DOI: 10.25179/tjem.2017-56528
Turk J Endocrinol Metab 2017;21:127-130

The Role of Gluten-free Diet and Intestinal Microbiota on Glycemic Control and Diabetes Development

Glutensiz Diet, İntestinal Mikrobiotanın Glisemik Kontrol ve Diyabet Gelişimindeki Rolü

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Abstract

A gluten-free diet offers immense health benefits in certain autoimmune diseases including dermatitis herpetiformis, rheumatoid arthritis, and neurologic disorders; besides its therapeutic potential has also been documented in other conditions such as diabetes mellitus, HIV-associated enteropathy, and celiac disease.

In animal models, a gluten-free diet has been associated with the reduced auto-inflammatory process, altered inflammatory cytokine response as well as intestinal microbiota leading to lower the incidence of diabetes. The acidic environment has also been shown to affect the gut microbiota resulting in reduced incidence and delayed onset of diabetes in genetically predisposed individuals.

In the current article, it has been proposed that intestinal microbiota play a major role in stimulating an immunological response; and the acidic environment affects the gut microbiota, and thus improves the immunological milieu. Gluten-free diets positively boost the immunological response in animal models and combat with autoimmune diseases in human beings by affecting the gut flora. The association between gluten-free diet, gut flora, immunological response, and environment may play a decisive role in plummeting the advancement of diabetes.

Keywords: Gluten-free diet, cytokines, intestinal microbiota, acidic environment, diabetes mellitus

Özet

Glutensiz diyet, dermatit herpetiformis, romatoid artrit ve nörolojik bozukluklar gibi otoimmün hastalıklarda sağlığa faydalı etkiler sunmaktadır; ayrıca diabetes mellitus, HIV ile ilişkili enteropati ve çölyak hastalığında da tedavideki olumlu etkinliği bildirilmiştir.

Hayvan modellerinde, glutensiz diyet otoinflamatuvar süreçde baskılanma ve değişen inflamatuvar sitokin yanıtı ile diyabet insidansında azaltmaya yol açan bağırsak mikrobiyota değişimi ile ilişkilendirilmiştir. Asidik ortamın bağırsak mikrobiyota ortamını etkilediği ve genetik olarak yatkın bireylerde diyabet insidansı azalttığı ve diyabetin başlamasını geciktirdiği gösterilmiştir.

Bu makale ile bağırsak mikrobiyotasının immünolojik cevabı uyarmada önemli bir rol oynadığı sunulmaktadır; ve asidik ortam bağırsak mikrobiyotasını etkileyerek immünolojik ortamı geliştirir. Glutensiz diyet, bağırsak florasını etkileyerek hayvan modellerinde immünolojik yanıtta ve insanda otoimmün hastalıklarla mücadelede olumlu yönde destek sağlamaktadır. Glutensiz diyet, bağırsak florası, immünolojik tepki ve immünolojik ortam arasındaki ilişki, diyabetin ilerlemesini azaltmada belirleyici rol oynayabilir.

Anahtar kelimeler: Glutensiz diet, sitokinler, intestinal mikrobiota, asidik çevre, diabetes mellitus

Introduction

Gluten is an important ingredient of wheat protein, as about 90% of the total protein content is gluten. Besides, it is also present in barley, oat, and rye (1–3), and these gluten-rich cereals constitute the major part of our diet. Gluten is a water-insoluble protein and consists of two major fractions, i.e., gliadin and glutenin. Gliadin is the aqueous alcohol-soluble fraction, and its firm peptide configuration renders it resistant to lytic enzyme system in the gastrointestinal tract and this distinct resistance is considered to trigger

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immune reactions and gluten sensitive diseases. Gluten reactions have recently been classified into three categories *viz.* allergic (wheat allergy), autoimmune (celiac disease, dermatitis herpetiformis, and gluten ataxia), and possibly immune-mediated (gluten sensitivity) (4). These reactions are perceived to be involved in the etiology of the underlying basis of autoimmune and idiopathic disease.

The Gluten-Rich Wheat-Flour Diet and Diabetes Mellitus

The gluten-containing wheat-flour diet has been associated with an increased frequency of diabetes mellitus in animals. In non-diabetic mice, feeding with wheat-flour diet increased the incidence of diabetes mellitus and insulitis severity, whereas feeding with hydrolyzed casein diet was found to reduce the incidence of diabetes. On the contrary, feeding a hypo-allergenic soybean-protein hydrolysate resulted in an incidence of diabetes mellitus and insulitis severity similar to that of the soybean-meal-fed group. It is assumed that protein hydrolysis may not affect occurrence and severity of diabetes (5). This study shows that feeding with the wheat-flour diet despite the presence of hydrolyzed protein plays a major role in the progression of diabetes. Concerning this study, mice fed on a wheat-based diet exhibited a higher incidence of diabetes, the signs of small intestinal enteropathy and higher mucosal levels of pro-inflammatory cytokines (6). In addition, wheat-free and barley protein-free diet were also found to be associated with reduced incidence and delayed onset of diabetes. Likewise, reduced insulin autoantibodies and lower insulitis scores were also recorded. Furthermore, the supplementation of fish-oil or vitamin D3 to the wheat-free diet did not provide any additional benefit toward subsiding the incidence of diabetes mellitus (7). These findings postulate that gluten content of wheat-based diet might have been associated with the increased incidence of diabetes.

Evidence for Benefits of Gluten-Free Diet Other Than Diabetes Mellitus

A gluten-free diet has been exhibited to deliver positive health benefits in certain autoimmune disease including dermatitis herpetiformis, neurological disorders, rheumatoid arthritis, along with other conditions such as diabetes mellitus, HIV-associated enteropathy and celiac disease (8).

In patients with IgA nephropathy, the average level of IgA was significantly declined in about 81.8% of cases with complete normalization in 63.6% patients after six months to one year of a gluten-free diet (9).

In a controlled case study, about 66 patients with active rheumatoid arthritis (RA) were evaluated and randomly kept on either a gluten-free vegan diet (38 patients) or a well-balanced non-vegan diet (28 patients) for one year. The improvement ratio of RA in the gluten-free vegan diet was 40.5%, against the 4% in the non-vegan group after the stipulated follow up period. Furthermore, the levels of immunoglobulin G (IgG) antibody against gliadin and beta-lactoglobulin were found to be lower in the gluten-free vegan group than the non-vegan group (10).

Besides, in case of diseases with uncertain etiology, a gluten-free diet has also been shown to offer encouraging benefits. In a questionnaire-based survey study, strictly gluten and/or casein-free diet were also found to improve autism spectrum disorders (ASD) behaviors, physiological symptoms, and social behaviors ($p< 0.05$). The study consists of a parental report of data collected on the efficacy of the gluten-free and/or casein-free diet using a 90-item online questionnaire from 387 parents or primary caregivers of children diagnosed with ASD. Authors suggested that various factors including gastrointestinal and immune system could play a role in response to diet interventions (11).

Furthermore, the gluten-free diet has recently been used for management of painful endometriosis-related symptoms. The Visual Analogue Scale (VAS) was used to assess the painful symptoms for dysmenorrhea, non-menstrual pelvic pain, and dyspareunia in 207 patients. A significant improvement was recorded in pain symptoms in 156 patients (75%) after 12 months of diet. Interestingly, a substantial increase in the scores for all domains of physical functioning, general health perception, vitality, social functioning, and mental health was also recorded in all the patients (12). The mechanism of pain-related symptoms might be related to immune regulation of gut flora. It has been advocated that gluten-free diet considerably contributes toward the improvement of immunological response and alleviation of immunological diseases severity.

Intestinal Microbiota, Immunological Milieu, Acidic pH Water Milieu, and Gluten-Free Diet

In animal models, a gluten-free diet has been associated with suppressing auto-inflammatory process, improving inflammatory cytokine secretion, and altering intestinal microbiota leading to a poor incidence of diabetes.

Dietary habits have a profound effect on both intestinal microbiota and glycemia. In non-obese diabetic mice, a gluten-containing diet was found to increase the prevalence of hyperglycemia, while the gluten-free diet decreased it. Besides, the fecal microbiota was also found to change according to the dietary contents. *Bifidobacterium* spp. were predominant in gluten-containing diet, whereas in gluten-free diet *Akkermansia* spp. were prevalent (13).

The gluten-free diet has been associated with lower incidence and delayed onset of diabetes after 320-day follow-up compared to standard diet in mouse models (14).

In an interim three-week observation study, 9 out of 19 (47%) non-obese diabetic mice on a standard diet developed diabetes, while 1 out of 19 (5%) developed diabetes on a gluten-free diet. This reduced diabetes occurrence could be attributed to the distinct fecal bacterial composition (15).

It has been shown that mice on a gluten-free diet had lower insulitis along with lower expression of natural killer group 2D (NKG2D) on natural killer (NK) cells and CD8+ T cells in spleen, auricular lymph nodes and pancreas-associated lymph nodes (16).

Alterations in intestinal microbiota have been indicated to reduce the risk of diabetes in mice. The authors suggested that progression of type-1 diabetes to later stages might have been delayed by early dietary management creating an acidic environment in ge-

netically predisposed individuals (17). In murine models with type-1 diabetes, the intestinal flora was shown to alter in favor of bacteroids in comparison to healthy controls (18, 19). The modified composition of microflora apparently affects T cells especially interleukin–17 (IL-17) producing T helper (T_h) and regulatory T cells (20–24). The T helper 17 (T_h17) cells play a potential role in protecting the pathogens and inducing inflammation and autoimmunity (25–27), whereas regulatory T cells prevent inflammation and confer immune tolerance (25, 28, 29). Recent studies have reported that segmented filamentous bacteria played a crucial role in inducing T_h17 cells localized in lamina propria of intestinal mucosa and lenfoid tissue (24, 30). Besides, increased IL-17 secreting T cells have also been observed in newly started type–1 diabetes (31).

Furthermore, the consumption of acidic water has also been reported to influence intestinal microbiota and the levels of T_h17 and T regulatory cells. Such an alteration in the fluidic pH has also been found to be associated with reduced occurrence of diabetes (17).

In a recent study, pregnant non-obese diabetic mice were fed on a gluten-free diet and their off-spring were marked with increased *Akkermansia* and Probacteria species. Further, the gluten-free fed offspring reportedly exhibited increased regulatory T cells and reduced gene expression of intestinal pro-inflammatory cytokines. In fetal and early postnatal stages, the gluten-free diet has been witnessed to reduce the incidence of diabetes in mouse models and it has been suggested that an altered intestinal microbiota may transform the intestinal and pancreatic immunological milieu to less inflammatory state (32).

It has been shown that the gut microbiota, type-1 diabetes incidence and rate of disease progression are significantly affected by the pH of water consumed. In acidic water, the transferred segmented filamentous bacteria suppressed the incidence of insulitis as well as type-1 diabetes in mice model (33).

These animal models advocate that intestinal microbiota play a dominant role in stimulating the immunological response, and acidic environment of intestine affects the gut microbiota and consequently alters the immunological status.

Gluten-Free Diet in Human Studies

The controlled and follow-up studies conducted in humans concerning gluten-free diet are scarce. In a recent study, 21 healthy volunteers were subjected to a gluten-free diet and observed for four weeks. After follow-up period, there was noticed a significant difference in the gut microbiota, where the class of clostridia was significantly reduced (34).

In human models, after a six-month of follow-up, the gluten-free diet did not affect autoantibody titers in individuals at high risk of type–1 diabetes. However, diet showed a beneficial effect on insulin secretion in individuals at high risk for type–1 diabetes (35). This could also be due to the limited follow-up period.

In a study carried out in Spain, about 10 healthy subjects were followed over a month on gluten-free diet. In fecal analyses, there was observed a significant reduction in *Bifidobacterium* and *Lactobacillus* groups while the notable upsurge in *Escherichia coli* and Enterobacteriaceae. Likewise, in a cytokine analysis following the gluten-free diet, titration of cytokines TNF-α, IFN-γ, and the chemokine IL–8 were reported to decline significantly (36).

In the light of recent evidence, the gluten-free diet may probably change the gastric pH to the acidic leading to alteration in gut microbiota and cytokine production cells. The acidic environment coupled with altered flora seems to reduce the diabetes incidence associated with a gluten-free diet.

Although the human studies have revealed an association of gluten-free diet with altered intestinal microbiota and improvement in inflammatory cytokines production. However, further studies are still required to evaluate the correlation between gluten-free diet and intestinal microbiota composition and to determine their clinical benefits in a comprehensive manner.

Conclusion

Diabetes mellitus displays an increasing prevalence throughout the world. The consumption of floury foods containing gluten may be responsible for the higher incidence of diabetes. The gluten-free diet has shown a beneficial effect on stimulating an immunological response in animal models and subsiding autoimmune disease in human beings by altering the intestinal flora. Gastric pH and intestinal microbiota vary according to food consumption and these alterations play important roles in abating the immunological dysregulation. In relation to these conclusions, the gluten-free diet has been revealed to reduce the incidence of diabetes in animal models and improve insulin response in human beings. However, further studies are still required to assess the cross-talks between gluten-free diet, gastric pH, intestinal microbiota and progression of diabetes.

Author Contributions

Concept: Evrim Cakir.Design: Evrim Cakir. Data Collection or Processing: Evrim Cakir. Analysis or Interpretation: Evrim Cakir. Literature Search: Evrim Cakir, Esra Ataoglu, Mustafa Yenigun. Writing: Evrim Cakir, Esra Ataoglu, Mustafa Yenigun.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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