

# TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS - AN UPDATE -

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## REZUMAT

Până nu demult diabetul zaharat tip 2 era considerat o boală afectând exclusiv vârsta adultă, fără nici o legătură cu copilăria sau adolescența. Această opinie suferă în prezent schimbări majore, deoarece, pe lângă creșterea prevalenței bolii la adult, se înregistrează în ultimii ani și o creștere a numărului de cazuri la copii, în special în anumite grupuri etnice. Mai mult, datorită epidemiei de obezitate la copii și tineri, inclusiv la cei de rasă albă, există îngrijorări majore privind creșterea incidenței diabetului zaharat tip 2 și în afara grupelor de risc obișnuite. Acest articol reprezintă o punere la punct a criteriilor de diagnostic, factorilor predispozanți și a tratamentului diabetului zaharat de tip 2 la copii și adolescenți.

**Cuvinte cheie:** diabet zaharat tip 2, copii, adolescenți, criterii de diagnostic, tratament

## ABSTRACT

It was not so long ago that type 2 diabetes mellitus was considered an exclusively adult disease, with no connection whatsoever to childhood and adolescence. This view is on the verge of changing fundamentally since, beside the rise in incidence in adult population, in the recent years type 2 diabetes is diagnosed more and more frequently in children, especially in some ethnic groups. Furthermore, since we are actually facing a constant growth in obesity prevalence in Caucasian children and adolescents, chances are that type 2 diabetes will be more frequently found in other populations, outside its usual target group. The present article is a review of current knowledge regarding diagnosis criteria, predisposing factors and clinical management of type 2 diabetes in children.

**Keywords:** type 2 diabetes, children, adolescents, diagnosis criteria, treatment

## INTRODUCTION

It was not so long ago that type 2 diabetes mellitus was considered an exclusively adult disease, with no connection whatsoever to childhood and adolescence. This view is on the verge of changing fundamentally since, beside the rise in incidence in adult population in the recent years, type 2 diabetes is diagnosed more and more frequently in children, especially in some ethnic groups.<sup>1,2</sup> In the past 10 years, in USA, the pediatric and adolescent population with type 2 diabetes has increased 10-fold, not to mention the fact it is highly probable that the number of yet-undiagnosed cases to be twice as much the number of known cases due to lack of disease awareness.<sup>3-9</sup>

Furthermore, although the prevalence of adolescent type 2 diabetes is known to be more prevalent in certain ethnic groups and also better documented in these groups (African Americans, North-American Indians, Hispanics),<sup>10-13</sup> we are actually facing a constant growth of diabetes in preadolescents. There is also growing concerns that, given the present obesity epidemics in youth, type 2 diabetes mellitus will also become more frequent in other populations, outside its usual target group.<sup>14-17</sup>

Type 2 diabetes is a multifaceted disease, its epidemiology and pathogenesis are two of its most extensively discussed issues. Main features of type 2 diabetes, as already established in adults, are: concomitant presence of insulin resistance and beta-cell failure in all patients, although in varying proportions from patient to patient, progressive nature of the disease, paralleling the decline in beta-cell function, and HbA<sub>1c</sub> lowering is associated with a decrease in the risk for developing and/or progression of microvascular complications.<sup>2</sup> Insulin secretion and sensitivity have been studied extensively in children and adolescents, in various ethnic groups and an already vast experience is currently available.<sup>5,18-21</sup>

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The importance of this type of diabetes in children and young people is paramount given the fact it is accompanied by other cardiovascular risk factors (hypercholesterolemia, hypertension, microalbuminuria) and frequently leads to complications 10 years after diagnosis or even earlier, since a large number of cases go undetected for a considerable length of time.<sup>22-25</sup>

There are multiple aspects of type 2 diabetes in teenagers that await clarification but until this is accomplished, we need to focus on improvement in diagnosis criteria and on optimisation of therapy.

## DIAGNOSIS

According to ADA Guidelines, criteria for diagnosis of diabetes and other alterations of glucose metabolism are the same as in adults and are presented in Table 1.<sup>26</sup>

**Laboratory tests** used for diagnosis of diabetes are:

- Plasma glucose: fasting or random measurement;
- Two-hour plasma glucose during oral glucose tolerance test (OGTT) with 75 g of glucose;
- Glycosuria is a screening method used in populational studies for detection of type 2 diabetes, despite its accepted limitations. Its presence requires a confirmatory measurement of blood glucose.

**Table 1.** Criteria for diagnosis of DM<sup>26</sup>

	Normoglycemia	IFG	IGT	Diabetes mellitus*
FPG	< 100 mg/dl	≥100 mg/dl and < 126 mg/dl		≥ 126 mg/dl
2h-PG during OGTT	< 140 mg/dl		≥140 mg/dl and < 200 mg/dl	≥ 200 mg/dl
Symptoms	-	-	-	symptoms of diabetes AND casual plasma glucose concentration ≥ 200 mg/dl

FPG= fasting plasma glucose; PG= plasma glucose; IFG= impaired fasting glucose; IGT= impaired glucose tolerance; OGTT= oral glucose tolerance test (glucose load with 75 g glucose dissolved in water)

\* In the absence of unequivocal hyperglycemia, a diagnosis of diabetes must be confirmed on a subsequent day, by measuring FPG, 2-h PG or random plasma glucose

More rarely in clinical practice, other laboratory tests are used:

- *Insulinemia* is usually above normal at diagnosis<sup>27,28</sup> and may be of help in establishing a definite diagnosis of type 2 diabetes. However, low insulin levels do not exclude type 2 diabetes.

- *C peptide* is most often increased, in contrast to type 1 diabetes, when it is decreased.

The latter two measurements are not routinely used for differentiating type 1 from type 2 diabetes in children.

Measurement of *specific antibodies against beta-*

*cell antigens (ICA-islet cell antibodies, GADA- glutamic acid decarboxylase antibodies, IA2, IA-insulin antibodies)* for diagnosis is performed solely for research purposes, due to its limited availability and high costs. However, the presence of diabetes antibodies will certainly transfer the patient in type 1 diabetes group.

## CLINICAL PRESENTATION

According to Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, type 2 diabetes is diagnosed in individuals who:<sup>29</sup>

- have insulin resistance and relative (rather than absolute) insulin deficiency;
- do not require insulin therapy for survival and
- do not have autoimmune destruction of beta-cells or other cause for diabetes (genetic defects, diseases of the exocrine pancreas, drugs).

However, not uncommonly, it is a difficult task, even for skilled clinicians experienced in treating children with type 1 diabetes, to distinguish between the former and type 2 diabetes, as there is a certain overlap between the two regarding the clinical features. In practice, one quarter to one third of children with type 2 diabetes present with inaugural ketoacidosis and subsequently manifest type 2 signs and symptoms; on the other hand, there are patients labeled at onset as

type 2 and eventually they behave as type 1 diabetes.

A synthesis of the main clinical features of type 2 diabetes in children and adolescents is presented below.

### Symptoms

The initial clinical presentation in youngsters with type 2 diabetes can be extremely variable, several situations being possible:<sup>1-3,30,31</sup>

a) ketoacidosis of variable severity or non-ketotic hyperglycemic hyperosmotic crisis, as a result of secretory failure of beta cells; this modality of onset does not completely rule out type 2 diabetes;

b) severe signs of insulin deficit: polyuria,

polyphagia, polydipsia and weight loss, with or without ketonuria, also suggesting type 1 diabetes;

c) moderate hyperglycemic signs: polyuria, nicturia, but without weight loss;

d) asymptomatic; the diagnosis is made by chance or during populational studies initiated for the same purpose;

e) signs of chronic diabetic complications.

Lack of ketosis at onset and family history of diabetes are highly suggestive of type 2 diabetes.<sup>4,10</sup>

#### **Race and ethnic group**

Individuals with the highest risk for type 2 diabetes belong to the Native American, Afro-american, American Hispanic and Asian populations (Bangladesh, Japan).<sup>10-13</sup> Caucasians are less afflicted in the present because the insulin resistance is less severe in youngsters from this population. However, in offsprings of mixed origin it is important to establish whether one of the parent belongs to the high risk group.<sup>17-21</sup>

#### **Age at diagnosis**

The majority of type 2 diabetes in youngsters is diagnosed at the age of 10 or greater, with a peak in incidence at puberty (between 12 and 14 years), and a constant ascending trend towards the age of 20. Of course, younger ages can also be involved, however less often.

Puberty (especially Tanner stages II, III and IV) favors the onset of type 2 diabetes since it is accompanied by pronounced insulin resistance, hyperinsulinemia both fasting and after oral glucose load,<sup>20</sup> processes that will diminish after puberty. Among other causes, insulin resistance is the result to the hypersecretion of growth hormone, characteristic for the age, an essential feature that explains the age at onset, situated around puberty.

#### **Obesity**

It has been demonstrated that overweight and obesity are associated very often with type 2 diabetes in children and young people, at all ages and in all high risk ethnic groups. In Pima Indians obesity is an early feature, especially in children born from diabetic mothers. Beside the contribution of diabetic intrauterine environment, another factor contributing to the development of obesity is artificial feeding initiated soon after birth, in the first days and weeks of life, before the age of 2 months.<sup>32</sup>

The prevalence of obesity among Pima children (aged between 0 and 19 years) has increased in the last decade and that could explain the rise in diabetes cases in encountered in this population. Sigal et al. find a rise in prevalence of obesity in US adolescents (age between 12 and 19 years) from 15% in 1980 to 21% in 1990, similar changes have been noted in US

Mexicans and black population.<sup>1</sup>

Similarly to adult population, the predisposition of children and adolescents to become obese is most probably unmasked by changes in life style such as the adoption of modern eating habits (sugar-containing drinks, fast-food) with high-caloric, high-sugar and high-fat diets and the decrease in the level of exercise (sitting for hours in front of TV or computer).

Total fat mass directly correlates with BMI and is responsible for approximately 55% of variations in insulin sensitivity.<sup>21</sup> Obese children are hyperinsulinemic but in the same time their insulin-dependent glucose disposal is 40 percent lower, compared to age-matched normal weight subjects. Furthermore, visceral fat in obese adolescents correlates with basal and glucose-stimulated hyperinsulinemia, and is inversely related with insulin sensitivity.

The more severe the obesity, the higher the risk to develop type 2 diabetes. Body Mass Index (BMI) reported to population-specific standardized curves for age and sex, as well as waist-to-hip ratio are useful tools for assessing the degree of obesity in clinical settings. A BMI over 85<sup>th</sup> percentile (obesity) or over 95<sup>th</sup> percentile (morbid obesity) results in a high risk for type 2 diabetes. If weight excess is expressed as percent from the ideal, type 2 diabetes is frequent in subjects more than 120 percent of ideal weight.<sup>2,3</sup>

#### **Family history of diabetes**

Most subjects (74 to 100%) diagnosed with type 2 diabetes in the first three decades of life have a family history positive for diabetes, thus indicating the importance of genetic predisposition.<sup>2,14</sup>

The prevalence of diabetes in Pima Indians is significantly higher in children born from mothers with diabetes; even more, all diabetic subjects younger than 25 had at least one diabetic parent, supporting the hypothesis of the autosomal dominant transmission pattern. However, diabetes is more frequent in children born in mothers with diabetes compared to children born from diabetic fathers, and compared to those whose mothers developed diabetes after the pregnancy or are non-diabetic.<sup>11</sup>

In Mexican-Americans, family history of diabetes is present in 87% of the cases, at least one generation is involved in 80% of the subjects, three or more generations in 47%. In Afro-American children, hyperinsulinemia and the decrease in insulin sensitivity are more severe in those who have a family history of type 2 diabetes.<sup>5,18,19</sup>

Therefore it is logical to assume that family history of diabetes is an important risk factor directly involved in diabetogenesis and correlated to insulin resistance.

The risk of a child to become diabetic is

proportional with the number of generations afflicted.

### **Acanthosis nigricans**

Acanthosis nigricans is a velvety hyperpigmentation of the skin, most often located on the back of the neck, axillae, knuckles and flexion folds. It is a frequent clinical sign, present in 60 to 90 percent of children with type 2 diabetes. In all populations, acanthosis is associated with obesity. The common link between acanthosis and obesity is represented by insulin resistance.

Type 2 diabetes is six times more frequent in African-Americans exhibiting acanthosis, compared to those without it.

It must be emphasized that inexperienced doctors can easily overlook grade 1 and 2 acanthosis, regardless of its location (back of the neck, axillae, interphalangeal joints, elbows and knees).<sup>33</sup>

### **Gender**

Type 2 diabetes predominantly affects female subjects, a fact confirmed by the majority of studies carried out in USA or elsewhere<sup>12</sup>

For example, all eight published cases of type 2

diabetes in children in UK were non-Caucasian females (Pakistani, Indian, Arabs).<sup>8</sup>

**Other signs of insulin resistance**, often seen in children with type 2 diabetes, are represented by: polycystic ovary syndrome, arterial hypertension and lipid abnormalities.<sup>2,4</sup>

## **DIFFERENTIAL DIAGNOSIS BETWEEN TYPE 1 AND 2 DIABETES IN YOUTH**

Type 1 and 2 diabetes in children are usually differentiated using clinical criteria (Table 2).<sup>1,2,31,34</sup>

## **SCREENING FOR TYPE 2 DIABETES IN YOUTH**

Since more research is needed in the area and large populational studies are lacking, screening guidelines for type 2 diabetes in children have been developed based on the clinical features of the patients. Current screening recommendations are presented in Table 3.<sup>2,26,27</sup>

**Table 2.** Clinical criteria for differentiation of type 1 and 2 diabetes in children

	<b>Type 1 diabetes</b>	<b>Type 2 diabetes</b>
Ethnic groups with highest incidence	Caucasians	Higher incidence in minority groups (African Americans, Native Americans)
Age at onset	Any age	Over 6 and usually over 9 years
Weight at onset	Usually underweight	Approximately 95 percent obese
Presentation	Ketoacidosis	Ketoacidosis can occur occasionally but is not usually present
	Fatigue and lack of energy	Sometimes fatigue and lack of energy
	Polydipsia and polyuria are common	Often asymptomatic (40 percent); Polyuria and/or polydipsia; Hypertension occurs in 30%
Familial	Not usually (10%)	High familial incidence (74-100%)
Acanthosis nigricans	Never	Usual onset at 10 to 12 years of age
Dependence on insulin	Lifelong	Episodic
Autoimmune markers	Usually present	Usually absent

**Table 3.** Which children should be screened for Type 2 diabetes?

<b>1. Weight</b>	
a. Children whose body mass index (BMI) is greater than the 85 <sup>th</sup> percentile for age and sex	
b. Children whose weight is greater than 120% of ideal for height	
	+
<b>2. Any two following risk factors are present</b>	
a. Age	
- Children older than 10 years of age	
- At the onset of puberty or at puberty, if it occurs earlier	
b. Family history of Type 2 diabetes in a first or second degree relative	
c. Ethnic background of African-American, Hispanic, American Indian, Asian, or Pacific Islands origin	
d. Signs of insulin resistance	
e. Presence of conditions associated with insulin resistance: e.g., acanthosis nigricans, polycystic ovary syndrome, high blood pressure, fat disorders	
<b>3. When should screening be performed?</b>	
Every two years	

### Methods of screening

- Measurement of fasting glycemia (after 8 or more hours of overnight fast) is the preferred method.
- OGTT is more expensive and is not routinely performed; its use is recommended when fasting blood glucose is normal but there is a strong clinical suspicion of type 2 diabetes.<sup>26</sup>
- Other investigations are reserved for special situations.

## TREATMENT OF TYPE 2 DIABETES IN YOUTH

**Treatment targets** are represented by fasting blood glucose less than 126 mg/dl, glycosylated hemoglobin under 7%, as well as by normalization of blood pressure and plasma lipid profile, frequently associated with type 2 diabetes. Achieving these targets will obviously reduce the risk of microangiopathic complications, and less the risk of macrovascular disease.<sup>26</sup>

**Initial treatment** greatly depends on the modality of onset.

Subjects presenting with **diabetic ketoacidosis or non-ketotic hyperglycemic hyperosmotic crisis** are referred to specialist and admitted in the hospital, where they are administered the classic treatment. Special consideration should be given to cerebral edema present at admission or developed during therapy.

**Severe clinical presentation** with polyuria, polydipsia, weight loss benefits from diet and insulin, followed by changing on oral medication, if the clinical evolution allows it.

Many young patients present with hyperinsulinemia, therefore exogenous insulin does not seem indicated. However, the correction of the relative insulin deficit might be responsible for the beneficial effects of insulin therapy, because it decreases glucose toxicity. The beneficial effect is more obvious at onset, in the presence of acidosis or if ketone levels in plasma and urine are very high. Some diabetologists prefer to start insulin and then to taper the doses, while introducing an oral agent, such as metformin, under the strict monitoring of glycemia and HbA<sub>1c</sub>. Once a regular program of exercise is started and the patient begins to lose weight, glucotoxicity is reduced and insulin requirement decreases.

According to current clinical experience, a preferred insulin regimen of the patient, family and doctor is represented by the administration of short-acting insulin analogues (lispro, aspart) before meals in association with an intermediate insulin at bedtime,

similar to multiple injections regimen in type 1 diabetes. There are many other possible combinations, such as the administration of two doses of intermediate insulin in the morning and in the evening. The insulin regimen should be established depending on pre- and post-prandial glucose values and adapted to individual circumstances. Recent studies suggest the use of short-acting insulin analogues before meals, in combination with a biguanide in the evening, to decrease the overnight hepatic gluconeogenesis. An alternative could be the injection of NPH in the evening, to prevent the dawn phenomenon, in combination with short-acting oral agents (meglitinides) for the control of post-prandial glycemic excursions.<sup>2,4,35,36</sup>

**Moderate or absent symptoms.** The therapeutic approach in these circumstances consists of:

**Life style intervention** is an important therapeutic mean and consists of a decrease in the caloric intake, introduction of regular aerobic exercise and a reduction in sedentary hours (less computer and TV time).<sup>36</sup>

In overweight or obese patients, *dietary counseling* and help towards achieving a slow but constant weight loss are key features of the treatment, with concomitant glucose monitoring. Successful dietary intervention is defined by a stop in weight gain, with a continuing growth in height, fasting blood glucose equal or less than 126 mg/dl ( $\leq 7$  mmol/l) and glycosylated hemoglobin of 7% or less.

Aerobic exercise, practiced on a daily basis, in association with a hypocaloric diet, is very useful in decreasing insulin resistance, but is often difficult for patients to adopt, especially if other family members are obese, overeating or sedentary. In these circumstances, efforts should be made to involve the entire family in the physical and dietary program.

Combining diet with physical exercise is effective in controlling blood pressure and glycemia, even if ideal weight is not always achieved.

### Pharmacological treatment

The most frequently used oral agent in children with type 2 diabetes is metformin, a biguanide that, beside decreasing insulin resistance, has other features that make it an advantageous choice: no risk of hypoglycemia, weight neutral (does not increase weight), decrease LDL cholesterol and triglycerides. Metformin is also effective in treating ovulatory anomalies in girls with PCOS, therefore reducing the risk of unwanted pregnancy.

A 16-week randomized clinical trial<sup>37</sup> that used metformin twice daily (total dose 1000 mg) vs. placebo, in 82 pediatric patients, aged between 10 and 16, with

type 2 diabetes, showed that metformin significantly improved glycemic control, with a decrease in blood glucose and in HbA<sub>1c</sub> (7.5% in metformin treated vs. 8.6% in placebo-treated). Apart from its effectiveness, metformin was also lacked severe side-effects, with a safety profile similar to adult population.

If monotherapy with metformin is not enough to reach optimal control after 3 to 6 months, some advocates the association of a sulfonylurea or repaglinide, while other prefer to start NPH insulin at bedtime, to reduce the hepatic glucose output. Sometimes, oral medication is completely abandoned in favor of insulin therapy.<sup>2,25,36</sup>

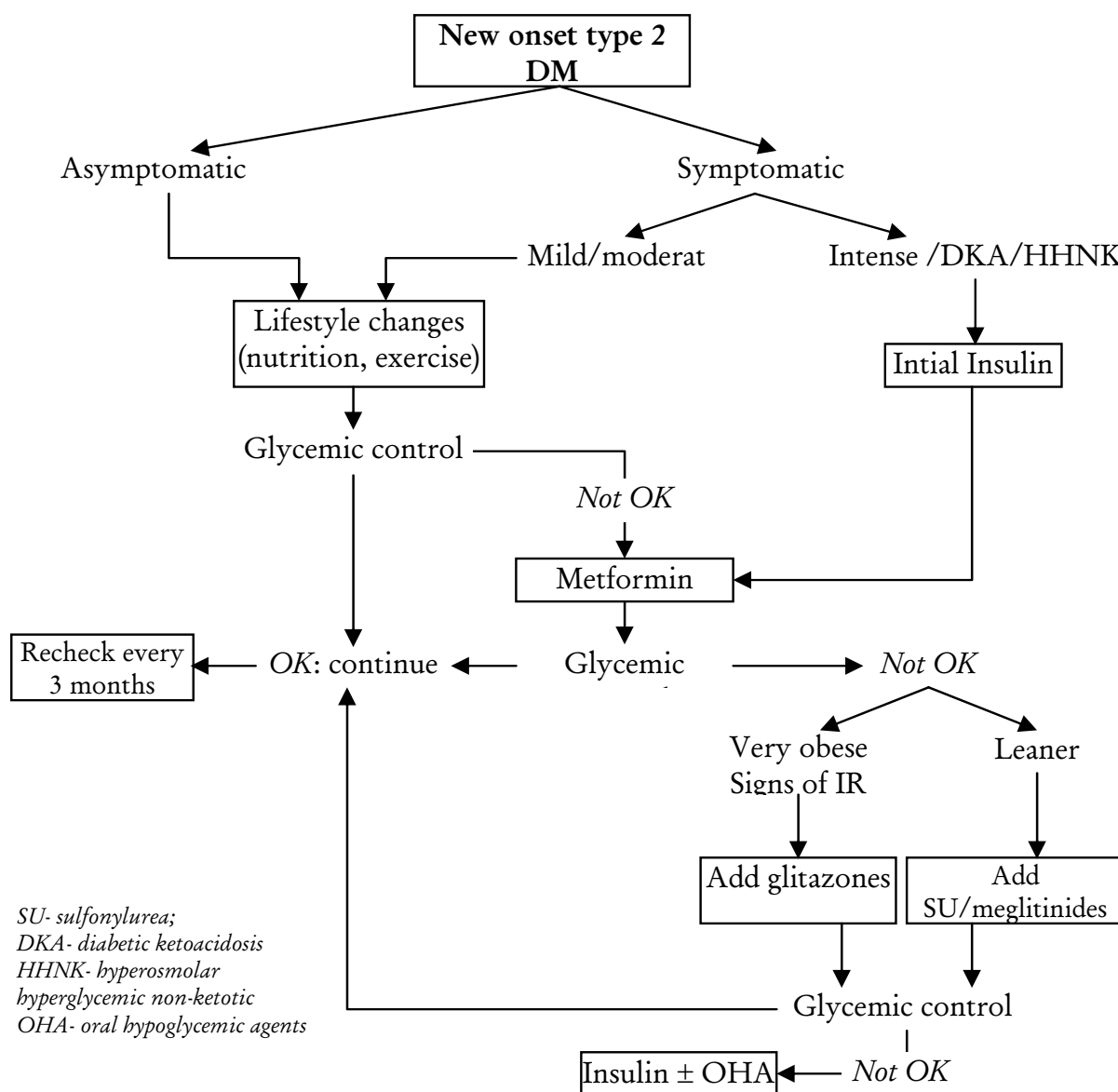
Oral antidiabetic drugs are contraindicated in pregnancy.

Figure 1 presents an algorithm for treating type 2 diabetes in children and adolescents.<sup>36</sup>

As mentioned above, type 2 diabetes mellitus is one of the disease states associated with the metabolic syndrome and children and adolescents make no exception. The other features which accompany it are often seen in association with diabetes and are addressed as comorbid conditions, most important being hypertension and dyslipidemia.<sup>22-24</sup>

If lifestyle measures fail to control blood pressure pharmacological treatment is also needed (angiotensin conversion enzyme inhibitors, alpha-blockers, long acting calcium blockers and low dose diuretics).<sup>36</sup>

Management of dyslipidemia in children is similar to adults and includes dietary changes and hypolipidemic drugs.<sup>22,24</sup> Treatment should start with diet and a goal of reducing LDL. Influencing dietary habits early may affect lifetime dietary choices. These recommendations are summarized in Table 4.<sup>36</sup>



**Figure 1.** Algorithm for treating type 2 diabetes in children and adolescents<sup>36</sup>

**Table 4.** Dietary recommendations

- 1.Reduce saturated fat intake to <7% of calories
- 2.Reduce dietary cholesterol intake to  $\approx$ 200mg/day
- 3.Decrease excess calories.
- 4.Add water soluble fiber to the diet.
- 5.Use stanol or sterol ester margarines.

If 6 weeks with the dietary modifications do not reduce LDL below 100 mg/dl, and if this adult target is to be used for children, pharmacotherapy may be utilized: resins, statins. Resins decrease cholesterol by binding to bile acids and thus inhibiting their reabsorption. Available formulations are: Colestipol, starting dose: 2 g/day, can be increased to a maximum dose of 16 grams per day; Cholestyramine 8 grams/day. Constipation, flatulence, and bloating are common side effects of the resins; as well as an increase in serum triglycerides, therefore are not indicated in hypertriglyceridemia is also present. Statins (e.g., Simvastatin, Atorvastatin) inhibit HMG-CoA reductase and *de novo* cholesterol production, up-regulating LDL receptors and increasing LDL clearance. Recommended dosages are those used in adults. Statins should not be used during pregnancy.

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## TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS - AN UPDATE -

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1. Main features of type 2 diabetes mellitus include all of the following except:
  - a. insulin resistance
  - b. absolute insulin deficiency
  - c. progressive nature of the disease
  - d. higher risk of complications with lower HbA<sub>1c</sub>
  - e. relative insulin deficiency
2. Criteria for diagnosing diabetes are:
  - a. fasting plasma glucose < 100 mg/dl
  - b. 2h-plasma glucose at TTGO > 200 mg/dl
  - c. fasting plasma glucose > 126 mg/dl
  - d. symptoms of diabetes + random plasma glucose > 200 mg/dl
  - e. presence of autoimmune markers against beta-cell antigens
3. Risk factors for type 2 diabetes in youth are:
  - a. underweight
  - b. overweight and obesity
  - c. particular ethnic background (African Americans, American Indians)
  - d. presence of acanthosis nigricans
  - e. family history of type 1 diabetes
4. Initial clinical presentation of type 2 diabetes in youth include:
  - a. ketoacidosis
  - b. asymptomatic
  - c. hyperglycemic signs (polyuria, polydipsia, weight loss)
  - d. hypertensive crisis
  - e. hypoglycemic coma
5. In patients presenting with ketoacidosis, main therapeutic mean is:
  - a. diet
  - b. physical exercise
  - c. oral antidiabetic agents
  - d. insulin
6. Signs of insulin resistance are all except:
  - a. polycystic ovary syndrome
  - b. acanthosis nigricans
  - c. low blood lipids
  - d. abdominal obesity
  - e. high blood pressure
7. Following concerning clinical features of type 2 diabetes in youth are true:
  - a. boys are more affected than girls
  - b. most frequently onset at puberty
  - c. higher incidence in certain racial groups
  - d. insulin is not needed for survival
  - e. family history of type 2 diabetes
8. Which drug has been shown in clinical studies to be effective and well tolerated in the treatment of children with type 2 diabetes mellitus:
  - a. a sulfonylurea
  - b. metformin
  - c. glitazones
  - d. resins
9. Which statements concerning the management of type 2 diabetes in children are true:
  - a. insulin is never needed for glycemic control
  - b. lifestyle intervention (diet, exercise) are effective measures as first line therapy in patients presenting with ketoacidosis
  - c. insulin can be discontinued once the acute decompensation has been overpassed, and replaced with oral drugs
  - d. if glycemic control is not achieved with monotherapy, a second antidiabetic medication can be added
  - e. concomitant treatment of hypertension and dyslipidemia is mandatory
10. Drugs used to treat dyslipidemia in children include:
  - a. ACE inhibitors
  - b. alfa-blockers
  - c. resins (Colestipol)
  - d. statins
  - e. long-acting calcium blockers

To complete the examination for CME evaluation turn the page for instructions and the response form.

Correct answers for CPhE: Particularities of pharmacotherapy during pregnancy. (TMJ 2004;2:201-7):  
1 - b; 2 - ce; 3 - abe; 4 - cd; 5 - ad; 6 - bd; 7 - cd; 8 - b; 9 - d; 10 - cd