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Role of gluten-free diet in pathogenesis of type 1 diabetes – what new?

Rola diety bezglutenowej w patogenezie cukrzycy typu 1 – co nowego?

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Abstract
Over the last decades, the association between coeliac disease and other autoimmune disorders, such as autoimmune thyroid diseases or diabetes mellitus type 1 has been well established through many studies, and to this day is subject to an on-going clinical and scientific investigation worldwide. Type 1 diabetes (T1D) and coeliac disease (CD) share a similar genetic background, with high susceptibility associated with the HLA-DQ2/DQ8 genotype. Interplay between ingested gluten and the subsequent development of type 1 diabetes has been revealed by studies in humans and animals. The study shows that a diet without gluten reduces the level of NKG2D receptor and its ligand expression in mice on a gluten-free (GF) diets. Thus, gluten may affect diabetes development by influencing proportional changes in immune cell populations or by modifying the cytokine/chemokine pattern towards an inflammatory profile. This supports an important role for gluten intake in the pathogenesis of type 1 diabetes. It is reasonable to conduct further researchto clarify whether a gluten-free dietcould prevent disease in susceptible individuals or be used with newly diagnosed patients to stop the disease. These observations may be important for the primary prevention of diabetes.
Key words:
gluten, gluten-free diet, prevention of type 1 diabetes

Streszczenie
W ostatnich dekadach związek pomiędzy występowaniem celiakii a innymi autoimmunologicznymi schorzeniami, takimi jak autoimmunologiczne schorzenia tarczycy czy cukrzyca typu 1, został ustalony w wielu badaniach i jest do dziś przedmiotem klinicznych i naukowych obserwacji na całym świecie. Cukrzyca typu 1 (T1DM) i choroba trzewna (CD) mają podobne tło genetyczne związane z genotypem HLA-DQ2 / DQ8. Współzależność pomiędzy spożywaniem glutenu a późniejszym rozwojem cukrzycy typu 1 została wykazana w badaniach u ludzi i u zwierząt doświadczalnych. Badania te dowiodły, że dieta bez zawartości glutenu obniża poziom receptora NKG2D i ekspresje jego ligandów u myszy (GF). Tak więc gluten może rzutować na rozwój cukrzycy poprzez wpływ na modyfikację wzoru stosunku cytokiny/chemokiny, powodującą profil zapalny. Potwierdza to ważną rolę spożycia glutenu w patogenezie cukrzycy typu 1. Uzasadnione jest prowadzenie dalszych badań w celu wyjaśnienia, czy dieta bezglutenowa może zapobiec chorobie u osób predysponowanych lub czy może być zastosowana u pacjentów ze świeżo rozpoznaną cukrzycą w celu zatrzymania jej rozwoju. Te obserwacje mogę być ważne w pierwotnej prewencji cukrzycy.
Słowa kluczowe:
gluten, dieta bezglutenowa, prewencja cukrzycy typu 1

Introduction

Type 1 diabetes is an autoimmune disease that is frequently accompanied by other illnesses, ex.: autoimmune thyroid disease, celiac disease, gastroenteritis, malignant anaemia, albinism [1–3].

Higher incidence of celiac disease in type 1 diabetes in comparison with the general population is known and appointed for a long time. The tissue infiltrations from immunocompetent cells, tissues destruction and specific organ hormonal reaction are observed in cell characterized autoimmune diseases, like type 1 diabetes as well as celiac disease. Concomitance of these two illnesses may be connected with an association between genetic (HLA system alleles DRB1*04 DQB1*0302, DRB1*03 DQB1*0201), immune (lymphocyte T, cytokines production) and environment factor (including infections) [4,5].

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In the opinion of many authors bacterial flora of bowels plays an essential role in the progress of autoimmune disorders, including celiac disease and type 1 diabetes [6,7].

The incidence of genotype HLA DQ varies in patients that suffer from celiac disease and type 1 diabetes in comparison with patients with just one of these illnesses.

HLA system genes play a significant role, the contribution of other factorsfrom beyond the HLA system stays unknown [8,9].

Another factor that may signalize the pathogenic correlation between these two diseases is a higher activity of zonulin – the protein responsible for loosening of epithelium cells tight joints and for the increase of epithelium permeability. The high concentration of zonulin leads to intestinal barrier function disorder so the antigenes involved in appearance and progression of celiac disease and related autoimmune disorders, eg. type 1 diabetes enter the organism [10].

It seems that significantly higher incidence of celiac disease in type 1 diabetes can be linked to genetic factor in HLA system as well as antygene mimicry phenomena. The islands of pancreas disorder in the initial progression phase of type 1 diabetes may lead to transglutaminase C release from β cells of the pancreas and induction of autoimmune response that initiate celiac disease development [11–13].

Gluten role as a factor stimulating autoimmunization process

Recently, more and more attention has been focused on gluten role as a factor stimulating autoimmunization process in bowels mucosa as well as in β-cells in islet of Langerhans [5].

A certain kind of news is the information that type 1 diabetes and celiac disease have similar genetic background related to HLA-DQ2 / DQ8. This statement has become a base for the research on gluten-free diet application in patients with this type of genetic system but without celiac disease symptoms in early period after type 1 diabetes diagnosis.

There is more and more information available about the influence of such a diet on regression of type 1 diabetes. It was revealed that gluten-free diet may have a positive influence on maintaining β-cells functions in patients with a high factor of genetic risk in type 1 diabetes progression. The mechanism of gluten-free diet for the protection of β-cells function has yet to be explained. The question whether a gluten-free diet practice in patients who are genetically predisposed to type 1 diabetes and celiac disease may prevent diabetes progression or whether it can be applied in patients with new diagnosed diabetes to slow down the progress of disease, needs further research.

Investigation and prevention of type 1 diabetes have a long-standing history. It is believed that the progression of this disease depends on not only genetic but also environmental factors that, in people genetically predisposed, can induct autoimmune processes [14,15].

The role of the induction of autoimmune processes that lead to diabetes progression is put down to bacterial flora, i.a [7].

Much attention is also paid to dietary factors [16,17].

Cow's milk is considered to be one of the dietary factors [18].

For many years, this factor has been the subject of research as a part of big international programme TRIGR (Trial to Reduce IDDM in Genetically at Risk) run in 77 science centres on 3 continents (Australia, Europe, North America) [19–21].

Another environmental factor that was a subject of research is gluten [17].

The experimental research on gluten-free diet application in diabetes prevention in mice has been conducted by Fund et al. since 90's of the last century [22,23]. These authors showed a significantly lower rate of diabetes occurrence in mice put on a gluten-free diet.

Recently, Sweden authors have issued a report in which they revealed that gluten-free diet application in mice decreases the level of NKG2D receptor and its ligand expression. These changes influence immune processes, hence they may contribute to lower occurrence of type 1 diabetes [24].

Interesting experimental cell research on gluten-free diet role in inhibition of type 1 diabetes progress in mice has been presented recently by Danish investigators [25].

American authors have drawn attention to the fact that the application of gluten-free diet in experimental research is associated with the change oinf bacterial flora of bowels, and these changes limit hyperglycemia occurrence in investigated mice [26].

Similar research was conducted by Danish investigators who stated that gluten-free diet application in pregnant mice and in new-born mice decreases incidence of diabetes what may be related to the changes in bacterial flora of bowels and therefore may limit the occurrence of immune reaction in bowels and pancreas [27]. Similar observations were performed by Canadian authors [28].

The attempts to determine factors that influence the progress of autoimmune processes, hence in effect contributing to the progress of diabetes, lead to the formulation of diabetes prevention programmes [29,30].

Nowadays, the most expanded actions are put in secondary prevention category that is applied after the start of an autoimmunization process. Its scope is to protect undestroyed β-cells of pancreas. As a part of this actions, experimental therapies are applied [31,32].

This kind of therapies is also used in Poland [33,34].

However, the special attention is paid to research on possibilities of primary prevention application.

The goal of this kind of prevention is the elimination or "neutralization" of pathogenetic factors that lead to disease progress. In the case of type 1 diabetes, the modification of environmental factors in the potential possibility. The exchange of genetic pool is currently not possible.

Due to the fact that among environmental factors, significant role is assigned to diet, hence the programmes aimed at determining nutritional factors that may influence on activating autoimmune processes in patients genetically predisposed to diabetes.

Researches mentioned above, mainly experimental ones, reveal that gluten may be one of such factors. Generally in the past it was stated that gluten intolerance occurs in patients who had type 1 diabetes diagnosed earlier. At present, it is believed that gluten may be the initial factor activating autoimmune processes in relation to β-cells [26,35].

For the time being, there are many ambiguities hence the researches require further continuation.

The comprehensive based-on-literature review of researches on trials of primary and secondary prevention application was presented by Skyler JS [36].

The research progress is very clear but the final effects will be known later [37].

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