Western European Journal of Medicine and Medical Science
Volume 2, Issue 4, April, 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

NEW INSIGHTS INTO THE ETIOPATHOGENESIS OF TYPE 1 DIABETES MELLITUS

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Diabetes mellitus (DM) is a large group of complex metabolic diseases characterized by chronic hyperglycemia due to impaired insulin secretion or action, or a combination of these disorders [1]. Disruption of insulin secretion and/or decreased tissue response to insulin as part of complex hormonal processes leads to impaired insulin action on target tissues, which in turn causes disturbances in carbohydrate, fat, and protein metabolism. Impaired insulin secretion and impaired insulin action can occur simultaneously in the same patient. Type 1 diabetes (DM 1) is an autoimmune disease in genetically predisposed individuals in which chronic lymphocytic insulitis leads to T-cell-mediated destruction of β-cells with the subsequent development of absolute insulin deficiency, with a propensity to develop diabetic ketoacidosis (DKA). DM 1 is characterized by chronic, immune-mediated destruction of pancreatic islet β-cells, which leads in most cases to absolute insulin deficiency. The destruction of β-cells occurs at different rates and becomes clinically significant when approximately 90% of β-cells are destroyed. DM 1 is a multifactorial disease, but the specific mechanisms of interaction between genetic predisposition, environmental factors, and the immune system underlying DM 1 remain unclear [1,2,3].

Autoimmune destruction of β-cells is a complex, multistep process during which both cellular and humoral immunity are activated. The first to infiltrate the islets of Langerhans are monocytes and macrophages, which release proinflammatory cytokines (IL-1, IL-6, TNF-α) and free radicals of oxygen, nitric oxide, and hydroxyl radicals. Cytokines induce apoptosis - programmed death of transformed or healthy cells [9,10,11]. Nitric oxide and other radicals damage deoxyribonucleic acid (DNA) of β-cells. Given the low antioxidant enzyme protection of β-cells, free radicals cause denaturation of proteins with destruction of β-cells. T lymphocytes activated by proinflammatory cytokines recognize denatured proteins and other products of β-cell destruction as antigens and become involved in the process of insulitis. DM 1-associated autoantibodies (ATs) are serologic markers of autoimmune destruction of β-cells. They include AT to glutamate decarboxylase (GADA), to tyrosine phosphatase (IA2), to insulin (IAA) and to zinc transporter 8 (ZnT8A). There is an age-related dissociation in the appearance of these ATs: IAA and GADA are more frequently expressed in children under 10 years of age, whereas IA2 and ZnT8A are expressed at older ages. The value of islet cell antibody (ICA) detection both in predicting DM 1 and in differential diagnosis with other types of diabetes has decreased with the emergence of stronger markers. Exposure to autoimmune DM 1 is determined by multiple genes: a full-genome association search has identified more than 60 loci involved in the development of DM 1 [3,4,5,6].

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HLA accounts for about 50% of all genetic systems involvedhere are ethnic differences, including in the territory of RUz. With the increasing incidence of DM 1 in a number of countries, a decrease in the relative contribution of the strongest HLA genotypes to the development of DM 1 is observed, indicating an increased role of environmental factors. Among other genes, the genes of insulin (INS), protein-tyrosine phosphatase, non-receptor type 22 (PTPN22), cytotoxic protein 4 associated with T-lymphocytes (CTLA4) and interleukin-2 receptor alpha subunit (IL2RA) make the highest contribution to the formation of susceptibility to DM 1. All of them are involved in the formation of autoimmunity against pancreatic β-cells. The environmental triggers (infectious, alimentary, or chemical) that initiate β-cell destruction remain unknown [7,8,9].

There are reports that enterovirus infection during pregnancy or throughout life, especially when infection occurs in early childhood, has been associated with the emergence of islet autoimmunity and DM 1. The results of prospective studies in individuals at increased risk of developing DM 1 have shown that the disease is a continuum that progresses sequentially through various identifiable stages until the onset of clinical symptoms, which has led to the identification of several stages of DM 1 [6,11,12,13].

Stage 1: Autoimmune process/Normoglycemia/No clinical manifestations. Stage 1 is characterized by the presence of signs of β-cell autoimmunity, defined by the presence of two or more positive autoantibody titers. At the same time, glycemic parameters do not exceed the normal range, and there are no clinical manifestations of DM. The duration of the first stage may be months or years. In prospective studies, in children at high risk of developing DM 1, the 5-year and 10-year risk of symptomatic disease is approximately 44% and 70%, respectively [1,2,15].

Stage 2: Autoimmune process/Dysglycemia/No clinical manifestations. In stage 2 of DM 1, carbohydrate metabolism abnormalities join the features of the β-cell autoimmune process, defined by the presence of two or more positive autoantibody titers. At this stage, the 5-year risk of developing clinical DM 1 is approximately 75%, and the lifetime risk approaches 100% [1,2,9,12].

Stage 3: Autoimmune Process/Dysglycemia/Clinical DM 1. Stage 3 represents the manifestation of DM 1 with a classic clinical picture that may include polyuria, polydipsia, weight loss, etc [4,9,20].

Stage 4: Mature DM. Approximately 80% of children with DM 1 experience a partial remission of DM 1 shortly after starting insulin therapy, or a "honeymoon period" lasting from a few weeks to six months, rarely for a year or more [17,18,19].

Remission of diabetes is temporary and does not mean that diabetes is cured. Complete remission - discontinuation of insulin without worsening of glycemic parameters. Partial remission - insulin requirement is less than 0.5 units/kg body weight and glycated hemoglobin (HbA1c) concentration in the blood is less than 7% [1,4,7,9,].

The clinical picture of DM varies from nonurgent manifestations to severe dehydration, DKA up to the development of coma. The rate of progression from the first clinical manifestations to the development of DKA varies from patient to patient, from a few days in children 1-2 years of age to several months in adolescentsOnce the diagnosis is established and insulin therapy is started, type 1 DM has a chronic course with periods of carbohydrate metabolism compensation and decompensation phases with or without ketosis/DKA phenomena. Decompensation of the disease may be due to both violations in the control of the disease on the part of the patient (infrequent control of glycemia, non-compliance with dietary

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recommendations and insulin therapy regimen), discontinuation of insulin delivery when using an insulin pump for various reasons, and due to the occurrence of intercurrent diseases. In DM 1, the risk of specific micro- and macrovascular complications is high. Characteristic for DM 1 complaints in the debut of the disease are thirst, frequent urination with phenomena of nocturnal and daytime urinary incontinence in young children, weight loss or unexplained lack of weight gain (in infants), weakness, fatigue, recurrent skin infections, inflammatory diseases of the external genitalia. When these complaints appear, the development of DKA is possible within a period of several days to several months. Clinical symptoms of DKA are dryness of skin and mucous membranes, acetone odor in exhaled air, vomiting, impaired consciousness, up to coma, even rare breathing with deep noisy inhalation and increased exhalation (Kussmaul's respiration) [1,2,3,4,5,8,9,10,].

It is recommended in patients with DM to determine the content of antibodies to pancreatic islet cell antigens in blood (autoantibodies to glutamate decarboxylase - GADA; autoantibodies to tyrosine phosphatase - IA-2; autoantibodies to zinc transporter 8 - ZnT8) for differential diagnosis and confirmation of DM 1 in doubtful cases [12; 13]. The presence of one or more autoantibodies associated with DM (autoantibodies to glutamate decarboxylase - GADA; autoantibodies to tyrosine phosphatase - IA-2; autoantibodies to zinc transporter 8 - ZnT8) confirms the diagnosis of DM 1. The absence of autoantibodies does not completely exclude DM 1 (so-called idiopathic DM 1), but may be a reason for further investigation. Given the possibility of other types of DM, molecular genetic testing should be considered in children with negative diabetic AB titers [3,6].

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