence of T2DM that remains much lower than that of T1DM.

***Key words**: Type 2 diabetes, youth, obesity*

Introduction

T2DM in children and adolescents is becoming a major public health concern throughout the world (1, 2). T2DM is a well known adult pathology that affected in the past mainly middle-aged and elderly adults, but in recent decades it has been registered a dramatic increase in the frequency of disease in young adults and also in children and adolescents. Until recently, most cases of DM in children and adolescents were T1DM, immune mediated. During the past two decades, the prevalence of childhood obesity has doubled in several parts of the world (3). Overweight children and teenagers have an increased risk of developing insulin resistance and then T2DM, hypertension, dyslipidemia, cardiovascular and other diseases. In addition, the impact of these diseases on mental and physical health and socio-economic status is enormous. In parallel with increasing obesity, there has been an increase in prevalence of T2DM in children and adolescents, initially described only in certain ethnic groups like Pima Indians from Arizona, Amero-Indian population and African-American population (4, 5). In recent years, several studies from the United States, but also from EU, have reported a high incidence of impaired carbohydrate metabolism and T2DM in Caucasian children and adolescents (6, 7).

Etiopathogenesis of T2DM in young people

In the etiopathogenesis of T2DM, obesity is a major risk factor but there are also involved other genetic and environmental factors like family history of T2DM, sedentary

lifestyle, puberty, female sex, acanthosis nigricans, polycystic ovary syndrome, and intrauterine growth retardation.

Obesity, especially abdominal obesity, is a major risk factor for the development of T2DM. For the time being, there are waist circumference percentiles in children and adolescents that allow us to make an accurate diagnosis of obesity. Adult parameters are used over 16 years of age, waist circumference above 80 cm in girls and 94 cm in boys or waist circumference values at or above the 90th percentile for both sexes are considered as criteria for abdominal obesity. Low birth weight, < 2500 g, following a poor intrauterine nutrition, may have repercussions on the fetus, causing significant endocrine and metabolic changes. Also high birth weight, > 4000 g, in macrosomic infants of diabetic mothers, is associated with development of T2DM and metabolic syndrome in adults.

During puberty in a genetically predisposed individual with risk factors that are present there is an inadequate insulin secretion and a decrease in glucose tolerance that may continue after puberty. The hallmark of this age is transient insulin resistance, determined by the specific hormonal constellation of puberty: sex hormones, cortisol and growth hormone.

Globally, physiopatogenesis data about T2DM in pediatric age group are also reduced; there are available long-term experimental and observational data from adult.

Insulin is essential for maintaining blood glucose homeostasis and regulating carbohydrate, lipid, and protein metabolism. Variations in insulin levels are followed by specific metabolic abnormalities. In the pathogenesis of insulin resistance are involved many factors. In the presence of increased adiposity, the insulin resistance represents the initial metabolic abnormality toward glucose intolerance. In insulin resistance, tissues have a diminished ability to respond normally to the action of insulin at the cellular level, due to genetic, metabolic and nutritional disorders. Immunohistochemical studies demonstrated that insulin receptors are unevenly distributed; these receptors are distributed mainly in adipose tissue, liver and muscle. Insulin receptor activity and number present physiological variations related to age (decreases with age), nutrition (hyperglucidic diet and/or hyperlipidic diet induces insulin resistance and extended fasting increases insulin sensitivity by invigorating the receptors), puberty, pregnancy (increase insulin resistance) (8). The contribution of visceral adiposity to insulin resistance is greater than subcutaneous adiposity.

In pathogenesis of glucose intolerance, at first, pancreatic beta cells are able to compensate insulin resistance by increasing insulin secretion. Compensatory hyperinsulinemia will maintain glucose homeostasis for a period of time. Hyperinsulinemia will induce an increase in appetite and implicitly in weight, which will emphasize obesity. In evolution, pancreatic beta cell function declines, and insufficient secretion of insulin will cause the transition from insulin resistance stage to the one of low glucose tolerance, and then to manifest diabetes (9, 10).

Hyperglycemia and hyperinsulinemia induce severe phenomenon of toxicity at endothelial level, in the vascular intima, with degenerative alterations that affect the vascular lumen and blood flow for the afferent territory.

Numerous studies have demonstrated that adipose tissue is an endocrine and also metabolic organ, very active, that produces increased amounts of hormones and adipocytokines, which affect the metabolism and cardiovascular regulation. The presence of chronic subclinical inflammation explains the increased risk of cardiovascular disease and T2DM associated with obesity. Therefore, there is an increasing interest in determination of adipokines, C-reactive protein, and fibrinogen. Studies of children with obesity have demonstrated the presence of subclinical inflammation since the age of 6 years old. Adiponectin can be considered as a biomarker of metabolic syndrome in children and adolescents with obesity (11, 12). To understand the relationship between obesity and insulin resistance is essential to elucidate the complex interactions between insulin and adipokines. TNF-alpha has permissive role for T2DM (13, 14).

At specific cellular level, insulin resistance manifests differently, according to initial cell function: insulin resistance in muscle cells reduces glucose uptake; within adipocytes it causes hydrolysis of stored triglycerides and increases the amount of plasma free fatty acids; in the liver, insulin resistance reduces glucose storage as glycogen, with increasing blood glucose levels. Initially, insulin resistance appears in the myocytes where decreases glucose uptake and indirectly increases blood glucose levels, and therefore, increased adipokines secretion emphasizes insulin resistance in the muscle and free fatty acids produced in excess by adipocytes are leading to fat accumulation in the liver, forcing the hepatocytes to initiate neoglucogenesis from fatty free acids and implicitly to contribute to the increase of blood glucose levels (15). If these phenomenons are of long standing, irreversible pancreatic pathological changes will appear in the presence of predisposing genetic factors, with the installation of T2DM.

The role of inheritance in the occurrence of T2DM emerge from the following findings: increased frequency in patients with positive family history, higher frequency in monozygotic twins towards dizygotic twins, the recurrence rate in siblings is greater than in general population and association of unrecognized genetic diseases in patients with T2DM. The defect in tissue sensitivity to insulin represents the key factor in individual predisposition to common diseases, such as hypertension, dyslipidemia and T2DM. Insulin resistance mechanism is not completely understood, but obesity and genetic factors play an important role.

Genes that are involved in the pathogenesis of insulin secretion and insulin resistance influence the risk for T2DM. PPAR gamma 2 gene (peroxisome proliferator activator receptor γ), peculiar to adipose tissue, interferes in the regulation of insulin action and carbohydrate metabolism. Association of Pro 12 Ala polymorphism of PPAR gamma 2 gene has been presented in several studies as being related to weight at birth since intrauterine period until adulthood, and being in relationship with obesity, insulin sensitivity and risk for T2DM. Since low or high birth weight is associated with increased risk for T2DM, it is assumed that changes in weight and body composition may be present from the birth in subjects with this polymorphism of Pro 12 Ala PPAR gamma 2 genes, which would explain the risk for late-

onset T2DM in subjects with this polymorphism (16). Pro 12 Ala polymorphism of PPAR gamma 2 gene was associated with increased risk for T2DM, especially in obese subjects, but not with childhood and adult obesity in general (17). Contradictory opinions about the association of this mutation and problems such as obesity, insulin sensitivity and T2DM have been reported by other authors who mentioned the association between Pro 12 Ala polymorphism, increased insulin sensitivity and reduced risk of T2DM (18).

Some polymorphisms in the TCF7L2 gene on chromosome 10q cause an increased risk for early occurrence of glucose intolerance in children with obesity, according to adults data, which demonstrated that TCF7L2 is a major susceptibility gene for T2DM (19, 20, 21).

Another gene that is associated with T2DM in children and adolescents is represented by KCNJ11 gene, which encodes Kir 6.2 subunit of the potassium ATP channel within the pancreatic beta cell essential in glucose-stimulated insulin secretion. The K allele of E23K variant of KCNJ11 is associated with T2DM in youth (22). In young Europeans with obesity, the Glu23Lys polymorphism in Kir 6.2 gene is associated with decreased level of blood insulin and increased level of plasma glucose, which may reveal a genetic effect in prediabetic stage in children and adolescents with obesity (23, 24).

Limited studies that were conducted in children have shown that T2DM and low glucose tolerance are characterized by impaired insulin secretion on a background of insulin resistance. It was shown that in adolescents with obesity and T2DM insulin sensitivity was 50% lower compared with obese adolescents without diabetes. The degree of impaired insulin secretion seems to be more severe than in adults, especially if it is taken into account the relatively short period of evolution of diabetes in youth (25, 26, 27). There are no systematic longitudinal studies for tracking the natural history of evolution of T2DM in adolescents at high risk. In adults, the study of UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that β cell function was decreased by 50% of normal at the moment of establishing the clinical diagnosis of T2DM. In children and adolescents at high risk for developing diabetes, the transition from normal glucose tolerance to low glucose tolerance was associated with rapid weight gain and insulin resistance, and evolution toward T2DM was still associated with an increase in body weight, decreased sensitivity to insulin and a severe decrease in insulin secretion (28).

Diagnostic criteria for T2DM in youth

T2DM is increasing in frequency in both young adult and the teenager, and raises serious problems of morbidity and mortality, but it is manifest through a period of latency without clinical symptoms, with variable duration, which can be evaluated by determining blood sugar levels, that have an acceptable sensitivity and specificity. For an early diagnosis of T2DM in adolescents, screening methods are very useful. American Diabetes Association (ADA) and American Academy of Pediatrics (AAP) recommend testing all children with weight gain or obesity (BMI above 85 percentile for age and sex), that are 10 years old or at the onset of puberty, with first-degree relatives with DM and one of

the following risk factors that are associated with insulin resistance: acanthosis nigricans, hypertension, dyslipidemia, fatty liver disease, polycystic ovary syndrome.

Screening tests for detection of T2DM include: determination of basal glucose, oral glucose tolerance test (OGTT), 2 hour postprandial blood glucose test and HbA1c (29).

The onset of T2DM in youth occurs most often during the second decade of life, with a mean age of diagnosis of 13.5 years, which coincides with the peak of physiologic pubertal insulin resistance; with a frequency that is higher in women compared to men; in over 75% of cases in young people where is a first or second degree relative with T2DM; in youth with BMI above 85 percentile for age and sex in most of the cases, however, in Japan 30% of cases were present in young people that were not obese (30).

Detection of T2DM: asymptomatic persons from high risk groups during periodic medical investigations; in the presence of ketosis or diabetic ketoacidosis, only 1/3 of newly diagnosed patients; syndrome of severe dehydration is very rare. It is not associated with HLA specificities or specific autoantibodies. It is known that obesity and insulin resistance can coexist with T1DM and ketoacidosis may accompany T2DM. Also, lately it was described double diabetes (T1DM + T2DM) which is characterized by the presence of obesity, insulin resistance and autoimmunity (demonstrated by the presence of glutamic acid decarboxylase antibodies – GAD and islet cell antibodies - ICA) in the moment of onset (31).

Diagnostic criteria for T2DM in children and adolescents are based on repeated blood glucose measurements and the presence or absence of clinical symptoms. Thus, diagnosis can be established on fasting blood glucose > 126 mg%, the post challenge plasma glucose > 200 mg% or, in classic form, in the presence of symptoms of diabetes that are associated with a casual plasma glucose > 200 mg%. If blood glucose levels are not edifying, it will be necessary periodic re-testing. (32)

There are cases in which glucose levels do not meet criteria for diabetes, but are too high to be considered normal. Impaired glucose tolerance and impaired fasting glycaemia are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes. The two types of tests are not interchangeable, impaired fasting glycaemia is a measure of disturbed carbohydrate metabolism in the basal state, while impaired glucose tolerance is a dynamic measure of carbohydrate intolerance after a standardized glucose load.

These stages are now referred to as "pre-diabetes", indicating the relatively high risk for development of diabetes in these patients. Frequently, these phases are associated with manifestations of metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), hypertension, and dyslipidemia of the high-triglyceride and low high density lipoprotein type.

After the diagnosis of diabetes is established, autoantibody testing should be considered in all pediatric patients who are diagnosed with T2DM. Testing autoantibody is necessary to perform also in overweight or obese children over 13 years of age with clinical diagnosis of T1DM, some of whom may have T2DM. (32)

Detection of low glucose tolerance status in adolescents with obesity would justify actions like changing lifestyle and diet, to improve prognosis and delay the occurrence of complications. In children, it is important to intervene in combating obesity by special diet programs and increased physical activity. Studies of adults and adolescents with obesity have shown that lifestyle changes can prevent or delay the appearance of T2DM in individuals at risk for diabetes (33, 34). Currently, the absence of clinical and metabolic indicators that could identify children and adolescents at high risk for low glucose tolerance or T2DM prevent clinicians to interfere early to stop the progression of metabolic disorders.

Using a standardized screening protocol for high risk groups, there was a four times higher prevalence of carbohydrate metabolism disorders in children and adolescents with BMI between percentiles 85 to 95 for age and sex. In pediatrics the studies used for evaluation of the effects of lifestyle changes on obesity and metabolic parameters are limited; there are also a few studies in subjects with low glucose tolerance that evaluated progression to T2DM. One of the main reasons is that although the child obesity rate is increased, low glucose tolerance and T2DM are known less than in adults.

In general, weight loss and/or prevention of weight gain are considered the most effective means of preventing T2DM in children who have risk factors for this disease (34, 35). In teenagers and young people with obesity it is important to study which one is the moment when characteristic changes of diabetes appear and which is the significance of diabetes risk in connection with increasing BMI. It is also very important to determine the real and effective methods of preventing such pathological conditions.

REFERENCES

1. American Diabetes Association. Type 2 diabetes in children and adolescents: Consensus conference report. *Diabetes Care* 23: 381–389. 2000.

2. Pinhas Hameil O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 146: 693–700. 2005.

3. Shaw J. Epidemiology of childhood type 2 diabetes and obesity. *Pediatric Diabetes* 8 (Suppl.9): 7-15. 2007.

4. Hannon S, Rao G, Arslanian S. Childhood Obesity and Type 2 Diabetes Mellitus. *Pediatrics* 116(2): 473-480. 2005.

5. Velasquez MP, Faustinelli PS, Cowan PA: Identifying Children at Risk for Obesity, Type 2 Diabetes and Cardiovascular Disease. *Diabetes Spectrum* 18 (4): 213-220. 2005.

6. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Gruters A. Type 2 diabetes and impaired glucose tolerance in European Children and adolescents with obesity – a problem that is no longer restricted to minority groups. *European Journal of Endocrinology* 151, 199-206. 2004.

7. Schober E, Holl RW, Grabert M, Thon A, Rami B, Kapellen T, Seewi O, Reinehr T. Diabetes mellitus type 2 in childhood and adolescents in Germany and parts of Austria. *Eur J Pediatr* 164: 705-707. 2005.

8. Lobstern T. Frelut ML. Prevalence of owerweight among children in Europe. *Obes Rev* 4: 195-200. 2003.

9. Arslanian SA. Insulin resistance and insulin secretion in childhood and adolescence: their role in type 2 diabetes; in **Silink M, Kida K, Rosenbloom A.**

Type 2 diabetes in Childhood and Adolescence: A Global Perspective. London, Dunitz, 93-116. 2003.

10. Marcovecchio M, Mohn A, Chiarelli F. Type 2 diabetes mellitus in children and adolescents. *J Endocrinol Invest* 28:853-863. 2005.

11. Winer JC, Zern TL, Taksali SE, Dziura J, Cali AM, Wollschlager M, Seyal AA, Weiss R, Burgert TS, Caprio S. Adiponectin in childhood and adolescent obesity and its association with inflammatory markers and components of the metabolic syndrome. 91(11) : 4415 -4423. 2006.

12. Valle M, Martos R, Gascón F, Cañete R, Zafra MA, Morales R. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. *Diabetes Metab.* 31(1):55-62. 2005.

13. Popa I, Brega D, Dragan M, Alexa A, Raica M. Obezitatea copilului si tesutul adipos. Ed. Mirton. Timisoara. 2001.

14. Dehghan A, Kardys I, Moniek PM, Uitterlinden AG, Sijbrands EJ, Bootsma AH, Stijnen T, HofmanA, Schram M, Witteman JC. Genetic Variation, C - Reactive Protein Levels, and Incidence of Diabetes. *Diabetes* 56:872-878. 2007.

15. C. Ionescu Tirgoviste. Tratat de diabetologie Paulescu. Ed. Academiei, 714-715. 2004.

16. Pihlajamaki J, Vanhala M, Vanhala P, Laakso M. The Pro 12 Ala, Polymorphosm of the PPAR gamma 2 Gene Regulates Weight From Birth to Adulthood. *Obes Res* 12: 187-190. 2004.

17. 17.Ghoussaini M, Meyre D, Lobbens S, Charpentier G, Clement K, Charles M, Tauber M, Weill J, Frogwell P. Implication of the Pro 12 Ala Polymorphism of the PPAR gamma 2 Gene in Type 2 Diabetes and Obesity in the French Population. *BMC Medical Genetics* 6:11. 2005.

18. Buzzetti R, Petrone A, Caiazzo AM, Alemanno I, Zavarella S, Capizzi M, Mein CA, Osborn JA, Vania A, Di Mario U. PPAR-gamma2 Pro12Ala Variant Is Associated with Greater Insulin Sensitivity in Childhood Obesity. *Pediatr Res* 57(1): 138-140. 2005.

19. 19.Groves J, Zeggini E, Minton J, Frayling M, Weedon N, Rayner W, Hitman AG, Walker M, Wiltshire S, Hattersley T, Mc Carthy I. Association Analysis of 6,736 U.K. Subjects Provides Replication and Confirms TCF7L2 as a Type 2 Diabetes Susceptibility Gene With a Substantial Effect on Individual Risk. *Diabetes* 55:2640-2644. 2006.

20. Körner A, Berndt J, Stumvoll M, Kiess W, Kovacs P. TCF7L2 Gene Polymorphisms Confer an Increased Risk for Early Impairment of Glucose Metabolism and Increased Height in Obese Children. *J Clin Endocrinol Metab* 92, 5, 1956-1960. 2005.

21. Korner A, Berndt J, Stumvoll M, Kiess W, Kovacs P. TCF7L2-gene polymorphisms confer an increased risk for early impairment of glucose metabolism and increased height in obese children. *J Clin Endocrinol Metab* 92: 1956-1960. 2007.

22. Gloyn AL, Weedon MN, Owen KR et al. Large-scale association studies of variants in gene encoding the pancreatic beta-cell KATP channel subunits Kir 6.2 (KCNJ11) and SUR 1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. *Diabetes* 52: 568-572. 2003.

23. Le Fur S, Fradin D, Boileau P, Bougnères P. Association of Kir6.2 and INS VNTR variants with glucose homeostasis in young obese. *Physiol Genomics* 11; 22(3):398-401. 2005.

24. Gill-Carey O, Hattersley AT. Genetics and type 2 diabetes in youth. *Pediatric diabetes* 7: 8 (Suppl. 9): 42-47. 2007.

25. Gungor N, Bacha F, Saad R, Janoski J, Arslanian S. Youth type 2 diabetes: insulinresistance, β -cell failure, or both. *Diabetes Care* 28:638-644. 2005.

26. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. Beta-cell function across the spectrum of glucose tolerance in obese youth. *Diabetes* 54:1735-1743. 2005.

27. Elder D, Prigeon R, WadwaR, Dolan L, D`alessio D. Beta-cell function, insulin sensitivity, and glucose tolerance in obese diabetic and nondiabetic adolescents and young adults. *J Clin Endocrinol Metab* 91:185-191. 2006.

28. Saad R, Gungor N, Arslanian S. Progression from normal glucose tolerance to type 2 diabetes in a

young girl: longitudinal changes in insulin sensitivity and secretion assesed by the clamp technique and surrogate estimates. *Pediatr Diabetes* 6:95-99. 2005.

29. American Diabetes Association. Screening for diabetes (Position Statement). *Diabetes Care* 25 (Suppl 1): S21-S24. 2002.

30. Sugihara S, Sasaki N, Kohno H, Amemya S, Tanaka T, Matsura N. The Committee for Medical Treatment of Childhood-onset Type 2 Diabetes mellitus, The Japanese Society for Pediatric Endocrinology. Survey of current medical treatments for childhoodonset Type 2 daibetes mellitus in Japan. *Clin Pediatr Endocrinol* 14(2): 65–75. 2005.

31. Alberti G., Zimmet P., Shaw J., Bloomgarden Z., Kaufman F., Silink M. Type 2 diabetes in the young: the evolving epidemic: the International Diabetes Federation Consensus Workshop. *Diabetes Care* 27:1.798-1.811. 2004.

32. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith G. Type 2 diabetes in the child and adolescent. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium. *Pediatric Diabetes* 10 (Suppl. 12): 17–32. 2009.

33. Diabetes Prevention Research Group. Efects of withdrawl from metformin on the development of diabetes in the diabetes prevention program. *Diabetes Care* 26:997-980. 2003.

34. Campbell K, Warers E, O Meara S, Kelly S, Summerbell C. Intervention for preventing obesity in children. *Cochrane Database Syst Rev* 3. 2004.

35. White NH, Pyle LL, Tamborlane WV, Geffner ME, Guandalini C. Clinical characteristics and co-morbidities in a large cohort of youth with type 2 diabetes mellitus (T2DM) who volunteered for the Treatment Option for type 2 Diabetes in Adolescents and youth (TODAY) Study. *Diabetes* 55:A67. 2006.