

Diabetes mellitus in childhood: an emerging condition in the 21st century

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SUMMARY

The International Diabetes Federation (IDF-2015) estimates the existence of 30,900 children under 15 years old with type 1 *diabetes mellitus* (DM1) in Brazil, and an increase of 3.0% per year is expected. This review focused on meta-analysis and pediatric diabetes update articles in order to draw attention to the need of planning coping strategies to support this serious public health problem in coming years. DM1 is considered an immuno-mediated disease with a complex transmission influenced by genetic and environmental factors responsible for a gradual destruction of the insulin producing pancreatic beta cells. Seroconversion to DM1-associated autoantibodies and abnormalities in metabolic tests that assess insulin secretion and glucose tolerance can be used as predictive criteria of beta cells functional reserve and the onset of the clinical disease. Symptomatic DM1 treatment is complex and the maintenance of good metabolic control is still the only effective strategy for preserving beta cell function. Disease duration and hyperglycemia are both risk factors for the onset of chronic vascular complications that negatively affect the quality of life and survival of these patients. In this regard, health teams must be trained to provide the best possible information on pediatric diabetes, through continuing education programs focused on enabling these young people and their families to diabetes self-management.

Keywords: type 1 *diabetes mellitus*, child, adolescent, epidemiology, metabolic control.

Study conducted at Unidade de Endocrinologia Pediátrica, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brazil

Article received: 6/29/2016

Accepted for publication: 7/26/2016

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<http://dx.doi.org/10.1590/1806-9282.62.06.594>

INTRODUCTION

Diabetes mellitus (DM) represents one of the most common metabolic disease in the world, with rising prevalence in recent decades.^{1,2} Most cases are generally classified into two major pathophysiological categories: type 1 *diabetes mellitus* (DM1), which progresses with absolute insulin deficiency and can be identified by genetic and pancreatic islet autoimmunity markers, and type 2 *diabetes mellitus* (DM2), which is the most prevalent form and involves a combination of resistance to the action of insulin with an insufficient compensatory response of insulin secretion.

The natural history of diabetes involves increased risk for acute and severe complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic state, and also chronic microvascular (retinopathy, nephropathy, peripheral and autonomic neuropathy) and macrovascular (coronary atherosclerotic vascular, cerebral and peripheral vascular disease) complications that negatively affect the quality of life and survival of these patients.³ Approximately 1 million people die every year as a result of diabetes, two-thirds of which in developing countries.⁴

The objectives of this article are to warn of the recent increase in the incidence and prevalence of childhood diabetes, as well as to present an update on the disease's pathophysiology, progression, and control, aimed at planning coping strategies for diabetes, which will likely become a serious public health problem in coming years.

METHOD

A literature review was conducted on the MEDLINE database searching for meta-analyses and update articles on *diabetes mellitus* in childhood, focused on the epidemiology, pathophysiology, progression, and control of the disease and its complications.

CLASSIFICATION OF DM IN CHILDHOOD AND ADOLESCENCE

The current classification is based on existing pathophysiological knowledge, including four clinical classes: DM1, DM2, gestational DM, and specific types of DM due to other causes.⁵

DM1 corresponds to 90% of cases in children aged less than 15 years, constituting one of the leading pediatric chronic diseases. Unfortunately, diabetes diagnosed in childhood presents an increased risk for complications at an early and productive phase of life, and may lead to a reduction of 10 to 20 years in the average life expectancy, especially in developing countries.⁶

In the last two decades, in parallel with the increase in childhood obesity, there has also been an increase in the incidence of DM2 in young people in some populations. Other forms of diabetes may affect children and adolescents, such as monogenic diabetes (neonatal diabetes, MODY – maturity onset diabetes of the young, mitochondrial diabetes, and lipotrophic diabetes), diabetes secondary to other pancreatic diseases, endocrinopathies, infections and cytotoxic drugs, and diabetes related to certain genetic syndromes, which may involve different treatments and prognoses.⁷

EPIDEMIOLOGY

At the beginning of the 20th century, DM in childhood was rare and rapidly fatal, with children under 7 years of age surviving around 2 years after diagnosis. However, since 1922, thanks to the isolation and therapeutic use of insulin, the course of diabetes in children changed to that of a condition in which prolonged survival was possible, though still with unknown progression. In the period between the two World Wars, the average incidence of DM in children under 15 years of age was estimated at 4.1 cases/100,000/year, doubling after the mid-1950s in both Northern Europe and in the USA.⁸ At the end of the

1970s, epidemiological studies showed, for the first time, a large geographic variation in the incidence of diabetes in children, and international research groups began to be formed, encouraging the creation of standardized records for the incidence of child diabetes.⁹

The EURODIAB (Europe and Diabetes) and DIAMOND (Diabetes Mondiale) programs, introduced in the 1980s, enabled the characterization of DM1 in relation to its geographic distribution, genetic and family factors, clinical features of the disease at diagnosis, and associations with other diseases, as well as proposing speculation about possible non-genetic determinants.¹⁰⁻¹² By the end of the 1990s, a difference of more than 350 times in the incidence of DM1 was already being reported among the 100 populations analyzed, noting that the incidence was higher in the 10-14 years age range in most of them. However, over time, the trend toward an increase was higher in the 0-4 years (4.0%) and 5-9 years (3.0%) age groups than in the 10-14 years (2.1%) age group. It was suggested that differences in the genetic combination or in environmental/behavioral factors, as well as genetic/environmental interrelationships could influence these trends, especially in countries experiencing rapid social change, where exposure to possible etiological factors of DM1 could lead to these rapid changes.^{12,13}

The analysis of this data set enabled the overall increase in the rate of incidence of DM1 in children under 15 years to be estimated at 3.0% per year in the period from 1960 to 1996, which was relatively larger in countries with low incidence of the disease, suggesting a change in the penetrance of susceptibility genes, possibly determined by interactions with environmental factors as yet unknown.⁹ More recent evidence suggests that the DM1 incidence rates are not increasing in older age groups, although there is an increase in the number of cases diagnosed in younger children.¹⁴⁻¹⁶

The global prevalence of DM1 is estimated at around 0.3 to 0.4%.¹⁷ The IDF has carried out estimates of the prevalence of DM in the world since 2000, noting a large increase in these figures, with significant regional variations.¹⁸ The IDF's Diabetes Atlas – 2015 estimates that every year around 86,000 children under the age of 15 develop DM1 worldwide, with a total of around 542,000 children with the disease; among the ten countries with the highest number of children with DM1, Brazil would occupy the third position, with 30,900 cases.¹⁹ However, the most complete analysis of those aged under 20 years comes from the American study SEARCH for Diabetes in Youth, which at the end of 2009 identified a prevalence of 2.22 cases/1,000 young people, representing 1.93/1,000 for DM1, 0.24/1,000 for DM2 and 0.05/1000 for other forms of diabetes.²⁰

TYPE 1 DIABETES MELLITUS

DM1 is considered an immuno-mediated disease that develops as a result of gradual destruction of insulin-producing pancreatic beta cells that eventually results in their total loss and complete dependence on exogenous insulin. Clinical presentation can occur at any age, but most patients will be diagnosed before the age of 30 years. The disease process begins months to years before the onset of clinical signs such as polyuria, polydipsia, weight loss, and diabetic ketoacidosis. However, the etiology and natural history of DM1 are not yet completely known, with genetic and environmental factors believed to participate. The genetic effect probably contributes 70 to 75% in the susceptibility to DM1, with environmental factors possibly initiating or stimulating the process that will lead to the destruction of the beta cells and the onset of the disease.⁹

RISK FACTORS ASSOCIATED WITH DM1

Despite HLA genes exerting a greater role in the etiology, other genes also contribute to the genetic effect, although the type of inheritance still remains unknown. Currently, the main markers of susceptibility to DM1 are considered to be class II HLA haplotypes *DRB1*0301-DQA1*0501-DQB1*0201* (DR3-DQ2 serotype) and *DRB1*0401-DQA1*0301-DQB1*0302* (DR4-DQ8 serotype), while *DRB1*0403* is negatively associated with DM1, and may protect or slow the progression to clinical disease.²¹ Recurrence among siblings of a patient with DM1 is 5%, which means a risk 15 times higher, reaching 65-70% between monozygotic twins, or even higher if the index case has developed the disease in childhood.²²

Genome-wide association studies have already identified more than 40 gene *loci* associated with the DM1 phenotype, generally involved in autoimmunity, the production and metabolism of insulin, and also the survival of the pancreatic beta cells.²³ Genes such as *IL2*, *CD25*, *INS*, *IL18RAP*, *IL10*, *IFH1*, and *PTPN22* appear to exert an influence on the speed of progression to DM1 after the onset of autoimmunity against the islet,²⁴ and predictive algorithms for DM1 that also incorporated non-HLA genetic markers such as the *PTPN22* or the *INS* gene increased the capacity to predict risk, especially in individuals with the DR3/DR4 haplotype in the general population.²⁵

The recent increase in the incidence of DM1 in children under 5 years of age appears to be a result of a faster progression to the onset of the disease, rather than a specific increased risk for the disease throughout life. The causes of this phenomenon are still unknown, and it is possible that the youngest group presents a higher proportion of HLA susceptibility genes or that there has been

an increase in the penetrance of these genes at younger ages due to harmful changes in the environment.^{17,26-28}

The mode of transmission of DM1 is complex and around 80 to 85% of new cases of the disease occur sporadically, without familial aggregation.²⁹ However, there is a higher prevalence of the disease among patients' first-degree relatives, primarily in populations with a high incidence of DM.³⁰

The variation in the incidence of DM1 associated with differences between ethnicities is not as substantial as geographical variations, suggesting an additional influence of environmental factors.²⁸ Some potential risk factors such as early fetal events, viral infections during the intra-uterine or postnatal period, early exposure to the components of cow's milk, and other nutritional factors could trigger the autoimmune process.^{31,32} Systematic reviews of observational studies have identified certain protective factors against the development of DM1, such as breast milk, atopy, and attending day care as indicative of early infections.³³⁻³⁵ There are also some risk factors, such as advanced maternal age, birth by cesarean section, and lower birth order.³⁶⁻³⁸ On the other hand, the role of the metabolism of vitamin D remains unclear.³⁹ The frequency of DM1 in childhood has already been associated with estimates of the wealth of populations, such as the gross domestic product, suggesting that lifestyle habits related to wealth may be responsible for changes in these trends.⁴⁰

PATHOPHYSIOLOGY

The pathophysiological model of DM1 was proposed by Eisenbarth⁴¹ in 1986 as a gradual deficiency of insulin production resulting from the destruction of pancreatic beta cells due to an autoimmune process mediated by T cells in individuals genetically susceptible to the disease, who were born with a normal number of beta cells but undergo a process of cell destruction, most likely after exposure to precipitating environmental factors. Beta cells are destroyed by an aggressive autoimmune response mediated by factors that include the infiltration of CD4+ and CD8+ T cells, as well as B cells and macrophages, resulting in insulinitis.⁴² Cellular immunity is accompanied by adaptive immunity and anti-insulin antibodies (IAA) are the first detectable markers of beta cell destruction, followed by the appearance of other types, such as anti-glutamic acid decarboxylase (GADA), transmembrane anti-tyrosine phosphatase (IA-2A), and anti-zinc transporter protein 8 (anti-ZnT8), directed against components of insulin secretory granules, whose presence would suggest the expansion of the destructive process. After the loss of approximately 85 to 95% of the beta cells, the classic symptoms of *dia-*

betes mellitus arise and the process of autoimmune aggression ends along with complete elimination of these cells.⁴³ However, studies suggest that beta cells can persist for a longer period in some individuals with DM1,⁴⁴ without ever achieving total destruction, and that other pancreatic characteristics could have a significant pathogenic role in DM1, such as the size of the pancreas, suggesting that multiple pathogenic mechanisms may lead to loss of pancreatic beta cells in DM1.⁴⁵⁻⁴⁷ Recently, the international collaborative study Network for Pancreatic Organ Donors with Diabetes (nPOD) was established with the aim of improving the understanding of the pathogenic process of DM1 and the interactions between beta cells and the immune system, through analysis of pancreas fragments or whole pancreas collected after the death of donors carrying autoantibodies associated with DM1, both in the pre-clinical phase and the established disease stage.⁴⁸

THE NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS

The model of DM1 as a chronic autoimmune disease that develops in stages still prevails today, after some modifications.⁴¹ The hypothesis is that individuals are born with varying degrees of genetic susceptibility to DM1 and that environmental influences starting quite early, operating during intrauterine life, and probably also during the first months of life, accelerate the onset and maintenance of autoimmune aggression. Physiological events common to the development of the immune system and the normal life cycle of beta cells could also influence these pathogenic processes.^{47,49} Innate immune dysregulation, which probably occurs in phases of activity and remission,⁵⁰ could be responsible for the emergence of early serological evidence of beta cell destruction, including the positivity of the autoantibodies associated with DM1. In most of these individuals, changes in insulin secretion and glucose tolerance may happen months to decades after detection of multiple autoantibodies against the islet; however, for reasons still unknown, not all of them will progress to clinical disease.⁵¹ In genetically predisposed individuals with multiple antibodies against the islet, the clinical symptoms usually follow a silent period, which can last from months to many years, referred to as asymptomatic DM1.⁵²

Owing to a lack of serological markers for specific cellular immunity, the presence of autoimmunity in DM1 has been screened via the positivity of serological autoantibodies (seroconversion) directed to the islet and the antigens of beta cells, which can be detected well before clinical evidence of the disease. Approximately 90% of patients with DM1 present two or more autoantibodies at the time of

diagnosis, and it is likely that the remaining 10% have antibodies against antigens that are still unknown. In children, IAA is often the first antibody to develop, while adults tend to have higher rates of GADA upon diagnosis.⁵³

Through the analysis of data collected by prospective studies on the natural history of DM1 in first-degree relatives of high-risk patients with HLA haplotypes monitored from birth, it was observed that the detection of multiple autoantibodies against the islet in these children could be interpreted as a pre-clinical stage of DM1. In addition, observation within a period of 10 years after seroconversion suggests that the lower the age upon the onset of autoimmunity directed at the islet, the quicker the progression to clinical diabetes before puberty, and that the processes responsible for this phenomenon must be operating before the age of 2 years, or even during pregnancy.⁵⁴⁻⁵⁷

Metabolic tests that evaluate insulin secretion ability and glycemic state are also used as criteria for predicting the functional reserve of beta cells and the clinical onset of DM1; they include: a) the intravenous glucose tolerance test (IGTT); b) the oral glucose tolerance test (OGTT); c) glycated hemoglobin concentrations (HbA_{1c}). The diagnostic criteria of glucose disorders according to the American Diabetes Association (ADA) – 2016⁵ are presented in Chart 1.

CHART 1 Diagnostic criteria of glucose disorders according to the American Diabetes Association (ADA) – 2016.⁵

Diagnosis	Fasting blood glucose (mg/dL)	2H-OGTT (mg/dL)	HbA _{1c} (%)
Normal	70 to 99	< 140	4.5 to 5.6
Prediabetes	100 to 125	140 to 199	5.7 to 6.4
<i>Diabetes mellitus</i>	≥ 126	≥ 200	≥ 6.5

2H-OGTT: 120 minute time of the oral glucose tolerance test; HbA_{1c}: glycated hemoglobin evaluated by laboratory test aligned with that used by the Diabetes Control and Complications Trial (DCCT).

PHASES OF TYPE 1 DIABETES MELLITUS

Prospective, longitudinal studies of individuals with genetic risk have shown that the pathogenic process progresses within a time *continuum*, from an asymptomatic pre-clinical phase to chronic diabetic disease with vascular complications, at a variable but predictable speed, enabling the characterization of well-defined stages (Figure 1) and currently adopted by various international societies of experts,⁵⁸ as presented below:

- Stage 1: Pre-symptomatic DM1 with positive autoimmunity (two or more autoantibodies against the islet) and normal blood glucose. This corresponds to the

immunological disease phase and, in many cases, progression to the clinical disease occurs in a period between 8 to 10 years.⁵⁹

- Stage 2: Pre-symptomatic DM1 with positive autoimmunity (two or more autoantibodies against the islet) and pre-diabetic dysglycemia (abnormal fasting glucose and/or reduced glucose tolerance in the OGTT). This corresponds to the almost irreversible stage of the disease, with functional loss of beta cells and the beginning of metabolic disease.⁵⁹ The risk of symptomatic disease within a period of 5 years is approximately 75%, reaching 100% over a lifetime.^{58,60}
- Stage 3: Symptomatic DM1, with positive autoimmunity (two or more autoantibodies against the islet) and diabetic dysglycemia (diabetic fasting glucose and/or diabetic OGTT, increase in HbA_{1c}). This corresponds to the autoimmune acceleration stage of the disease,⁵⁹ with the presence of typical signs and symptoms of DM1.⁵⁸ Progression of the symptomatic phase of DM1 can further be classified as: a) initial phase; b) established DM1 phase; c) established DM1 phase with chronic complications⁶¹ (Figure 1).

The ability to screen DM1 risk and identify a pre-symptomatic stage can promote a window of opportunities for the implementation of possible interventions able to prevent or delay the onset of clinical symptoms.

SYMPTOMATIC DM1

In the initial phase, the clinical diagnosis is usually established by the presence of the classic symptoms of diabetes, which should be immediately investigated through random blood glucose sample collection (diagnosis at ≥ 200 mg/dL at any time of the day) and quick urine tests confirming the presence of glycosuria and possible ketonuria.⁵ However, lack of recognition of the classic symptomatology or an atypical clinical presentation increases the risk of severe diabetic ketoacidosis (DKA). Unfortunately, 25 to 40% of diagnoses of DM1 in childhood are still performed in situations of acute metabolic decompensation with DKA, especially in children under 4 years of age from populations with limited information about diabetes, so that classic symptoms are not recognized.^{62,63}

In approximately 80% of children and adolescents, the daily needs of insulin diminishes temporarily after the start of insulin therapy, probably due to a functional recovery of beta cells still present due to reversal of glucotoxicity, with improved endogenous insulin secretion as well as sensitivity in peripheral tissues.⁶¹ This partial remission phase of DM1, also known as the honeymoon period, begins within days to weeks after the start of insulin therapy and can last for months or years; plasma glucose concentrations tend to be stable within the bounds of normality, although fluctuations may occur depending on diet and physical activity. It has been suggested that

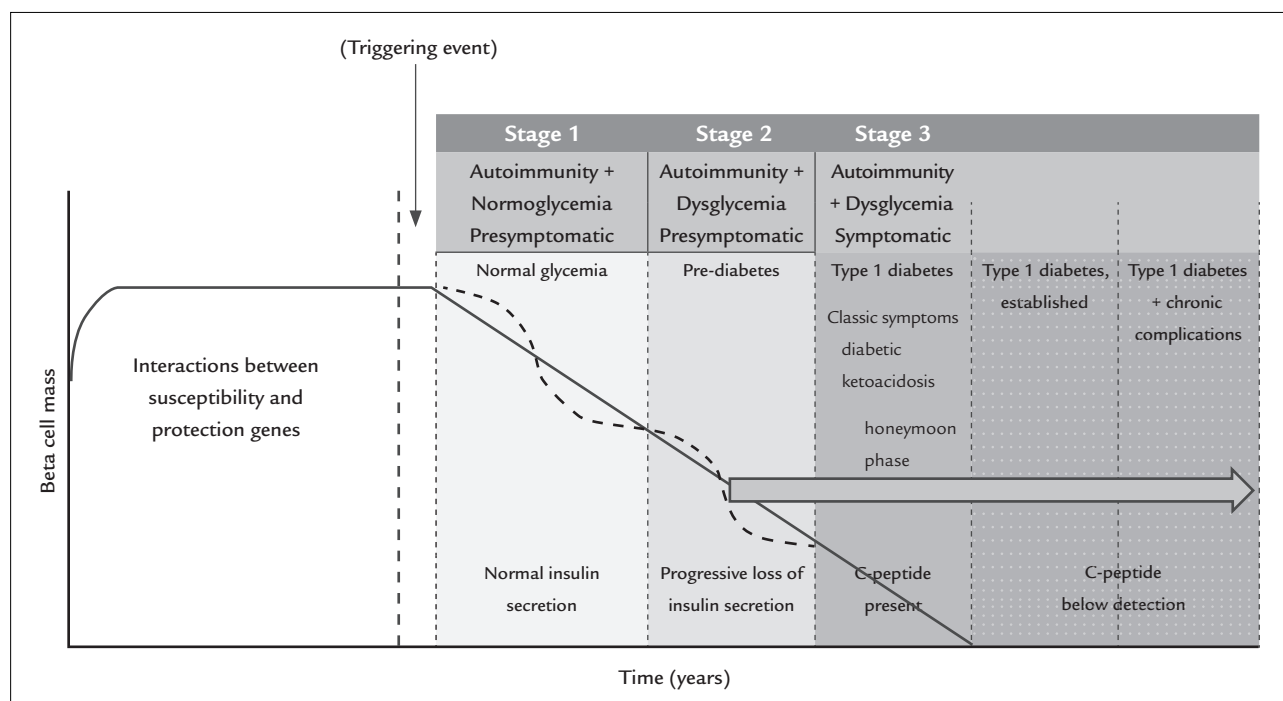


FIGURE 1 Stages of type 1 *diabetes mellitus*. Modified from Insel RA et al.⁵⁸

the preservation of this functional reserve can lower the risk of developing vascular complications and episodes of severe hypoglycemia.^{52,64}

To date, exogenous insulin therapy is the only form of insulin replacement in children and adolescents with DM1 and continued diabetes self-management education is the method for promoting the integration of the various insulin administration regimens into daily life, as well as techniques for a nutritional management, regular physical activity, intensive glucose monitoring aimed at empowering the patient and their caregivers to keep glycemic control as normal as possible for the greatest amount of time possible.⁶¹

Insulin therapy attempts to mimic the physiological secretions of insulin by the pancreas, although no current regimen carries out this function satisfactorily, and there is a need to individualize the proposed therapy for each patient according to their routine and insulin sensitivity at different times of the day. There are several therapeutic regimens that combine intermediate or long acting insulin with rapid or ultra-rapid insulin; however, those that recommend one or two daily doses of insulin are inefficient in most patients with DM1.

Through multiple subcutaneous injections of insulin or continuous subcutaneous infusion system (insulin pump), basal-bolus insulin therapy has been shown to be the most effective in maintaining considerable residual insulin secretion during the first year of the disease and more stable metabolic control after several years, with lower levels of HbA_{1c}, lower daily doses of insulin, and a reduction in the risk of severe hypoglycemia,^{65,66} which forms the rationale for the development of new therapeutic interventions able to preserve the function of beta cells in newly diagnosed patients.

Prospective clinical studies have definitively shown that strict glucose control from the onset of the disease can delay or even prevent the onset of chronic vascular complications associated with diabetes.⁶⁷⁻⁶⁹ However, prevention strategies must also be established for severe, recurrent and nocturnal hypoglycemia.^{70,71} This objective requires patients to master over insulin replacement algorithms as a function of a complex range of physiological parameters, including knowledge of the carbohydrate content in the diet and its metabolism, personal glycemic parameters and the need for adjustments in special situations such as physical activity, menstrual cycle, and intercurrent diseases. This complexity of self-management, still present today, leads to a large percentage of patients being unable to achieve the recommended glycemic control.

In the last 20 years, there have been significant advances in the treatment of diabetes thanks to new medi-

cations and technologies. On the other hand, the health systems in general have not adapted to this evolution. Even today, a large percentage of people with DM1 are unable to perform or pay for the necessary care, and patients and health teams continue to face difficulties related to integrating the control of diabetes into the routines of daily life.⁷²

Vascular complications related to diabetes are usually not observed in children and adolescents, but functional and structural abnormalities may already be present a few years after diagnosis, and disease duration and magnitude of exposure to hyperglycemia constitute the main factors associated with its development.⁷³

CONCLUSION

Effective control of diabetes requires a partnership between an informed and proactive multidisciplinary team and motivated patients that are active in their self-management. Given the current growing estimates of cases of DM1 in childhood in Brazil, it has become urgent to equip the public health system for the training of teams capable of providing the best information possible on childhood diabetes, through continued education programs, in order to minimize the impact of the disease both on quality of life and the productive longevity of this population.

RESUMO

Diabetes mellitus na infância: uma condição emergente no século 21

A Federação Internacional de Diabetes (IDF-2015) estima a existência no Brasil de 30.900 menores de 15 anos portadores de *diabetes mellitus* tipo 1 (DM1), com previsão de aumento de 3,0% ao ano. Esta revisão buscou artigos de metanálise e atualização em diabetes infantil com o objetivo de alertar para a necessidade do planejamento de estratégias de enfrentamento deste que tende a ser um sério problema de saúde pública para os próximos anos. O DM1 é considerado uma doença imunomediada de transmissão complexa, influenciada por fatores genéticos e ambientais determinantes da destruição gradual das células beta pancreáticas produtoras de insulina. A positividade sorológica dos autoanticorpos associados ao DM1 e a alteração de testes metabólicos que avaliam a secreção de insulina e o estado glicêmico podem ser utilizados como critérios de previsão da reserva funcional de células beta e do início clínico da doença. O tratamento do DM1 sintomático é complexo, e a manutenção do bom controle metabólico é ainda a única estratégia efe-

tiva de preservação das células beta ainda funcionantes. Tempo de duração da doença e hiperglicemia são fatores de risco para a instalação das complicações vasculares crônicas, que afetam negativamente a qualidade de vida e a sobrevivência desses indivíduos. Torna-se necessária a formação de equipes de saúde preparadas para fornecer a melhor informação possível em diabetes infantil, através de programas de educação continuada, com potencial de capacitar esses jovens e suas famílias para o autocuidado.

Palavras-chave: *diabetes mellitus* tipo 1, criança, adolescente, epidemiologia, controle metabólico.

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