Review article

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DIABETES MELLITUS IN CHILDHOOD: FACTS AND CONTROVERSIES

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We are in the midst of a diabetes pandemic. In 2000, 171 million people worldwide were affected by the disease with projections that it will affect 366 million by 2030. The incidence of type 1 a diabetes has been doubling approximately every two decades. Perhaps the most striking change in diabetes over recent years has been the convergence of previously distinctive phenotypes. The possibility that type 1 and type 2 diabetes are merely poles of a single spectrum, where variation in the tempo of beta cell loss is determined by age at onset and symptoms at presentation, has important implications. Beta cell deficiency underlies both type 1 and type 2 diabetes, and restoration or replacement of beta cell function is therefore the logical long-term solution to therapy. New beta cells derived from embryonic stem cells may be an interesting future strategy for the treatment of diabetes, but this approach appears to be far from ready for clinical application. "The accelerator hypothesis" proposes that insulin resistance remains the driver responsible for acceleration of beta cell loss among those with reactive immunoresponse genes. Children who develop type 1 diabetes are taller and heavier than their peers. The consequence of more rapid growth is insulin resistance, when beta cells become more active and more antigenic for the immune system. Although immunomodulatory therapy slows the tempo of beta cell loss, insulin resensitization may be an intervention that is more physiological, less toxic and considerably cheaper and would encourage a lifestyle change in the prevention of childhood diabetes.

Key words: Diabetes mellitus ▪ Accelerator hypothesis ▪ Prevention of diabetes

Introduction

The rise in the incidence of diabetes mellitus in children has reached a disturbing rate, so it may rightfully be called epidemic of the 21st century. The number of new patients has been doubling every second decade. Every 10 seconds one person in the world dies of diabetes, and two new persons become ill. The incidence growth is the largest in the population of children under the age of 14. Until 1995, around 135 million people had diabetes, whereas in 2000 that number rose to 171 million. If this trend continues, we can expect that 366 million people will have diabetes by 2035 (1-4). The incidence of type 1 diabetes (T1DM) declines from the north to the south of Europe with the exception of Sardinia in the south, which is marked as a "hot spot" (5). Compared to the other countries of the former Yugoslavia, Montenegro has the highest incidence of type 1 diabetes mellitus in the 0-14 age group – 13.4/100000 (6). The standardized incidence of T1DM in Serbia is 8.1/100,000 (7), in Croatia 8.9/100,000 (8), in Slovenia 11.1/100,000 (4), in Bosnia and Herzegovina (Canton of Tuzla) 6.9/100,000 (9) and in Macedonia 3.6/100,000 children per year (10). The incidence of type 2 diabetes (T2DM) which was quite rare in children until 1990 (1-2 % of all patients) is also growing, and in the USA it has already reached 30-50% which is the consequence of the growing incidence of obesity in children and youth (11, 12). Homo sapiens has become homo obesus.

Diabetes is a genetic, immunological and metabolic disorder. It is characterized by hyperglycaemia, hyperlipidaemia, hyperaminoacidemia and disturbed energy metabolism. More than 30 years ago T1DM was connected with an HLA genotype followed by the lymphocyte infiltration of island cells and the occurrence of auto-antibodies to the protein components of pancreatic beta cells. The classification of diabetes includes 4 main types:

1) type 1 diabetes mellitus (A-autoimmune and B-idiopathic form),
2) type 2 diabetes mellitus
3) other specific forms of diabetes (genetic – MODY 1-6, disorders of the exocrine pancreas, diabetes in other endocrinopathies) and
4) gestation diabetes.

Childhood diabetes changes its well known face

Perhaps the most striking change in diabetes over recent years has been the convergence of previously strictly distinctive entities. Until recently, it was easy to distinguish type 1 from type 2 diabetes, especially in children. However, what occurs now is the so called mixed form or hybrid diabetes which shows the characteristics of both types (13). Thus, T1DM was clearly marked as diabetes occurring in children and young persons, ketosis-prone diabetes, and newly discovered patients become dehydrated and thin. The concentration of insulin in the serum is low, auto-antibodies to island cells are present, and insulin is necessary for survival. T2DM occurred in older obese persons, it was not ketosis-prone, and it was not the consequence of insulinopenia but of insulin resistance, and auto-antibodies were usually not present. Insulin is not necessary for survival in type 1 diabetes, but in some patients it is certainly necessary to achieve better metabolic control.

Although newly diagnosed T1DM children present themselves in a cachectic and dehydrated state, the reality is changing. Newly diagnosed T1DM children show accelerated growth, they are often obese, dehydration is mild and besides a very distinguished hyperglycemic syndrome, they are not so prone to ketosis, and most importantly, the age limit has changed to preschool, toddler and even infants. New types of diabetes are appearing in the literature, such as the hybrid type of diabetes or 1/2 diabetes,

then LADA (latent autoimmune diabetes in adults), LADY (latent autoimmune diabetes in young) and fulminant type 1 diabetes (13-16). The last type was described in Japan and Korea which occurred massively in children and adults who ate corn polluted with rodenticide. Like the very name indicates, the beginning was abrupt, the development was fulminant with heavy diabetes ketoacydosis, whereas the auto-antibodies were negative (16, 17). Like other specific autoimmune diseases, type 1 diabetes mellitus is also the result of a complex interaction of genetic factors, external and endogenous factors and only a specific combination will result in a disease (picture 1). Genetic factors are: HLA-DR ¾, HLA-DQ 2/8, INS/VNTR, on chromosomes 6 and 11, as well as immunoregulatory CTLA-4 (18, 19). The external factors which are most often blamed for diabetes are viruses (especially Coxacki B4, Rubella, Parotitis) (20-24), early diet of cow milk (bovine proteins and bovine insulin present in milk), then vitamin D deficiency, the use of antibiotics (quinolone used by the mother deposited in her bones and released during pregnancy and breast feeding) (21), giving birth by Caesarean section, because there is no passage through the genital tract so the newborn is immediately colonized by hospital germs (22), food toxins, preservatives and pesticides, cola-drinks, physical and psychological stress in the family and school. The endogenous non-preventable factors are sex, age, accelerated growth, puberty and strong emotional sensitivity (23, 24).

The autoimmune insulitis in type 1 diabetes leads to the destruction of pancreatic beta cells and insulin deficiency. According to the current theory, the beta cell loss is progressive and definite. However, new facts show that the destiny of beta cells in autoimmune diabetes can be different: necrosis, apoptosis, permanent suppression, or recovery. Regeneration occurs even after multiannual duration of diabetes and continues throughout life.

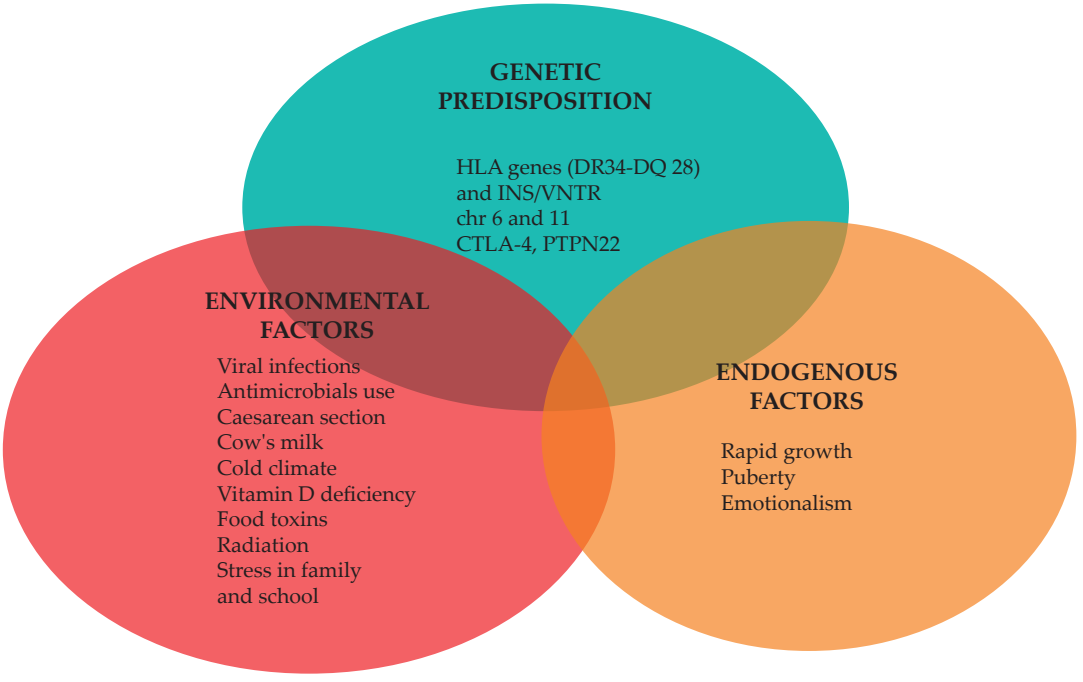

Figure 1 *Complexity of the interplay between genetic, environmental and endogenous factors in childhood diabetes (5, 19, 24, 26)*

Another theory indicates that beta cells are irreversibly destroyed in diabetes. But this theory has also been refuted by the finding that replication is possible even in older persons, it is most often meagre but under some conditions it may be increased tenfold (25). Insulin resistance is specific for type 2 diabetes. A new fact is that type 1 diabetes is preceded by the stadium of insulin resistance, whereas type 2 diabetes involves the loss of beta cells through apoptosis (26-27). Some authors go even further by claiming that type 1 and type 2 diabetes are parts of the spectrum of the same disease and the difference is only in the velocity of the beta cell destruction (28, 29). There are two attractive theories that stood out in recent years which explain the increase in the incidence of diabetes in the youngest (27, 28).

Wilkin's Hypothesis of Acceleration

According to Wilkin the first step in the occurrence of both types of diabetes is the genetic tendency towards beta cell apoptosis (29). Such a constitution in the second phase leads to acceleration (physical inactivity, excessive nutrition and obesity) which leads to beta cell stress (picture 2). In the third phase blood glucose is already elevated and the toxic effects of hyperglycaemia activates the autoimmune process (28-31). Key evidence of the acceleration hypothesis are the following:

1. The growth of incidence of type 1 diabetes happens simultaneously with the growth of incidence of obesity in children,
2. Children who get diabetes have greater body mass than their peers,
3. Obese children develop diabetes earlier (obesity is the only factor where there is a direct correlation between the level of obesity and the occurrence of diabetes), which is proof of true acceleration,
4. The contribution of genes in type 1 diabetes has been reduced in the latest generation because of the large pressure of the environmental factor,
5. In two identical twins, the one that will get diabetes has more prominent insulin resistance and
6. Insulin resistance leads to the acceleration of beta cell loss in those with reactive HLA genes.

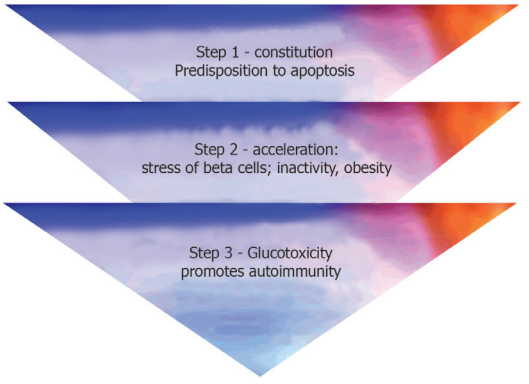

Figure 2 *Wilkin's accelerator hypothesis: constitution and accelerators promote autoimmunity (28, 29)*

Wilkin thinks that the hypothesis is developed enough to carry out a study with insulin sensitizers such as metformin or tiazolidinedionas. Reclassification of diabetes could result in different types of prevention through a change of life habits. Namely, prevention based on the autoimmune paradigm of type 1 diabetes did not result in a decrease in the incidence. On the contrary, the incidence is growing unstoppably. The effects of metformin which reduces beta cell apoptosis, reduces oxidative stress markers and slows down the aggravation glycoregulation are justification for intervention with this medicine in the prevention of T1DM (32).

Our experiences with the use of metformin in newly diagnosed T1DM children are favourable (33). We used metmorfin combined with insulin, after 7-10 days after diagnosis in decompensated, or immediately in compensated patients. Children treated with metformin go faster into remission, and some of them even had complete remission for lon-

ger than 2 years. Further research is necessary in a randomised control study (33, 34).

The Overload Hypothesis

Similar to the previous hypothesis, this one also blames irregular nutrition and overeating for the growth of the incidence of diabetes. Pregnant women are becoming heavier and heavier, just like their foetuses and newborns. While the foetus is still in the uterus, it already has fat accumulated in deposits which cause the overload of beta cells. These children grow rapidly and enter puberty earlier. Besides, reduced physical activity, vitamin D insufficiency and energy loaded food lead to insulin resistance, hyper-function and hypertrophy, and later apoptosis and beta cell destruction (27).

Prevention Strategies

Numerous attempts at prevention, the purpose of which was to avoid and postpone the occurrence of T1DM, such as:

1. detection of genetically predisposed individuals and vaccination,
2. breast feeding, or if that is not possible, the use of hydrolysed formulas,
3. optimal intake of vitamin D,
4. delaying the introduction of cereals in nutrition,
5. limitation of the use of antibiotics, and
6. the use of probiotics

have not produced so far any convincing results (5, 19).

These hypotheses impose new prevention strategies which imply regular nutrition, maintenance of optimal body mass and physical activity. Prevention practically becomes the same for both types of diabetes and for all age categories.

New Therapy Options: replacement of beta cell mass with stem cells or preservation and renewal of beta cells

The purpose of many elaborate pieces of research in the world is to turn diabetes into a curable disease without insulin injections as the only therapy option. Some of the new medications are in the final stage of testing.

Since both types of diabetes are characterised by a significant beta cell deficiency, primarily caused by beta cell apoptosis, the idea of mass replacement with new beta cells from embryo stem cells represents an interesting strategy, but it is still far from clinical application. Human embryo cells can be differentiated so they can produce and release insulin, but in vitro they still react to different secretagogues but not to glucose. Besides, it is difficult to reproduce the complex organisation of island cells in which the insulin secretion is regulated by neural, endocrine and paracrine mechanisms. There are also some ethical obstacles and finally, it is still impossible to control the proliferative activity of embryo cells which possess the risk of tumour formation (25).

The current clinical studies have as a goal to stop the autoimmune process and preserve, and possibly renew beta cell mass (35). To that purpose, scientists are testing the following agents:

Anti-gene specific therapy

- DiaPep277(HSP)-p277 heat shock protein, and
- Dyamid (rhGAD65- recombinant human glutamic acid decarboxylase 65) Imunomodulatorna terapija
- Anti CD3 antibodies (Ala-Ala) monoclonal antibodies directed at T lymphocytes

Anti-inflammatory therapy

- Anakinra (IL1 RAb) – antibody to the IL1 receptor.

However, the emphasis is on the fact that the individual reaction of subjects is still

unpredictable in the application of these medications, especially in childhood.

Nicotinamide, which in experiments successfully prevented diabetes in mice, has become completely inefficient. Namely, nicotinamide protected the beta cells of rodents from chemically (streptozocine) induced necrosis but not from the apoptosis induced with cytokinins (36-37). Cyclosporine was also used in attempts to treat newly diagnosed diabetes patients, but besides its toxicity it turned out that it increases beta cell apoptosis (38).

Conclusion

Despite intensive research in the last 30 years based on autoimmune paradigms and increased knowledge of the mechanisms of beta cell destruction, as well as impressive attempts at their replacement and preservation, the cause of diabetes has not been fully explained and there is no safe way of prevention and treatment. Insulin re-sensitization could be a more natural intervention, less toxic and considerably cheaper. Beta cell stress should be reduced through a change in dietary habits and physical activity. We are still waiting for a major breakthrough in diabetes treatment, like the one that happened in 1921 when scientists discovered and used insulin for the first time. Until then, paediatric diabetologists can only ensure optimal insulin compensation, to make the metabolism of a sick child as normal as possible, to guide him through the different stages of the disease, growing up and the challenges of puberty, until full maturity and an active life, which is hard but worth the effort.

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