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Pregled
Review

TYPE 2 DIABETES MELLITUS IN CHILDREN: THE STORY STARTS WITH OBESITY

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In the past type 2 diabetes mellitus (DM) was considered a disease of adults and older overweight individuals. Currently there is an epidemic of type 2 DM in youth that is linked to widespread increase of obesity among children. Type 2 diabetes mellitus in this age group presents the challenge to the clinician since it must be distinguished from type 1 diabetes mellitus and maturity-onset diabetes of young (MODY). The risk factors for pediatric type 2 DM are: 1. obesity and increased body mass index; 2. family history of type 2 DM; 3. membership in an ethnic minority; 4. puberty; 5. female gender; and 6. features of syndrome X. The link between these factors is insulin resistance (IR) that plays a pivotal role in the pathophysiology of type 2 DM. Both IR and β-cell failure are present in the fully established diabetic state. Insulin and metformin have been approved for pharmacologic treatment of type 2 DM in children. Other oral agents are also used, but our knowledge of their value is limited by a lack of data on their safety and efficacy in children. Prevention of obesity is the cornerstone in the prevention of type 2 DM in youth.

Descriptors: TYPE 2 DIABETES MELLITUS; CHILDREN; ADOLESCENTS; OBESITY; INSULIN RESISTANCE

INTRODUCTION

The incidence of Type 2 Diabetes Mellitus (Type 2 DM) is steadily escalating worldwide in a wide range of ethnic and socio-economic groups. It has been estimated that 140 million people worldwide are affected with diabetes mellitus. This number is projected to increase to 300 million people in next 25 years (1). Type 2 diabetes mellitus accounts for 90-95% of all cases. In the past Type 2 DM was considered to be the disease of overweight elderly adults. However, in the early 1990s pediatric endocrinologists started to recognize the increased incidence of Type 2 DM in pediatric population. This incidence is related to an increased incidence of obesity among the youth (2). Diabetes ranks number one in direct cost for health care of any disease category in the United States. Most of the costs are due to complications arising from the disease. The emergence of Type 2 DM as an important disease of children is likely to increase the health care burden especially since the chronic complications will occur at a much younger age than traditionally expected.

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OBESITY AS A RISK FACTOR FOR TYPE 2 DM

Epidemiology of Obesity

Obesity is increasing worldwide and is already presents a significant health problem. World Health Organization declared obesity to be a worldwide epidemic (3). There has been a worldwide increase of obesity among the children as well. Several studies suggested the evidence of increasing obesity among the children. In the US the National Health Examination Survey and the National Health and Nutrition Examination 1988 to 1994 found 22% of children to be over 85th centile and 10.9% of children to be over 95th centile for weight (4). In all age groups females are at a higher risk than males. Obese children tend to become obese adults. tend to become obese adults. This is particularly important since obesity is rapidly emerging as a global epidemic and has significant related co-morbidity it will have profound public health consequences in the future.

Definition of Obesity

Obesity is defined as excess of body fat. Body mass index (BMI) is internationally accepted as a standard for the assessment of obesity in adults and correlates well with body fat. The charts for the BMI measurements in children have been developed. In adults BMI of more than 25 kg/m2 is considered overweight; more then 30 kg/m2 obese and more than 40 kg/m2 morbidly obese (5). Distribution of body fat has two major types. Abdominal distribution of adipose tissue also known as "apple form" (android obesity) is considered to be a risk factor for insulin resistance (IR), cardiovascular disease, type 2 DM, stroke and hyperlipidemia. In contrast, more peripheral body fat distribution or "pear form" (gynoid obesity) carries much a lesser risk for above mentioned complications (6). Waist-to-hip ratio is very useful and convenient method to access

body fat distribution. In adults ratio of >0.9 in males and >0.8 in females is associated with the increased risk of insulin resistance and associated comorbidities (4).

Standards have not been established for the pediatric population although centripetal adiposity has been shown to correlate positively with insulin levels. Although waist-to-hip ratio is satisfactory and useful for epidemiologic studies, additional methods (such as computed tomography and nuclear magnetic resonance) should be used for more precise quantification of subcutaneous adiposity.

Causes of Obesity

In the majority of children who suffer from obesity there is no demonstrable predisposing condition or disease as a cause of obesity. Dietary history often reveals that more calories are ingested as food than are expended. Positive energy balance and obesity result either from excessive caloric intake or overeating, from decreased energy expenditure or as a combination of both. Very limited number of children will have identifiable cause for obesity. Hormonal and endocrine causes are usually limited to hypothyroidism, growth hormone deficiency and Cushing's syndrome and are always associated with poor linear growth. Prader-Willi, Laurence-Moon-Bardet-Biedl or Alstrom syndrome are the genetic examples where obesity is the key feature of the syndrome (6).

Predisposition for obesity and type 2 DM may be familial. In genetically predisposed individuals exposure to a variety of environmental factors will lead to obesity. Obesity is considered to be "disease of civilization" or a phenomenon of urbanization. Food abundance in western societies associated with the sedentary life styles is major culprit for the increased incidence of obesity. Children consume excessive amounts of concentrated sugars especially in a form of soft drinks and sweets. Diets in Western countries are high in fat and concentrated carbohydrates. On the other hand the level of physical activity has declined dramatically. Urbanization phenomena caused the change from hunters and gatherers to sedentary life style. Television watching and computer use have been on a rise among the children and adolescents. It has been shown that for each hour of TV watching the prevalence of obesity increased by 2% in adolescents (7).

Complications of Obesity

Childhood obesity probably would have further and long-term consequences extending into the adulthood and increasing the likelihood of adult morbidity and mortality. Obesity was identified as one of the five major risk factors for cardiovascular disease in the pediatric age group. Obesity has the undesirable effect on children's lipid and lipoprotein values. In Bogalusa Heart study in a children aged 5-17 years obesity was positively related to serum VLDL and negatively to HDL. In addition abdominal adiposity in childhood is unfavorably associated with triglyceride, HDL and LDL levels.

Orthopedic sequelae include genu varum, valgus deformities, slipped capital femoral epiphysis and tibia vara. Idiopathic increase in intracranial pressure-pseudotumor cerebri appears to be associated with obesity in adolescents as it is in adults. Obstructive sleep apnea could be the most life-threatening complication of obesity. It is associated with obesity-hypoventilation syndrome and could envelop into cor-pumonale. The likelihood of gallstone formation is increased in obesity and is related to increased billiary excretion of cholesterol in obese individuals. Obesity accounts for 8-33% of the gallstones observed in children. Fatty liver metamorphosis is frequently seen in obese children and especially adolescents. Between 40-50% of severely obese children show laboratory evidence of steatohepatitis that could be associated with liver fibrosis and cirrhosis. It happens as a consequence of increased lipolysis and insulin resistance. Endocrine consequences of obesity in children include insulin resistance, type 2 DM and hyperandrogenism in females, irregular menstrual cycles and polycystic ovarian syndrome (PCOS). Obesity is risk factor for a variety of psycho-emotional and social problems related to low self-esteem or various degrees of discrimination (6).

Treatment of Obesity

The cornerstone of therapy for obesity is well balanced diet that will achieve caloric deficit. Diet should consist of 55% of calories from carbohydrates, 30% of calories from fat and 15% of calories from protein. This is of particular importance in a growing child in order to preserve linear growth. The change in the total number of calories consumed daily is usually sufficient to achieve the weight loss, rather then sticking to certain types of diet. High fat or high protein diets are not recommended for the growing children and adolescents (6). Concentrated sugars in form of soft drinks, deserts and sweets should be either eliminated from diet or allowed in minimal quantities. Digestion of complex carbohydrates utilizes the energy in contrast to digestion of fat that could be stored directly in a form of triglycerides with minimal energy expenditure.

Exercise and sufficient physical activity are other important elements in managing obesity although they probably have greater impact on weight maintenance then on the weight loss. Sedentary life styles have led to decreased activity and increased television watching. There has been linear relationship between television watching and obesity (7). To increase energy expenditure such children should have planned and regular physical activity including some kind of aerobic exercise at least 3-4 times per week.

Behavioral modifications and lifestyle changes are mandatory in any child or adolescent with obesity. Without family involvement and support failure rates and recidivism are high. Parental involvement is essential when treating childhood obesity. Adults are in charge of meal choices, food purchasing and preparation and are role models in developing healthy eating habits.

Although variety of drugs has been used to treat obesity in adults these drugs have been more or less successful and some of them have had potentially life treating effects. Drug therapy is still considered experimental and is not approved in children. Surgical procedures for weight reduction (i.e. restriction gastroplasty and jejunoileal shunting) have

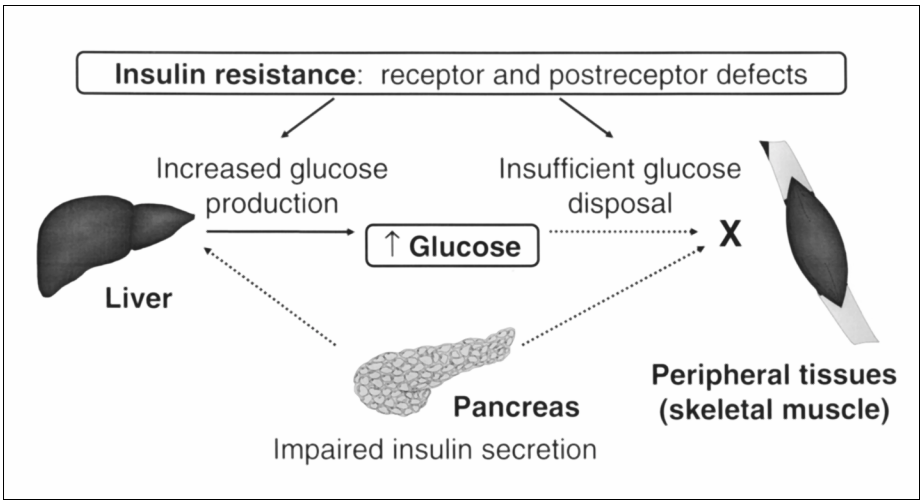

Figure 1
Causes of hyperglycemia in type 2 diabetes (19)

Slika 1.
Uzroci hiperglikemije kod tip 2 šećerne bolesti (19)

been used in very small number of pediatric patients. Accordingly, these therapeutic modalities should be considered only in a morbid obesity with significant complications (6).

Obesity and Insulin Resistance

Glucose homeostasis is regulated by a fine balance between insulin secretion by pancreatic β-cell and insulin action on insulin sensitive tissues. Insulin resistance usually occurs when a given amount of insulin fails to stimulate glucose uptake by a muscle than it does in an "insulin sensitive" individual. Majority of obese individuals develop insulin resistance and impaired glucose tolerance that eventually leads to type 2 DM. However, insulin resistance alone is not sufficient to develop full-blown hyperglycemia. Insulin resistance usually leads to hyperinsulinemia and increased free fatty acid release (FFA) with normal glucose levels. Significant hyperglycemia develops when insulin secretory response is not sufficient to overcome the defect of insulin action on muscle. In addition elevated plasma FFA levels inhibit insulin stimulated glucose uptake by muscle and stimulate hepatic glucose production. Hyperglycemia occurs in type 2 DM when liver continues to secrete normal amounts of glucose into the enlarged plasma glucose pool of insulin resistant individuals (Fig. 1) (9).

Insulin secretory response by pancreatic β-cell eventually diminishes and β-cell failure occurs. Both insulin resistance and β-cell failure coexist in essentially all patients with type 2 DM (Fig. 2).

The initial problem in children with type 2 DM is insulin resistance. Several factors influence insulin sensitivity:

- Age: insulin sensitivity in puberty is generally about 30% lower than in prepubertal children and adults, most likely because of increased production of growth hormone;
- Gender: girls have been shown to be more insulin resistant than boys when data are controlled for BMI;
- Ethnicity: insulin sensitivity has been shown to be about 35-40% lower in African-American children and adolescents than in Caucasians when matched for age, sex, and weight; and
- Body composition: the slope of the decline in insulin sensitivity gets steeper as the percentage of visceral fat increases, compared with subcutaneous fat (10).

TYPE 2 DIABETES MELLITUS IN YOUTH

In the past type 2 DM has not been considered a pediatric disease. Currently there is an alarming increase of type 2 DM among children. It is following the increased incidence of obesity among children and adolescents. It occurs in all socio-economic and ethnic groups although incidence is higher in children from minority populations such as African-American, Hispanic American and Native American. The incidence ranges from 8-45% of new diabetes case depending on location and patient population (11).

In 15-19 year-old Pima Indians in Arizona, USA the prevalence of type 2 DM rose from 24 to 38 per 1000 boys (58% increase) and from 27 to 53 per 1000 girls (96% increase) between the periods of 1967-1976 and 1987-1996 (12). Over a period of one decade the incidence of diagnosed type 2 DM had risen 10-fold from 0.7 per 100.000 to 7.2 per 100.000 cases in a 10-19 year-old

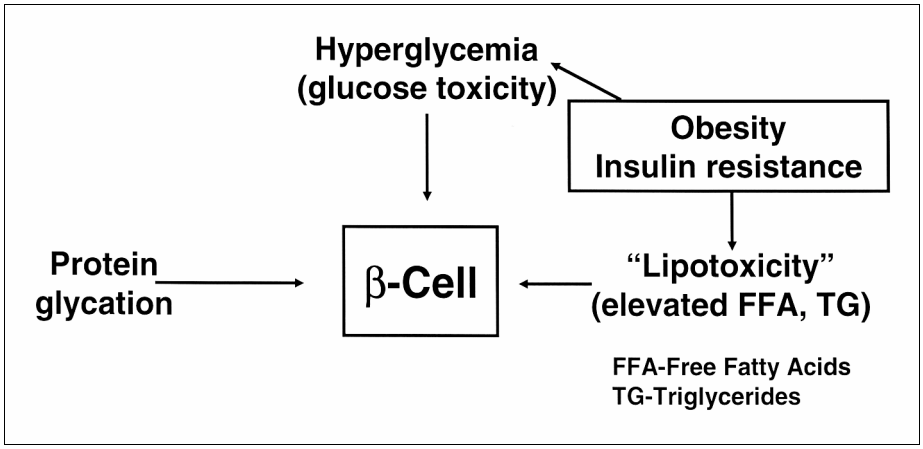

Figure 2
Multiple factors may drive progressive decline of β-cell function (19)

Slika 2.
Više čimbenika vode progresivnom zatajenju beta stanične funkcije(19)

Table 1
Characteristics of diabetes seen in children and adolescents

Tablica 1.
Obilježja šećerne bolesti u djece i adolescenata

	T1DM	T2DM	MODY
Gender	F=M	F>M	F=M
Age at Dx	Troughout childhood	Puberty	Puberty
Ethnic group	All	African-American, Hispanic, Native American	Caucasian
Genetics	Polygenic	Polygenic	Autosomal Dominant
Autoimmunity	Common	Uncommon	No
Obesity	Uncommon	Common	Uncommon
Acanthosis Nigricans	No	Yes	No
F HX	Infrequent	Frequent	Frequent
Insulin sensitivity	Normal	Decreased	Normal
Insulin dependence	Lifelong	Episodic	No

African-American and white children referred to a major pediatric center in Cincinnati, Ohio, USA (13).

In spite of such a disturbing trend data on type 2 DM in children and adolescents are still limited.

In addition to obesity as a risk factor for the development of type 2 DM, individuals who were born with intrauterine growth retardation have increased risk of insulin resistance and of type 2 DM as young adults (14,15).

Clinical characteristics and presentation

Most of youngsters with type 2 DM are obese, and belong to minority populations. In addition they have a strong family history of type 2 DM in first-and second-degree relatives, have some elements of syndrome X, have some degree of acanthosis nigricans and typically present at the time of puberty. There is female predominance with 4-6 female patients for every male patient affected (16).

Children and adolescents with type 2 DM could preset with a wide spectrum of symptoms. Clinical presentation could range from: an asymptomatic child with the incidental diagnosis on routine medical check up and findings of glycosuria; adolescent female with complains of chronic vaginal candidiasis; to the patient who presents with classical symptoms of diabetes with polyuria, polydipsia and weight loss. Weight loss could be the only presenting symptom and is frequently overlooked in otherwise obese individual. Presentation in ketoacidosis is uncommon and less severe comparing to type 1 DM (17).

Distinction from type 1 DM and other forms of diabetes is often not possible immediately at the time of diagnosis. Usually it will take few months before insulin requirements start declining (Table 1).

Biochemical profile shows less severe impairment in type 2 DM comparing to type 1 DM. Plasma glucose levels are less elevated, ketones are less frequently present, and ketoacidosis is infrequent. In contrast, C-peptide and insulin levels are often very elevated and autoimmune antibodies are not present.

Acanthosis nigricans of various degrees is almost pathognomonic for insulin resistance and type 2 DM in youth. It is usually noticed easily in individuals with darker skin but it might be difficult to notice in fair skin individuals (Fig. 3).

Management of Type 2 Diabetes Mellitus

The goal of therapy of type 2 DM in youth is to achieve appropriate glycemic control and to prevent microvascular and macrovascular complications. Chronic

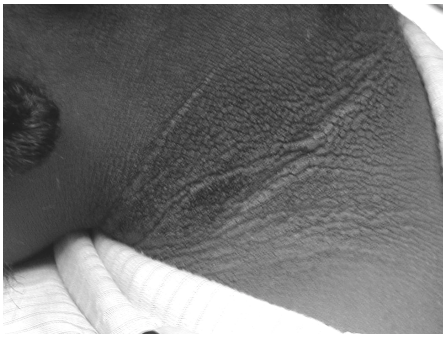

Figure 3
Acanthosis Nigricans on the neck

Slika 3.
Acanthosis Nigricans na vratu

complications could potentially occur at significantly younger age if individuals are diagnosed with type 2 DM during the childhood or adolescence. This poses a potentially significant problem in medical care expenses and the quality of life of those patients. Therefore every effort should be made to diagnose these patients in a timely fashion and treat them to avoid development of serious chronic complications like retinopathy, nephropathy and neuropathy. A variety of oral glucose lowering agents is available for the treatment of adults with type 2 DM (Fig. 4).

They all vary in their capacity to lower the HgbA1C and when used in a combination have additive effect in improving metabolic control (10). Only metformin has been approved for use in children and adolescents with type 2 DM in the USA. Other oral agents are used, but our knowledge of their value is limited by a lack of data on their safety and efficacy in children (Table 2) (18).

Treatment

Pharmacological therapy is directed toward decreasing insulin resistance, increasing insulin secretion or slowing postprandial glucose absorption.

Biguanides-Metformin

Biguanides such as metformin have unique mechanism of action. Metformin decreases blood glucose levels by acting on insulin target cells in the liver, muscle and fat. Hepatic glucose production is reduced due to decreased gluconeogenesis. Insulin-stimulated glucose up-

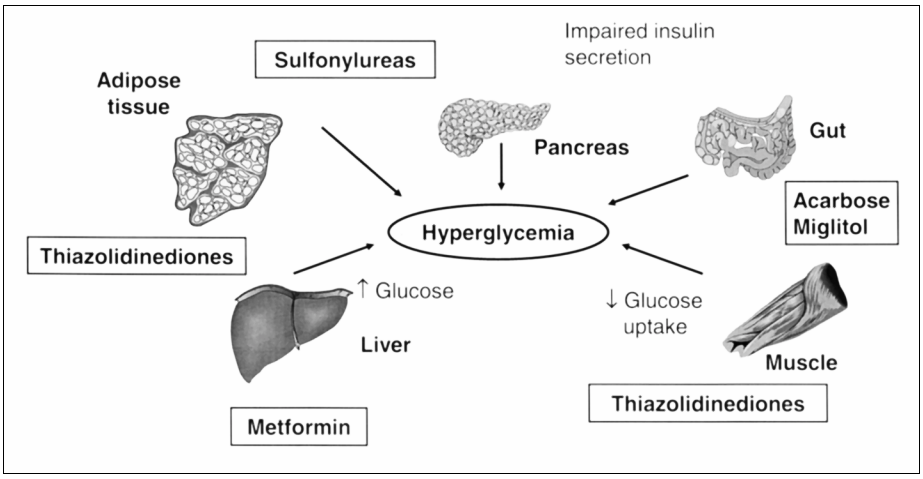

Figure 4
Oral therapy for type 2 diabetes: sites of action (19)

Slika 4.
Oralna terapija u tip 2 šećernoj bolesti: mjesta djelovanja (19)

take in peripheral tissues, particularly muscle, contributes to the decrease in blood glucose levels. Metformin rarely causes hypoglycemia. Weight gain is limited and weight loss usually occurs.

Long-term use of metformin could reduce plasma HgbA1C by 1-2%. It also decreases low-density lipoprotein (LDL)-cholesterol and triglycerides levels. It could normalize ovulatory abnormality in girls with PCOS. The side effects with metformin therapy include gastrointestinal problems such as abdominal pain, diarrhea and nausea. They could occur in as many as 50% of patients. Metformin is not tolerated in about 4% of patients. The risk of lactic acidosis does not appear to be the problem in young individuals. Metformin is contraindicated in patients with impaired renal function, hepatic disease or congestive heart failure. It should be temporarily discontinued before the administration of radiographic materials. Twice a daily dosing may affect compliance with the administration of the drug in some patients (10, 19).

Thiazolidinediones

Thiazolidinediones (TZD) bind to nuclear proteins activating peroxisome proliferator activator receptors (PPAR), which are orphan steroid receptors found primarily in adipocytes. The result of binding is increased formation of the proteins involved in the nuclear-based actions of insulin, including cell growth, and adipose cell differentiation, the regulation of insulin receptor activity and glucose transport into the cell. These actions increase insulin sensitivity in the liver, muscle and adipose tissue and decrease hepatic glucose output. Glycemic control is achieved without hypoglycemia. Thiazolidinediones have positive effect on the lipid profile. Recent studies indicate that they might cause preservation of β-cell function and may have protective renal effects. They are safe to use in renal insufficiency. They reduce intrahepatic and visceral amount of fat but increase subcutaneous fat and may attribute to weight gain in some patients. Studies of long-term therapy with thiazolidinediones in adults reduced HgbA1C by 0.5-1.3%. Thiazolidinediones have delayed onset of action and it might take a couple of weeks before full effect is achieved. They could cause fluid retention and formation of edema. They could cause elevations of liver enzymes and monitoring of liver function is mandatory. Pediatric clinical trials are ongoing worldwide (10, 19).

Combination therapy has been used in adults and might offer some benefits for pediatric population as well. Advantages of metformin and thiazolidinediones combination therapy are numerous: reduced insulin resistance; cardiovascular protection; potential preservation of β-cells; minimal hypoglycemia and less weight gain (19).

Insulin Secretagogues-Sulfonylureas

Sulfonylureas (SU) increase insulin secretion and are useful when there is partial β-cell failure. They have high initial response rate and could be administered once a day. They have no effect on insulin sensitivity and no effect on vascular dysfunction. One of the major side effects is hypoglycemia and that makes them unattractive for the use in pediatric population. They may exacerbate visceral and subcutaneous fat accumulation and weight gain. They should be used with caution in patients with renal and hepatic dysfunction (10, 19).

α-Glucosidase inhibitors

α-Glucosidase (α-Gl) inhibitors such as acarbose, reduce the absorption of carbohydrates in the upper small in-

Table 2
Metabolic effects of oral hypoglycemic agents in monotherapy

Tablica 2.
Metabolička djelovanja oralnih hipoglikemijskih lijekova u monoterapijskom pristupu

	TZD	Metformin	SU	α-GI
Weight	↑	↓	↑	↔
LDL	↑	+/– or ↓	↔	↔
HDL	↑↑	+/– or ↑	↔	↔
Triglicerides	↓ or ↔	↓	↔	↔
FFA	↓↓↓	↓↓	↓	↔
Insulin Resistance	↓↓	↓	↔	↔
Hypertension	↓	↔	↔	↔

HDL=High Density Lipoproteins; LDL=Low Density Lipoproteins; FFA=Free Fatty Acids
TZD=Thiazolidinediones; SU=Sulfonylureas; α-Gl=α-Glucosidase inhibitor

testine by inhibiting the breakdown of oligosaccharides and delaying the absorption in the lower small intestine. This delay reduces the rise of postprandial plasma glucose. Flatulence is a major side effect which makes it unattractive and for the use in most children and adolescents (10).

Treatment guidelines

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive treatment of adults with type 2 DM improved metabolic control and decreased the risk of microvascular disease (20). There is the evidence that microvascular complication of DM could be extraordinarily aggressive in youth with type 2 DM. In Japanese children with type 2 DM the incipient retinopathy was detected by fluorescin angiography in 36% of patients at the time of diagnosis and in 39% at 2 year's follow up (21).

In Pima Indian children studied at the time of diagnosis 7% had hypercholesterolemia, 18% had hypertension and 22% had microalbuminuria. In ten year follow up study 60% of these patients had microalbuminuria, and 17% had macroalbuminuria (22).

The goals of therapy for children and adolescents with type 2 DM include achieving and maintaining HgbA1C levels at 7% or less, maintaining fasting plasma glucose levels less than 6 mmol/l (120 mg/dl). Attaining healthy weight is "conditio sine qua non" when managing youth with type 2 DM. The recommendations for weight management are the same as in obesity and are described above.

Initial management with diet, exercise and weight management alone could be sufficient for certain number of patients but majority of them will need to start oral hypoglycemic agents. Insulin therapy may be indicated initially in addition to oral hypoglycemic agent in some patients in order to overcome the effects of glucosetoxicity and especially in patients with ketoacidosis. As metabolic control improves and weight decreases gradual decrease in dose and discontinuation of insulin is recommended to prevent further weight gain (10).

If monotherapy with metformin is not successful over a period of 3-6 months, sulfonylureas could be added to the regimen. Insulin is added if treatment goals are not achieved using oral agents. Clinical studies on the use of thiazolidinediones in pediatric population are under way. Until more definitive results are available it might be prudent to limit their use in children.

Treatment of co-morbidities

The major goal of the treatment of DM is to reduce the risk of microvascular and macrovascular complications. The coexistence of type 2 DM with obesity, hyperlipidemia and hypertension place these patients at greater risk of developing early cardiovascular disease. Therefore every effort should be made to keep lipid levels within the reference range. If initial diet management and weight loss do not improve the lipid profile in 2-3 months lipid lowering medications should be incorporated into the treatment regimen. The most commonly used lipid-lowering agents are statins.

Patients should be evaluated for the presence of microalbuminuria at the time of diagnosis and annually afterward. Blood pressure should be monitored regularly. If detected, hypertension and microalbuminuria should be treated aggressively with angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors may improve insulin sensitivity and may slow the progression of retinopathy. They reduce adverse cardiovascular outcomes among subjects at increased risk for cardiovascular disease (19). Annual eye exams by ophthalmologist are recommended in order to screen for retinopathy.

CONCLUSIONS

Current epidemics of obesity and type 2 DM in youth are worrisome. The prevention and treatment of obesity and type 2 DM in youth is a daunting challenge because of the enormous behavioral influence, difficulty in reversing obesity and typical nonadherence in this age group. The emerging epidemic of type 2 DM in children and adolescents presents a serious public health problem. The full effect of this epidemic will be felt as these children become adults and develop long-term complications of diabetes. Clinicians must make every effort to prevent type 2 DM in youth by altering those factors that are modifiable in high-risk children.

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Sažetak

DIJABETES MELITUS TIPA 2 U DJECE: PRIČA KOJA POČINJE S PRETILOŠĆU

J. Popović

U prošlosti se tip 2 šećerna bolest (T2ŠB) smatrala oboljenjem odraslih i starijih debelih osoba. Danas uočavamo epidemiju T2ŠB kod mladih osoba a povezana je s široko rasprostranjenim povećanjem učestalosti debljine u djece. T2ŠB u ovoj životnoj grupi predstavlja izazov kliničarima i mora se razlikovati od tip 1 šećerne bolesti i staračke šećerne bolesti mladih ljudi (maturity-onset diabetes of young - MODY). Rizični čimbenici za nastup T2ŠB kod pedijatrijskih pacijenata su: 1. debljina i povećanje indeksa tjelesne mase; 2. prisustvo T2ŠB unutar obitelji; 3. pripadnost određenoj etničkoj grupi; 4. pubertet; 5. ženski spol; i 6. znakovi sindroma X. Povezanost navedenih čimbenika je inzulinska rezistencija (IR) koja igra središnju ulogu u patofiziologiji T2ŠB. IR kao i beta stanično zatajenje su prisutni u potpuno razvijenom stanju šećerne bolesti. Inzulin i metformin su poboljšali farmakološki terapijski pristup T2ŠB kod djece. Koriste se i drugi peroralni lijekovi ali naše znanje o korisnosti istih je ograničeno u nedostatku podataka o sigurnosti i efikasnosti u djece. Prevencija debljine je temelj prevencije T2ŠB u mladih osoba.

Deskriptori: TIP 2 ŠEĆERNA BOLEST; DJECA; ADOLESCENTI; DEBLJINA; INZULINSKA REZISTENCIJA