

Diabetes as autoimmune disease - Diabetes type I

Evgenija Homsak

Department for Laboratory Diagnostics, University Clinical
Centre Maribor, Maribor, Slovenia

Corresponding author: evgenija.homsak@ukc-mb.si

Introduction

Type 1 diabetes mellitus (T1D), also known as insulin - dependent diabetes mellitus, is a chronic immune mediated disease that is characterized by selective loss of insulin producing β cells of the pancreatic islets in genetically susceptible subjects. The majority (95%) of cases are attributable to an autoimmune-mediated destruction of β cells (type 1a) while a small minority (5%) of cases results from an idiopathic destruction or failure of β cells (type 1b) (1). T1D is observed in approximately 5-10% of diabetes mellitus patient. It may be present at any age and with equal affection of both sexes. It appears most typically in early life with a peak around the puberty, but one-fourth of cases are diagnosed in adults. T1D remains the most common form of diabetes in childhood, accounting for approximately two-thirds of new diagnoses of diabetes in patients ≤ 19 years of age in the United States, despite the increasing rate of type 2 diabetes. The incidence of T1D varies 50-100 fold around the world, with the highest rates in northern Europe, with 57.4 cases/100.000 per year in Finland and with relatively low incidence of 0.6/100.000 in China (2). The incidence of childhood T1D is rising rapidly in all population, especially in the age under 5 years, that suggests a strong environmental contribution. Lately, through several studies, there are strong efforts to understand and explain pathogenesis and find the new therapeutic options of the disease according to potential auto-antigens (insulin) and different environmental factors, as an important key in the development of T1D. But the role of specific factors such as viruses or ingested food (milk) remains controversial (3,4). Diagnosis of clinical

manifested T1D is based traditionally on diabetes mellitus typical clinical symptoms: polyuria, increased thirst, weight loss, weakness, hunger, recurrent infection and in severe insulinopenia the patient are prone to diabetic ketoacidosis. Important diagnostic parameters are also for T1D characteristic HLA gene and especially different auto-antibodies against antigens of β cells, which could be present several years before clinical manifestation of disease.

Pathogenesis

T1D is an autoimmune disorder against the β cells of the pancreatic islets, that remain only 10-20% functioning at the time of diagnosis. For T1D is characteristic subclinical prodrome of variable duration, as the pathogenetic process begins years before the clinical onset, when the tolerance to self-autoantigens is lost (5). The whole process and factors that contribute to and influence the destruction of the β cells is still not known. Still limited current knowledge of pathogenesis of T1D as autoimmune disease is based on several important known facts, which have been gained through several studies, mostly using animal models and confirmed by human clinical trials. This process occurs in genetically susceptible subjects, is probably triggered by one or more environmental agents, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. Important genetic predisposition in the presence of not yet defined triggers and modulators from the environment could influence on modulation of immune system to lose the tolerance to auto-antigens and results with several autoimmune reactions, local inflammation (insulinitis), specific T cell (LyT) and B cell (LyB) responses, autoantibody production, and cell destructions. The proposed mechanism of autoimmune inflammation process start with presentation of self antigens on antigen presenting cells (dendritic, LyB, macrophage), that after releasing interleukin (IL)-12 activate LyT (CD4 T) that produce important key cytokine INF- γ . They inhibit Th2 cytokine production, enhance production of toxic cytokine (IL- β , TNF- α) and free radical by mac-

rophage, and activate cytotoxic CD8T cells that affects the β cells. Important connection between LyT and LyB causes activation of LyB for production of auto-antibodies. Auto-antibodies, several cytokines, cytotoxic CD8T cells with releasing perforine, granzymes or by Fas-mediated apoptosis affect and progressively destroy the β cells. Additionally local chemokine production attracts auto-reactive lymphocytes that potentiate the destructive autoimmune process. (4,5,6) In pathogenesis of T1D we could find some similarities with other autoimmune diseases, like celiac disease; the common genetic susceptibility, unknown hypothetical trigger from environment, infection, driving auto-antigen, autoantibodies and outcome (1/5 of with HLA conferred susceptibility progresses to clinical disease).

Genetics: Disease susceptibility is highly associated with the inheritance or presence of certain human leukocyte antigen (HLA), which is characteristic for autoimmune diseases. HLA molecules are responsible for presentation of peptides (also auto-antigens) to Ly T cells and are involved in thymic selection of new generated T cell repertoire (central tolerance), to avoid potential autoimmune clones that could be released into the periphery. Therefore, a defect within the thymus or presence of specific HLA molecules allows autoimmune T cells to escape central tolerance. HLA genes on short arm of chromosome 6p21.3 with alleles DR3 and DR4 as well as the associated alleles DQ2 and DQ8, that are expressed either as DR3DQ2 or DR4DQ8, are present in more than 90% of individuals with T1D (7). Remain 10% of T1D might have influence of 20 non-HLA genes. Among them are important polymorphisms on insulin locus on chromosome 11p5.5 (PTPN22 and INS VNTR) that contributes approximately 10% to the familial aggregation of disease (8). As with HLA, peripheral T cell repertoires may be significantly influenced by polymorphisms in the insulin gene affecting thymocyte selection. Recent studies identifies autoimmune disease associated polymorphisms of T cell regulatory gene CTLA-4 (chromosome 2q22), that reduce the efficiency of regulatory function of LyT4CD4 cells (9). Understanding the genetics of T1D as well the determination of susceptible pop-

ulation is important for predicting disease, accuracy of diagnosis, prognosis and treatment.

LyT and LyB involvement: Autoimmunity and involvement of LyT is further supported with the presence of specific LyT infiltrates within inflamed islets of pancreas of patient with T1D, according to Imagawa and co-workers, who found close correlation between serological and histological markers and histological evidence of cellular autoimmunity (10). Insulitis as autoimmune inflammation could be present years before hyperglycemia is evident. Ly B cells also serve as antigen presenting cells and as autoantibodies producing cells (6). Both Ly as important actors of disease could be target of the future therapeutic options.

Autoantibodies: There are five disease related autoantibodies: islet cell antibodies (ICA), insulin autoantibodies (IAA) with epitope on B-chain of insulin molecule, autoantibodies against 65-kDa isoform of glutamic acid decarboxylase (GAD65), tyrosine phosphatase related IA-2 molecule or insulinoma associate antigen-2 antibodies (IA-2) and zinc transporter protein (ZnT8). Presence of autoantibodies are evident years before clinical onset and are mostly the first sign of autoimmune process, that will or not progress to T1D. Several studies confirm their important role in prediction of the disease development and appearance according to the detection of different specific autoantibodies (4,5,11). Mrena and co-workers in the Finnish DIPP study observed that presence of positivity for only a single autoantibody specificity for several years represents in most cases harmless non-progressive β cell autoimmunity, whereas the presence of two or more autoantibodies reflects a progressive process (10). But their direct pathogenetic role is controversial, since transfer of autoantibodies, using serum of diabetic humans, alone did not reconstitute disease and that plasmapheresis provides little therapeutic benefit (6,12).

Environment factors as a triggers and drivers of disease: There is still unexplained cause of initiation of the autoimmune process and why the auto-antigens become auto-antigenic. The factors that control progression from insulitis (inflammation of the β cells) to diabetes remain largely un-

known. Understanding this may provide new opportunities for preventing disease among population with high risk for developing T1D or halt progression of the β cells lost.

There are recently several approaches for preventing studies that might contribute to knowledge of disease process. The lack of complete concordance among monozygotic twins (only 20-40%) indicates that both genetic and environmental factors contribute to the pathogenesis of T1D. There are several environmental candidates that might trigger and modulate this autoimmune process: early introduction of milk food (bovine insulin, milk casein), entero-viruses (rubella, coxsackie), infection, vitamin D. But unfortunately recent studies gave us controversial results and have not been able yet to confirm their unequivocal role. And there are also several autoantigens as trigger candidates: insulin, GAD65, which could represent the potential future therapeutic target. (4,5,6)

Diagnosis

The presence of autoantibodies confirms the T1D. But they are also capable to identify insulin-requiring older patients who are initially diagnosed with type 2 diabetes. They typically have GAD65 or IA-2. These adult patients have a form of latent autoimmune diabetes in adult (LADA) or slow progressive insulin dependent diabetes mellitus (SPIDDM) (6). They can have pronounced hyperglycemia and after therapy with oral hypoglycemic agents for several months or years, they may become insulin dependent.

Diagnosis of T1D is still based on typical clinical symptoms, as the consequences of the end stage of progressed disease. Determination and monitoring of glucose levels by measuring concentration of glucose, glycosylated haemoglobin (HbA1c), fructosamine, according to ADA and WHO criteria, is important. But promising screening marker for general population would be genetics and autoantibodies that could define the risk population for possible preventing treatment in the future.

Thus, genetic markers for T1D are present from birth, immune markers are detectable after the onset of the autoimmune process, and metabolic markers can be detected with sensitive tests once enough β cell damage has occurred, but before the onset of symptomatic hyperglycemia. This long latent period is a reflection of the large number of functioning β cells that must be lost before hyperglycemia occurs.

New therapeutic options

The complete puzzle of pathogenetic process of T1D, with known all (f)actors, will give us the opportunity for new therapeutic options. Recent studies are concern on immune therapy at three different stages. Primary prevention is treatment of individuals at increased genetic risk, without known presence of autoantibodies. There were and still are several ongoing studies that try to find out probable environment factors (nonautoantigens) and autoantigens as well, that could as therapeutic agent reduce T1D incidence in genetically predisposed infants (hydrolyzed casein milk formula, Vitamin D, insulin). Secondary prevention is targeted at individuals with persistent islet autoantibodies. Ongoing trials involve non-autoantigen and autoantigen specific therapies (Bacillus Calmette-Guerin vaccine, anti-CD3 monoclonal antibodies, oral and nasal insulin, recombinant GAD65). Trial interventions at onset of T1D also included non- and autoantigen approaches (proinsuline peptide). According to current results, primary prevention studies are the major goal in the future as would aim to induce immunological tolerance to islet autoantigens. Unfortunately completed secondary prevention and intervention trials show little promise of achieving the preservation of β cell function. (5)

There are, as already used and as a future direction for managing the onset T1D disease, new approaches of different alternative source of islet cells: as pancreas transplant, islet cell transplant, xenogenic islet cells (humanized pig islet cells), expansion and trans-differentiation of pancreatic duct cells, fetal pancreatic stem cells and β cell

precursors, embryonic stem cells, and engineering other cells to produce insulin (duodenal K cells, hepatocytes, pituitary cells have been successfully transfected). (6)

Conclusion

Diagnosis of T1D is no longer the matter of only young population, despite the incidence in early childhood rising in world population. The recognition of LADA type is becoming important also for the adult patients, who have been previously not

diagnosed. Both populations need reasonable treatment and possible prevention steps as well to prevent the disease progress to the end stage. Importance of understanding the complete pathogenic process of T1D is very important not only for diagnoses approaches, but also for prediction and probable prevention of disease in genetic susceptible or general population. According to these knowledge there would be the possibility for creation and developing the new therapeutic approaches that will help manage the disease on several points of its development, especially to prevent islet autoimmunity or halt progressive β cell destruction.

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