Type 2 diabetes in children and adolescents: literature review

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Abstract

Objective: the objective of this manuscript was to perform a critical review of epidemiology, pathophysiology, diagnosis and treatment of T2DM in youth.

Sources of data: this review is based on the relevant literature published. The sources available for the authors were integrated with sources identified through Medline database. The key words used for searching were “Type 2 Diabetes in the Youth” in the last ten years.

Summary of the findings: the pathophysiology (altered beta-cell function and insulin resistance) of T2DM in youth is similar to adult’s pathophysiology. Familiar Type 2 diabetes history, presence of obesity, acanthosis nigricans, high fasting plasma C-peptide levels and absence of islet-cell auto-antibodies are important clues to diagnostic the T2DM in youth. Five to 25% of these patients can present ketosis at diagnosis. Insulin therapy can be discontinued during the evolution. Compliance to diet and an exercise program essential aspects of the treatment of adolescents.

Conclusion: as obesity in the young is currently increasing in several developed or developing countries, T2DM in the youth can be consider an emergent problem also in our population.


Introduction

During the first half of the twentieth century it was observed that diabetes mellitus in children and adolescents manifests in different ways. While the majority of patients present symptoms of polyuria, polydipsia, dehydration and ketosis at clinical onset, with rapid deterioration of clinical status requiring insulin use to reverse the trend, it was also observed that some children present an insidious form of the disease, although not always accompanied by ketosis. This group of children, which constitutes a minority of cases, during the initial phases of the disease, does not depend upon insulin therapy to survive.1

Later, primarily during the last three decades, research in the areas of genetics, immunology and metabolism were able to better individualize hyperglycemic symptoms in children and adolescents, revealing their great variety. In addition to classic type 1 diabetes, MODY (maturity onset diabetes of the young),2 diabetes mellitus type 2 (DM2) of the young and even rarer forms such as “atypical” diabetes,3 variants of the disease associated with mitochondrial DNA mutations4 and Wolfram syndrome,5 were defined.
An increase in the incidence of diabetes mellitus among children and adolescents is observed in many different communities. Efforts are being made at many levels with the objective of detecting factors responsible for the appearance of the disease within this age group that are susceptible to correction or intervention. In parallel with the ever greater number of cases, an increasing incidence of forms of the disease is observed, primarily in specific ethnic groups until then considered rare within this age group, as is the case of DM2.

In recent years a growing increase has been observed in the prevalence of DM2 among young people. In the past, this form corresponded to between 1-2% of juvenile diabetes cases. Currently it is observed that between 8 and 45% of new diabetes cases diagnosed within this age group in the United States, do not have a demonstrated autoimmune etiology.

This manuscript discusses the varying aspects of juvenile DM2.

Epidemiology

Diabetes Mellitus 2 was considered a rarity in adolescence until recently. However, in recent decades, in industrialized countries, many authors have been reporting a large increase in the incidence of diabetes in adolescents with similar characteristics to those of DM2 in adults.

The increase in the incidence of this pathology in young people was originally observed among certain ethnic minorities, such as the Pima Indians who inhabit the state of Arizona (USA). In this population a frequency of more than one percent of diabetic individuals was observed among those between 15 and 24 years old, the great majority of whom were not exogenous insulin dependent, presenting a significant association with obesity. The prevalence of this type of diabetes was 22.3/1000 for the age group 10 - 14 and 50.9/1000 in the age group 15 - 19. Later, elevated prevalence’s were described among native Canadian populations. Pinhas-Hamiel et al. studying urban adolescent populations, registered increases by a factor of ten in the incidence of this form of DM between 1982 and 1994. In the year 1994, DM2 already accounted for 33% of new diabetes cases diagnosed among individuals between 10 and 19 years old in the metropolitan region of Cincinnati (USA). In addition to indigenous populations, children and adolescents of Mexican (Mexican Americans) and African (African Americans) origins resident in America have shown a greater susceptibility to the disease than Caucasians. Sixth-nine to 75% of adolescents suffering from DM2 of the young are African Americans in the USA.

The increase in juvenile DM2 is not exclusive to North America. Among Japanese schoolchildren, the incidence has increased, in twenty years, from 0.2 to 7.6 per 100 thousand individuals. A study involving a sample of the Lebanese population revealed incidences of 19.6 and 35.3 per 100 thousand individuals (for males and females respectively). The studies show that the average age at diagnosis is between twelve and fourteen. The female sex, among children, adolescents and young adults, proved to be more susceptible to the risk of developing DM2 in practically all of the communities studied, with the exception of a group of individuals younger than 15 years of age pertaining to the Lebanese population in which both sexes were shown to have a similar level of prevalence.

The increase in the prevalence of obesity in adolescence recorded in recent years could explain to a great extent the increase of DM2 in young populations. Studies relating high rates of obesity in childhood and adolescence to sedentary lifestyles and changes in nutritional habits, frequently to diets with high calorie and fat contents. Further studies demonstrate that obesity in childhood and adolescence constitute an important risk factor for the development of plurimetabolic syndromes, associated with cardiovascular diseases on maturity.

Pathophysiology

Classic diabetes mellitus type 2 is characterized by a combination of resistance to the effect of insulin and the incapacity of beta cells to maintain an adequate level of insulin secretion.

Resistance to the action of insulin (IR) is an early and primary abnormality within the course of the disease. It is characterized by a decrease in the ability of insulin to stimulate the use of glucose by the muscles and by adipose tissue, where the suppression of lipase controlled by this hormone is compromised. The excessive supply of free fatty acids further alters the transportation of glucose in the skeletal muscles in addition to functioning as a potent insulin activity inhibitor. Free fatty acids can also interfere with the transendothelial transport of insulin.

Resistance to the action of insulin in the liver leads to an increase of hepatic glucose production. During the initial phase the increase of glycemia levels is compensated for by an increase in insulin secretion, but as the process persists for prolonged periods a glucotoxic effect is associated. A glucotoxic effect is defined as an increased resistance to the effects of insulin and a decrease in beta cell function due to chronic hyperglycemia.

Certain factors are related to the expression of IR, such as genetic and racial factors, puberty, obesity and birth weight. Insulin resistance may be genetically determined as was evident in the study performed by Eriksson et al. which found a decreased level of insulin activity and hyperinsulinemia among the first degree, non-diabetic relatives of DM2 patients.

The effect of race on IR is more complex and becomes confused to a certain extent with other variables such as
obesity, but its role becomes evident when the basal insulin of African American children is compared to that of Caucasians. Healthy African American adolescents have a 30% lower sensitivity to insulin and greater first and second phase insulin secretion levels than that of their Caucasian controls. Among African Americans, girls present an even lower sensitivity to insulin than boys, which would explain the high rates of DM 2 in African American adolescents, particularly girls.\textsuperscript{26}

The average age of young people at DM 2 diagnosis is approximately 13 years, which coincides with the middle of puberty.\textsuperscript{19} Studies of children using the euglycemic clamp technique demonstrate that puberty is associated with relative IR (a reduction of approximately 30% in insulin activity during puberty when compared with pre-pubescent children). This phenomenon is compensated for by an increase in insulin secretion, and does not result, under normal conditions, in significant glycemia alterations. The growth hormone (GH) and the type 1 insulin-like growth factor (IGF-1) appear to be, at least in part, responsible for the increased resistance to insulin observed during puberty.\textsuperscript{28,30} Growth hormone acts as a lipase stimulant, provoking an increase in free fatty acid oxidation, which results in a reduced sensitivity to the action of insulin.\textsuperscript{29} The effect of the androgenic action, which is characteristic of puberty, is the subject of discussion. Dihydroepiandrosterone sulfate (DHEAS) levels appear to be inversely related with a reduced peripheral glucose capture, however insulinemia and C-peptide reductions have not been observed to be associated to the increase in sexual hormones.\textsuperscript{28}

Obesity in childhood is associated with increased fasting insulin concentrations and an exaggerated insulin response to intravenous glucose.\textsuperscript{31,33} The presence of high levels of fasting insulin is predictive of obesity in adolescence. A study performed by our group on children and adolescents in greater São Paulo found evidence of enhanced resistance to insulin activity in overweight patients with family histories of type 2 diabetes, suggesting that within this age group the effects of insulin can be obstructed by obesity, as has been observed in adults,\textsuperscript{34} which is a condition of risk of diabetes. It the study referred to, criteria for obesity and overweight shared the same lifestyle as the subjects, characterized by high levels of fat consumption and were sedentary.\textsuperscript{26}

Another risk factor for the development of DM 2 is low birth weight. Phillips et al. observed that adults who were born with low weights had a sevenfold risk of developing glucose intolerance and DM 2.\textsuperscript{38} These studies suggest that inadequate intrauterine nutrition in creased the risk of developing IR during the individual’s life. Currently a number of different theories exist to explain this association.\textsuperscript{31}

Among the Pima Indians, both low and high birth weights are DM 2 risk factors. The relationship with high weight is illustrated by the exposure of the fetus to gestational diabetes. The elevated prevalence of DM 2 among the offspring of women who present diabetes during gestation suggests that an abnormal intrauterine environment is the factor most responsible for the high number of diabetes cases. Factors associated with the intrauterine environment, such as the concentration of glucose, amino acids, lipids and ketones among other substances, could exercise a direct effect on the fetus, increasing insulin secretion and perhaps leading to the development of IR in the child.\textsuperscript{39}

Clinical Status

The age of greatest incidence of DM 2 of the young is close to 13 years, related to stage III of the Tanner Classification.

Children with DM 2 are generally asymptomatic or have few symptoms for long periods, with 50% of them being referred to specialist services due to glycosuria or hyperglycemia found by a routine examination. Thirty percent of the patients present mild polyuria and polydipsia and discreet weight loss. Certain patients may present a history of vaginal monoliasis (candida).

Approximately 33% of patients present ketonuria at diagnosis and 5 - 25% may evolve to ketoacidosis. In these cases a diagnosis differentiating between types 1 and 2 DM can be made from the clinical history or the evolution of the disease, based on the extent to which the need for daily insulin diminishes more than expected during the habitual\textsuperscript{1,8,12,40}

Obesity, as has been shown, presents constantly with DM 2 of the young. Approximately 70 to 90% of these children are obese and 38% present morbid obesity. A study of adolescents with DM 2, within a population from Cincinnati, (USA)\textsuperscript{35} showed that the average corporeal mass index was 38 Kg/m\textsuperscript{2}. Obesity and family history appear to have a cumulative effect on the risk of developing the disease since the impact of obesity on DM 2 risk is greater among children with positive family histories.

Acanthosis nigricans (AN) which is present in almost 90% of these children is a cutaneous manifestation of IR, which consists of hyper pigmentation with thickening of the posterior regions of the neck, axilla and groin area, with a velvety aspect. Histologically it is characterized by papillomatosis and hyperkeratosis which is a darkening due
to the thickening of the superficial epithelium which contains keratin. There is hyperplasia of all elements of the dermis and epidermis which suggests stimulation by a local growth factor. Increased IGF-1 and epidermal growth factor (EGF) are implicated in this process.41

Lipid disorders characterized by increased total cholesterol and LDL cholesterol, as well as triglycerides and systemic arterial hypertension occur in children with DM 2 at a frequency of 6-15%.42

**Diagnosis**

In the majority of patients, DM 2 diagnosis can be made based on clinical presentations and the course the disease takes. DM 2 should be suspected, above all among obese adolescent Negroid patients, often with no clinical complaints, who have a family history of the disease and present hyperglycemia and/or glycosuria in a routine examination.

Individuals with MODY, should be distinguished from those with DM 2 of the young. With MODY family history is observed to be preeminent, involving three or more consecutive generations, which is compatible with a dominant autosomal pattern of hereditary transmission. The most common form of presentation among non-obese children or adolescents is mild and asymptomatic hyperglycemia. Some patients may only present discrete fasting hyperglycemia for years while others exhibit varying degrees of glucose intolerance for many years before the appearance of diabetes. It is estimated that variants of MODY correspond to between one and five percent of all DM forms in the industrialized nations.43

In a patient with abrupt onset diabetes the presence of obesity should be checked (Figure 1). A patient with acute onset diabetes, who is not obese and does not belong to a high-risk ethnic group is more likely to be a DM 1 carrier. When the patient is obese other tests may be necessary, such as fasting C-peptide measurement and occasionally anti beta cell auto-antibody assay. In the young suffering from DM 2, these auto-antibodies are not normally present and C-peptide levels are generally normal or elevated, although not so high as might be expected for the degree of hyperglycemia. C-peptide levels should be tested after compensating clinically with fasting glycemia close to 120 mg/dl, in order to rule out possible glucotoxic effects on the beta cells.

Katzef et al., analyzing C-peptide levels in two groups of children, one Pima Indians with DM 2 and the other Caucasians with DM 1, showed that urine or plasma testing for C-peptide was sufficient to discriminate between the two groups.44 The low values found for the Caucasian children reflect insulinopenia typical of DM 1, while the Pima Indians’ diabetes, even when of early onset, is not related to insulinopenia.44 Thus C-peptide values greater than 0.6 ng/ml (0.2 nmol/l) or, after overloading with oral Sustacal®, greater than 1.5 ng/ml (0.6 nmol/L) demonstrate significant insulin reserves.45

Positive tests for insulin auto-antibodies, glutamic acid decarboxylase (GAD) or tyrosine phosphatase (IA2) are present in 85-98% of autoimmune origin DM 1 patients. In obese patients with histories suggestive of DM 2, who develop ketoacidosis on diagnosis, the prevalence of auto-antibodies (ICA islet cell antibodies, anti-IA2 - GAD 65 auto-antibodies) is at most 15%.46,47

The frequency of beta cell auto-antibodies in healthy Caucasian children is between 1 and 4%, and as such the presence of auto-antibodies in isolation is not sufficient to rule out DM 2 of the young, or to confirm a diagnosis of DM 1.

A study evaluating a sample population from Greater Sao Paulo, found a frequency of 1.4% of positive anti-GAD test results in adolescents with no family history of either type 1 or 2 diabetes. Among first degree relatives of Brazilian DM 1 patients, positivity varies from 3.5% to 10.4% for anti-GAD and from 2.7% to 3.6% for anti-IA2.45,48 Within a group of adolescent relatives of DM2 patients no positivity was observed, whether for anti-GAD, or for anti-IA2.34

A diagnosis of childhood DM 2 should be made taking into consideration clinical criteria such as the age and sex of the patient, the presence of obesity and family history of DM 2. We currently have no data which would enable us to consider race as a risk factor due to the high level of miscegenation in Brazil.

After these criteria have been applied, doubtful cases, primarily those with initial ketoacidosis, should be submitted for an investigation of beta cell function by means of C-peptide level tests and autoimmune process marker detection through islet cell auto-antibody (anti-GAD, anti-IA2, ICA and anti-insulin) testing (Figure 1).

According to the American Diabetes Association Consensus screening for DM2 should be performed during childhood of all obese children (those with a CMI above the 85th percentile for age and sex, or whose weight is over 120% of the ideal for their stature) who present two or more of the following risk factors:

- family history of DM 2 in 1st or 2nd degree relatives;
- a high-risk ethnic group (American Indians, African Americans, Hispanics, Asians/inhabitants of the Pacific islands);
- symptoms of IR or conditions associated with IR (acanthosis nigricans, arterial hypertension, dislipidemia, polycystic ovary syndrome).

Screening should be performed every two years from the age of ten onwards preferably by means of fasting glycemia assay.12

Fasting glycemia levels, based on criteria currently adopted for the diagnosis of DM 2, are the same for both adults and children.1 Notwithstanding it is interesting to
report that classification into percentiles of fasting glycemia results obtained from a group of 305 normal children and adolescents revealed the following distribution: 5th percentile: 77 mg/dl; 25th: 84 mg/dl; 50th: 90 mg/dl; 95th: 106 mg/dl and 99th: 108 mg/dl. These figures, obtained in a recent study of a sample of young people from the population of Greater São Paulo, suggest that only approximately 5% of adolescents have fasting glycemia levels between 106 and 108 mg/dl.34

**Treatment**

The treatment objectives for DM 2 of the young do not differ from those proposed for DM 1: which are, to maintain the patient asymptomatic, to prevent acute and chronic hyperglycemia complications, attempting to achieve normoglycemia without frequent hypoglycemia and to maintain a normal rhythm of growth and development, in addition to weight control.

Nevertheless the challenges faced in treating DM 2 of the young are many. The insidious nature of the syndrome, the delay in seeking medical care and the late recognition of the disease by the pediatrician as yet unfamiliar with its pathology, are among such factors. Adolescents, at clinical onset of the disease, already have an established behavior pattern with relation to nutrition and physical activity. Resistance to changes in habits, added to the characteristics of the age group and also the fact that these individuals do not feel themselves to be “ill enough”, contribute to the low level of adherence to treatment.49

As with DM 1, the success of treatment lies in education. Obese children and adolescents and their parents should receive clear explanations about the pathogenesis of obesity and the risks associated with developing DM 2. The fundamental point of treatment is lifestyle modification, including dietary modifications and increased physical activity. This approach attempts to recognize original nutritional habits, suggesting changes which will result in weight reduction without compromising the rhythm of growth as well as stimulating daily physical activity such as walking, cycling and climbing stairs. It is recommended that all members of the family adopt the same healthy nutritional characteristics and perform exercise together or individually.

A diet with calorie restriction appropriate for the patient’s age improves glucose tolerance and insulin sensitivity by reducing hepatic glucose production.50 Exercise increases peripheral insulin sensitivity by reducing the mass of fat.

Treatment with reformed diet and increased exercise is successful when the patient continues to have normal growth,

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**Figure 1** - Diagnosis of the type of diabetes in children and adolescents
with weight control, fasting glycemia close to normal (less than 120 mg/dl) and glycated hemoglobin close to normal values. When treatment objectives are not attained by lifestyle modification alone pharmaceutical treatment is indicated.

Pharmacological therapy for DM 2 in children and adolescents is still the subject of discussion. In general, conduct is based on experience obtained through the treatment of adults. Therefore a plan based on staged dietary control associated with physical exercise and the use of an oral hypoglycemic agent and insulin, enjoys wide consensus.1,42

Sulphonylurea increases insulin secretion and can be used with patients suffering from MODY. Adolescents with DM2, however, are hyperinsulinemic and the first choice of medication is Metformin. Metformin acts by reducing hepatic glucose production, increases the sensitivity of the liver to insulin and increases the capture of glucose in the muscles, without direct effects on pancreatic beta cells. This drug has the advantage, over sulphonylurea, of equally reducing glycated hemoglobin without the risks of hypoglycemia and contributes to weight loss or at least to arresting its increase. Furthermore it aids the reduction of LDL cholesterol and triglyceride levels and contributes to the normalization of ovulatory abnormalities in girls with polycystic ovary syndrome. The most common side effects of Metformin are anorexia, nausea and diarrhea. On rare occasions it may cause a reduction in vitamin B12 absorption. Lactic acidosis is a rare, but serious complication, and therefore Metformin is contraindicated for patients with reduced renal or hepatic function or in the presence of hypoxia or severe infection. In such situations insulin is indicated.

Insulin should be used in all highly symptomatic cases, where ketoacidosis and glycemia are initially above 300 mg/dl. Once DM 2 of the young has been identified, the insulin dosage should be progressively discontinued, to the extent that the patient remains euglycemic until complete withdrawal, at which point the patient continues with the diet and exercise, associated with Metformin if necessary. It is important to remember that it has recently been demonstrated with an adult American population that lifestyle intervention (diet associated with physical exercise) is more effective than Metformin at reducing the incidence of diabetes.51

A recently published multicenter study,52 confirmed the safety and efficacy of Metformin in the treatment of pediatric DM 2. Side effects found in up to 25% of the patients were diarrhea and/or abdominal pain. These effects occurred at the start of treatment, but were significantly reduced with the passage of time and the reduction of the Metformin dosage.

Prevention
The largest studies into the prevention of DM 2 have been performed on the Pima Indians because in this case we are dealing with the group with the greatest DM 2 incidence across all age groups.

In 1990, a program of screening, diagnosis and treatment for diabetes during childhood was carried out at an elementary school at the Gila River indigenous community. The study documented a high level of obesity and family histories of diabetes in addition to a high incidence of DM 2 in the children. The children with glycemia above 200 mg/dl, two hours after an oral glucose overload were referred for treatment. Those with post-prandial glycemia levels between 140 and 200 mg/dl were referred for a directed education program (diet and exercise) at home and at school and these high risk children were also stimulated to participate in educational camps with diabetic children. The program proved to be effective in improving levels of physical activity among these children as well as helping with weight control.52

The results obtained in the QUEST study, in which the effect upon the high-risk children and their parents of the changes in lifestyle was evaluated, revealed the efficacy of the nutritional program and of physical activity in preventing DM 2 and in reducing weight gain. Based on these results strategies in the area of public health can be established with the objective of preventing this disease.53

References
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