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TYPE 1 DIABETES AND GLUTEN INTAKE

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Abstract

Type 1 diabetes is a chronical disease which comes along with dependence on insulin lifelong. Among newly diagnosed patients, incidence of type 1 diabetes has increased. Meanwhile, there is a decrease in the prevalence of high-risk HLA haplotypes. This situation coincides with increasing factors such as the use of antibiotics, popularity of low fiber intake, and high intake of gluten, suggesting environmental factors may potentiate autoimmunity in beta cells. The hypothesis is that gluten may be affective on immune cell populations and profile of cytokine, lead to gut microbiota's dysbiosis. Studies have shown that gluten intake increases risk of type 1 diabetes as well as no effect, and it has been suggested that gluten exposure during fetal life and time of first exposure may be a factor. In studies on gluten-free diet, results such as better glycaemic control and reduction in hypoglycaemia have been obtained. Although there are inferences that high gluten intake is related to a rise in the risk of type 1 diabetes, there are some opposite inferences. This review article has been prepared by reviewing the literature within last eight years and it was aimed to evaluate the mechanisms of gluten in development of type 1 diabetes.

Keywords: type 1 diabetes, gluten, islet autoimmunity

1. Introduction

Type 1 diabetes is a disease which is chronic, and it is commonly observed in childhood. Pancreatic β cells' immune-mediated destruction has a part, and the result is that there is a dependence on insulin from external sources lifelong (Lund-Blix et al., 2019). The asymptomatic prediabetic period is termed as islet autoimmunity (IA). This period is also known to be highly predictive of type 1 diabetes. The character of this period is islet autoantibodies' appearing (Johnson et al., 2021). For the children who can be considered as having a high risk at type 1 diabetes, seroconversion to islet autoimmunity is known to happen after 6 months of age in general. Its peak time is also known to happen at 12-24 months of age (Norris et al., 2020). It is known that type 1 diabetes can occur at any age. However, it mostly occurs in the period of being a child or in the period of life when a child develops into an adult, meaning adolescence. Intense observation of type 1 diabetes is between the ages of 5-7 and as puberty approaches (Toni et al., 2017). Genetic susceptibility is a factor which is well established in type 1 diabetes' development. Alongside that, there is an increasing rate when it comes to the incidence of the disease. This is why, it has been suggested that environmental factors can also have an essential share in the state of the disease to be developed (Lund-Blix et al., 2019).

Gluten was introduced into our habitual nourishment around 10,000 years ago in Mesopotamia. It was a place where our progenitors started eating grains. Today, grains are an important root of nutrition worldwide and it accounts for more than half of the world's daily calorie intake (Haupt-Jorgensen et al., 2018). Nowadays, gluten has become a frequently mentioned food due to its association with different diseases (Kutlu, 2019). It has been hypothesized that gluten is one of the environmental factors. And it is actively participating in the state of being developed for type 1

diabetes (Lund-Blix et al.,2019). In this study, the leading aim is to evaluate the possible mechanisms and effects of gluten in the development of type 1 diabetes.

2. Type 1 Diabetes

The state, which is characterized as insulin deficiency being absolute, i.e., type 1 diabetes, occurs in case of insulin-secreting β cells' autoimmune destruction, and other hereditary or acquired conditions. It is known that it can also be observed in the complete absence of insulin receptors, but this is known as a rare situation (Yau et al., 2021). Intensive efforts have been made to understand, prevent, and treat type 1 diabetes. It has been found that it is autoimmune and ultimately driven by T cells. It has also been found that autoantibodies exist, and these autoantibodies can be used for diagnosis (Buschard, 2022). While genetic susceptibility taking part as the setting, immune activation becomes a matter and after that, the disease is known to progress through presymptomatic stages defined by the presence of autoantibodies and impaired glucose intolerance, which is caused by additional loss of β-cell function and it eventually results as clinical diabetes (Yau et al., 2021). The disease begins with autoreactive T cells, and these cells cause insulin-producing beta cells' destruction in pancreas. The result which comes due to that is known as hyperinsulinemia and hyperglycaemia. It is a multifactorial disease with genetic background and environmental factors. It is known that genetic susceptibility and environmental factors interact and trigger the autoimmune response against beta cells (Infante et al., 2019). Its aetiology and pathogenesis are not completely understood (Haupt-Jorgensen et al., 2018; Johnson et al., 2021). Also, autoimmune diseases predominantly affect females, but type 1 diabetes affects both females and males equally. However, it is slightly more predominant for males in younger children. The acute clinical findings of the disease include dehydration, weight loss, electrolyte disturbances, polyuria, increased thirst, and metabolic decompensation and at more severe levels, diabetic ketoacidosis and non-ketotic hyperosmolar coma are observed (Yau et al., 2021). In diabetic ketoacidosis (DKA), kussmaul breathing, fatigue, nausea, and vomiting may be observed (Sapra et al., 2022). The microvascular complications of type 1 diabetes which appears originally are neuropathy, retinopathy, and nephropathy, but it can also produce an effect on the heart, cognitive function, and other organs. Meanwhile, macrovascular complications are known to occur as atherosclerosis and thrombosis in the heart, peripheral arteries, and brain. Hypoglycaemia and ketoacidosis which take place as the complications of the disease are life-threatening (DiMeglio et al., 2018). When medical nutrition therapy is not followed, the risk of microvascular and macrovascular complications of diabetes increases because of conditions such as long-term failure to achieve glycaemic control and HbA1c levels above 7% (Özkan et al., 2022).

After the finding of insulin in 1922, type 1 diabetes has changed from a fateful disease to a disease which can be treatable (DiMeglio et al., 2018). Multiple ways such as immunosuppressive therapies and antigen therapies have been tried to prevent type 1 diabetes (Buschard, 2022). Type 1 diabetes necessitates cautious monitoring of blood glucose levels. The administration of insulin several times a day through various routes is also required. It has a significant impact on the lives of patients and their families (Giwa et al., 2020). The fundamental aim of diabetes treatment is to keep the individual's blood glucose as similar as it can be to the physiologic range (Troncone et al.,

2022). In diabetes management, plans should be made in the form of nutrition, physical activity, insulin treatment and complication follow-up to ensure glycaemic control. An individual can lead a healthy life with a healthy lifestyle and diabetes-related complications can be delayed. Individuals should be followed up at intervals of at least 1-3 months (Ertem et al., 2021).

3. Type 1 Diabetes, Its Incidence and Environmental Risk Factors

Type 1 diabetes' incidence is known as increasing worldwide (Haupt-Jorgensen et al., 2017). It is mostly being observed in Finland, Italy, Sardinia and least in China, India, and Venezuela (Toni et al., 2022). In children aged ≤14 years, during the period which covers 1990-1999, the standard yearly rise in type 1 diabetes' incidence was reported to be 2.8%. Another epidemiologic study predicted that the incidence in European children who are under five years of age would double between 2005 and 2020 (Haupt-Jorgensen et al., 2018). The estimation for worldwide is that 600,900 children under 15 years of age live with type 1 diabetes. Also, 98,200 children under 15 years of age develop type 1 diabetes each year (Troncone et al., 2022). In a study conducted in Ankara in 1993, on the prevalence of type 1 diabetes, the prevalence in the 6-18 age group was reported as 27/100,000; in a study conducted in Istanbul in 2009 as 67/100,000; and in a national study conducted in 2014, the prevalence in the 0-18 age group was reported as 75/100,000 (Çarkçı and Özsoy, 2020). Highest incidence of the disease is known to occur between the ages of 10 and 14. However, it is clinically known that it can occur at almost any age from early infancy to the 9th decade of life (Giwa et al., 2020). The concordance rate between monozygotic twins in type 1 diabetes is 25-50%. By that means, it has been suggested that, alongside the genetics, environmental factors can also play a role (Haupt-Jorgensen et al., 2017). Currently, it is not achievable to hinder the disease. Environmental factors also have not yet been identified (Lund-Blix et al., 2019). HLA class II region, HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes are known to explain fifty precent genetic risk of the disease. The association between many environmental factors and transformation from increased susceptibility to type 1 diabetes has been created. When it comes to these factors, it can be said that; vaccines, toxins, physiologic stress, cow's milk, and dietary gluten can be included (Haupt-Jorgensen et al., 2018). In addition to these factors, anthropometric development, viruses, maternal age and weight, ethnic origin, number of siblings, microbiota, geographical location and seasons can also be included (Giwa et al., 2020). Even though, for gut microbiota, it has been thought that it has an essential share in type 1 diabetes' pathogenesis, the causality relationship has not yet been established. It has been observed that there is a rise in intestinal permeability and a decrease in bacteria which protects intestinal permeability in patients who have type 1 diabetes. Therefore, it has been thought that the interruption in the normal course for intestinal microbiota in childhood disrupts the developing immune system. So that, it also may be a pathogenic factor (Haupt-Jorgensen et al., 2018). Either type 1 diabetes' development or islet autoimmunity's development, dietary factors are also thought to be involved. Many studies have been based on when certain foods are introduced during infancy and the amount and frequency of consumption of certain foods during childhood (Johnson et al., 2021). Worldwide, wheat is the staple food after corn and rice. This is why many studies have suggested that wheat in the diet is diabetogenic (Gorelick et al., 2017). It is known that most of the children who develop type 1 diabetes before they reach 10 years of age have seroconversion in the first two years of life. By that means, it has been suggested that early life exposures might play an essential role in type 1 diabetes' development. In the context of foods, these exposures have been

evaluated through formula, cow's milk, breast milk, and cereal sources (Giwa et al., 2020). Recently, among newly diagnosed patients, incidence of type diabetes has increased. Meanwhile, there is a decrease in the prevalence of high-risk HLA haplotypes. This situation coincides with increasing factors such as the use of antibiotics, the popularity of low fiber intake, and a high intake of gluten, suggesting that environmental factors may potentiate autoimmunity in beta cells (Sargin et al., 2022).

4. Gluten

The endosperm storage tissues of wheat, barley and rye contain high amounts of gluten. Gluten is being assorted as a prolamine which comprises polymeric glutenines and monomeric gliadins as chemically. And most gluten components are known as hydrophobic amino acids, glutamine and proline. Having such structure, gluten resists to complete the process of degrading by pancreatic, brush border and gastric enzymes (Haupt-Jorgensen et al., 2018). Prolamins are not soluble in water, yet they are soluble in alcohol. Meanwhile, glutelins are not soluble in both alcohol and water. The terms glutenin and gliadin refer to wheat's glutelin and prolamin fractions. Meanwhile, the terms hordein, avenin, secalin refer to the prolamin fraction of barley, oats and rye respectively. Gluten is a general term for the glutelin and prolamin fractions of barley, rye, wheat and sometimes for oats (Passali et al., 2020). When gluten-related diseases are considered, the first and most common disease that comes to mind is celiac disease (Kutlu, 2019).

4.1. Gluten-Free Diet

The gluten-free diet is a lifelong elimination diet which replaces grains such as rye, wheat, barley, triticale, and products derived from them with gluten-free grains such as corn, rice, millet, sorghum, teff, pseudo-grains such as buckwheat, amaranth, psyllium, quinoa, and starchy foods such as potatoes and legumes. While oats are tolerated by most diabetics on a gluten-free diet, there are some reports that a small number of diabetics develop reactions to oats. Since contamination of oats with gluten-containing foods raises concern, the use of oats not labelled as ‘gluten-free’ is not recommended (Altınok and Gökşen, 2020). Deficiencies of some nutrients such as energy, protein, dietary fiber, vitamins, and minerals may occur in gluten-free diet followers. Gluten-free diets should meet macro and micronutrient requirements to prevent these deficiencies. It should also be balanced and feasible (Ulusoy and Rakıcıoğlu, 2019).

4.2. Gluten as an Environmental Risk Factor

Gluten's possible effects in type 1 diabetes’ development are uncertain. However, it has been considered that it may create a more proinflammatory cytokine profile, alter the immune cell populations or causes gut microbiota's dysbiosis (Lund-Blix et al., 2019). Gluten proteins found in rye, wheat and barley are thought to be more immunogenic than other efficiently hydrolysed dietary proteins, as they are rich in proline and glutamine and are therefore hydrophobic and resistant to intestinal degradation. At the same time, since the process leading to islet autoimmunity is thought to start in fetal life, being exposed to gluten in prenatal period and type 1 diabetes' development are considered to be associated with each other (Antvorskov et al., 2018). Type 1 diabetes and celiac disease are both caused by T cells or autoantibodies that begin to effect on the cells, tissues, or molecules of the

organism producing them. Such diseases can also be described as autoimmune diseases, and it is known that gluten intake is important in celiac disease. This is why, it has been suggested that gluten intake might be essential in type 1 diabetes (Johnson et al., 2021). As known, there is evidence which suggests that gluten is affective on β cells. And this evidence also suggests that gluten is affective on the other important and possible components which are associated with type 1 diabetes' development. Such components include the gut permeability, innate and adaptive immune system and pro-inflammation. On top of potentially activating the autoimmune response which can lead to β cell islets' destruction and to insulin production by that means, for gliadin, it is now known that it has reached to the pancreas. This is thought to cause inflammation and β cell stress (Söderström et al., 2022). At the same time, high-risk HLA molecules, which have also been mentioned among the genetic factors leading to type 1 diabetes, are known to bind certain parts of glutenin or islet self-antigens and present them to antigen-responsive T cells. Appropriate proinflammatory environment can cause autoimmune response and this can result with a destruction in pancreatic beta cells or intestinal enterocytes (Goodwin et al., 2019). Complex mixture of various storage proteins in wheat flour can be mentioned as glutenines, globulins, gliadins, and triticins. Among all these, α-gliadins are known to have the most toxic epitopes. And these epitopes are associated with celiac disease. It has been thought that wheat proteins are being engaged as a participant in the beginning of type 1 diabetes. However, it is still uncertain whether wheat gluten or other wheat storage proteins are liable to be called to account as the primary cause for the rise in increased rate of type 1 diabetes' beginning (Gorelick et al., 2017). Dietary gluten intake is thought to increase over time due to gluten added to industrially baked bread, but there is very little data on its quantitative effect (Norris et al., 2020). At the same time, gluten intolerance is known to potentiate dysbiosis as well as increased endotoxin circulation, intestinal permeability, and systemic inflammation (Sargin et al., 2022).

5. Type 1 Diabetes, Gluten and Gluten-Free Diet

Dietary proteins such as gluten have been considered as a trigger in the development of type 1 diabetes. In a study by Hakola et al. (2019), high intake of oats, dietary fiber, gluten, gluten-containing cereals were found to be related to a rise for the risk of islet autoimmunity in children who have genetic susceptibility towards type 1 diabetes. In a study by Lund-Blix et al. (2019), which aimed to investigate gluten intake, islet autoimmunity's development and type 1 diabetes' progression, gluten intake of children at risk for the development of type 1 diabetes was monitored and no relation between gluten intake and islet autoimmunity or a justification for reducing gluten intake between 1-2 years of age was found. In the same study, gluten to be introduced at <4 months of age was found to be related to a rise in the risk of progression from islet autoimmunity to type 1 diabetes compared to being introduced at 4-5.9 months of age. In a study conducted by Gorelick et al. (2017) on mice using modern wheat sources in diets and alternative wheat sources that do not contain wheat and antigenic determinants which are related to type 1 diabetes, a lower incidence of type 1 diabetes was observed in mice consuming alternative sources, suggesting that alternative sources can be used to reduce the incidence of type 1 diabetes. Based on a study showing that intranasal gliadin intake prevents autoimmune diabetes in diabetic and nonobese mice, Haupt-Jorgensen et al. (2017) conducted a study to investigate whether bakers were exposed to intranasal gliadin intake during work and whether there was an inverse association between this situation and type 1 diabetes. It has been considered that being exposed to gluten

in nasal mucosal way during work is related to lower rates of type 1 diabetes and that intranasal gliadin intake may be an easy and safe approach to prevent type 1 diabetes in at-risk or prediabetic individuals. It has been considered that the process leading to islet autoimmunity may start in fetal life (Antvorskov et al., 2018). In a study by Antvorskov et al. (2018) examining the relationship between gluten exposure in the prenatal period and the development of type 1 diabetes in children, it was concluded that for mothers to intake high gluten during pregnancy might cause a rise in the risk of type 1 diabetes development in children. In a study by Lund-Blix et al. (2020), which aimed to investigate the relation between maternal and child gluten intake and the development of type 1 diabetes in children, pregnant women's gluten intake was not found to be related to type 1 diabetes' development, but it was stated that high gluten consumption by the children at a young age might lead to a rise in the risk of type 1 diabetes. In a study by Johnson et al. (2021), which aimed to investigate the risk of islet autoimmunity and type 1 diabetes in the offspring with maternal gluten consumption in the last stage of pregnancy, no association was found between maternal gluten consumption and the risk of islet autoimmunity or type 1 diabetes development in the offspring. Based on a study showing that a gluten-free diet during pregnancy improved autoimmune diabetes in offspring of nonobese diabetic mice, Haupt-Jorgensen et al. (2018), in a study aiming to explain the mechanism behind the protective effects of a gluten-free diet against diabetes, concluded that a gluten-free diet during pregnancy improved the symptoms of celiac disease and autoimmune diabetes in offspring, reduced inflammation, there was no change in beta cell volume, but an increase in the number of islets. While being effective particularly in the gut where it affects the composition of the microbiota, gluten also has many effects on body. Gluten can increase intestinal permeability and lead to enteropathy in type 1 diabetes. For food particles such as gliadin peptides to do not cross the intestinal barrier and react on the gut, gluten-free diet reduces intestinal permeability. The gluten-free diet is also thought to lead to a reduction in beta cell stress by reducing insulin release. And it is thought that such incidence may preserve islet cell numbers, reduce insulitis, and improve type 1 diabetes (Haupt-Jorgensen et al., 2018). In a study conducted by Kaur et al. (2020), which aimed to evaluate the effects that would occur in terms of hypoglycaemia frequency, HbA1c level and insulin requirement when a gluten-free diet was given to patients with type 1 diabetes, it was concluded that a decrease in hypoglycaemia attacks and better glycaemic control were observed in patients with a gluten-free diet. In a study by Neuman et al. (2020) investigating the relationship between a gluten-free diet and a possible decrease in beta cell capacity in children with recently diagnosed type 1 diabetes mellitus who did not have celiac disease, it was found that a gluten-free diet maintained for more than one year was associated with better HbA1c values and a prolonged period of partial remission. At the same time, there was a hint of a slowdown in the decline in C-peptide values, but it was not possible to draw a definitive conclusion. Also, in a study by Neuman et al. (2023), it was aimed to evaluate gluten-free diet's role in the changes which are related to gut bacteriome composition and in its functional capacity, also it was aimed to evaluate gluten-free diet's role on beta cell function. And it was found that the changes were not related to the rate of progress of beta cell capacity loss. And it has been considered that the protective effect of gluten-free diet might be through some other ways. In a study by Söderström et al. (2022), which aimed to evaluate whether a gluten-free diet would have a positive effect on glycaemic control in children with type 1 diabetes and included a sample of 23 children, it was concluded that a gluten-free diet had positive effects in terms of lower HbA1c levels and better glycaemic control. In a meta-analysis and systematic review conducted by Burayzat et al. (2022), which aimed to evaluate whether a gluten-free diet had an effect on body mass index and HbA1c in children and adolescents with type 1 diabetes and asymptomatic celiac

disease, no significant effect of a gluten-free diet on body mass index or HbA1c level was found, but it was stated that there may be a protective effect for other complications due to the pathology of both chronic diseases.

6. Conclusion

In this review article which aims to evaluate the possible effects of gluten on the development of type 1 diabetes, potential mechanisms and various studies are presented. It is observed that better glycaemic control is achieved, the balance in the gut microbiota is maintained, islet cells are protected, stress on beta cells is reduced, a less inflammatory environment is created, and high gluten intake is related to an increased risk of type 1 diabetes. However, there are also contrary conclusions. Considering the differences in research structures, limitations, diversity, and insufficient knowledge on possible mechanisms, it doesn't seem possible to make a definite conclusion in this context. Since gluten-free diet may bring some nutrient deficiencies with itself, more studies are needed to clearly reveal the possible mechanisms, effect status and results before making an inference. The literature should be enriched by planning diverse and effective studies with larger samples.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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