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The effect of a gluten-free diet in patients with autoimmune thyroiditis, type 1 diabetes mellitus, psoriasis, metabolic syndrome and without gluten-related disorder - a literature review

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Abstract

Introduction and aim of the study: The growing awareness of gluten-related disorders has led to widespread misinformation about the gluten-free diet(GFD). The potential benefits of removing gluten are not well evaluated, yet it is often recommended or self-implemented by patients without robust supporting evidence. This paper aims to determine whether eliminating gluten from the diet provides proven benefits for individuals with specific diseases, including autoimmune thyroiditis (AIT), type 1 diabetes (T1D), psoriasis, and metabolic syndrome, who do not have a diagnosed gluten-related disorder.

Description of the state of knowledge: Adhering to a gluten-free diet may benefit patients with AIT and T1D even without celiac disease, although there is no clear evidence that it alleviates AIT or T1D symptoms and the improvements are not significant enough to recommend it universally. Further research on humans is needed to explore the potential preventive effect of GFD on T1D risk and prolonging partial remission. For psoriasis, a GFD can be beneficial for patients with gluten-related antibodies, potentially reducing or clearing skin lesions, but it shows no benefit for those without these antibodies. The data on the GFD's impact on cardiovascular disease remains contradictory and unreliable.

Conclusion: For psoriasis patients who test positive for gluten-related antibodies, a gluten-free diet can be recommended. Current studies do not substantiate the necessity for patients with AIT, T1D or metabolic syndrome to completely eliminate gluten from their diet.

Keywords: gluten-free diet; autoimmune thyroiditis; diabetes mellitus type 1; psoriasis; cardiovascular risk; exclusion diet

Introduction and Purpose

With the increasing recognition of gluten/wheat-related disorders in both academic and clinical circles over the past few decades, misinformation about the gluten-free diet (GFD) and its effects on health has proliferated among the general public. The potential benefits of

removing gluten have not been adequately evaluated, yet recently it is frequently recommended despite lacking robust evidence to support it [1].

The aim of this paper is to assess whether, according to the current state of knowledge, there are proven benefits of eliminating gluten from the diet in subjects with selected diseases, but with no diagnosis of a concomitant gluten-related disorder. Based on available sources, the diseases we discussed include autoimmune thyroiditis, diabetes mellitus type 1, metabolic syndrome and cardiovascular risk.

The major aspects we focused on are prevention and management of the disease, differences in laboratory manifestation, clinical course as well as potential adverse events.

Material and Methodology

A literature search was conducted on PubMed and Google Scholar, with particular attention to papers published from 2019 to 2024. The studies concerning patients with a coexisting gluten-related disorder diagnosis were excluded from the final analysis. Literature was screened using the following keywords “gluten free diet AND non-celiac”, “gluten free diet AND thyroiditis”,“gluten free AND diabetes mellitus”, “gluten free AND psoriasis”, “gluten free AND metabolic syndrome”, “ gluten free diet AND autoimmunity” “gluten free diet AND autoimmune diseases”. Manual searches of bibliographies of the articles were also performed to identify additional studies to be included. We focused on population-based cohort studies, clinical trials examining the therapeutic benefit of a gluten-free diet.

State of knowledge

1. Gluten and its effect on the human intestine

Gluten is a mix of proteins found in many cereal species that constitute the basis of the human diet, such as wheat and its species (namely gliadin and glutenin), rye (secalin and secalinin), barley (hordein and hordenin) as well as oats (avenin and avenalin). These proteins contain many amino acid repeats, particularly rich in proline and glutamine, and are resistant to intestinal proteases [2,3]. As a consequence, incomplete digestion leading to creation of residues can cause an activation of the immune system, increase intestinal permeability and trigger gluten-related disorders in genetically predisposed subjects [4].

Recently, increased intestinal permeability, sometimes referred to as “leaky gut” has also been associated with the pathogenesis of chronic inflammatory diseases (CID). Enterocytes

secrete zonulin, a pivotal modulator of barrier integrity that removes a component of intercellular tight junction - the zonula occludens 1 [5]. Its secretion is triggered predominantly by two factors - bacteria overgrowth and gluten. Gliadin activates the CXCR3 receptor and triggers zonulin release via its interaction with MyD88 (myeloid differentiation primary response 88), subsequently leading to increased gut permeability. This suggests that gluten is mistakenly identified by the zonulin pathway as a potentially harmful component of a microorganism [6]. In healthy tissue the excessive production of zonulin is temporary, however in genetically predisposed patients it can be up-regulated resulting in increased antigen trafficking and a breakdown of tolerance, which leads to CID. Thus, eliminating gluten-containing foods is sometimes claimed to be advantageous [1].

2. Gluten-free diet

Gluten free diet requires the total elimination of gluten-containing foods, including the gluten proteins found in wheat, kamut, triticale, barley, rye, oats, and other similar grains. The diet is recommended for various gluten-related disorders and the list of cereals that must be excluded depends on the specific disorder affecting the patient [4]. Due to these dietary limitations, patients are advised to replace gluten-containing foods with gluten-free sources of carbohydrates (such as rice, corn, quinoa, legumes, buckwheat), nutritious foods (vegetables, fruits, fish, meat) and even artificial products. Gluten free products, defined as containing less than 20 ppm of gluten, taking into account potential contamination during the manufacturing process, are also at times richer in saturated fat, sugar and salt [7] and have reduced levels of proteins, fiber, and vitamins, e.g. 25-hydroxyvitamin D (25(OH)D) [8]. A gluten-free diet has often been linked to a higher risk of micronutrient deficiencies, hyperlipidemia, hyperglycemia, and coronary artery disease [9].

In contrast, some studies indicate that young healthy individuals who avoid gluten generally have a better nutritional profile, likely because they pay more attention to maintaining a healthy lifestyle by avoiding processed foods and increasing their intake of fruits and vegetables. However, they were also more prone to adopt unhealthy weight control practices [10].

An additional point to consider is the impact of a gluten-free regimen on gut microbiota, as it also plays a role in the intestinal permeability. Current evidence indicates that GFD can decrease bacterial diversity and alter the composition of the gut microbiota, particularly in

healthy individuals, leading to a reduction in probiotic species like Bifidobacteria and an increase in opportunistic pathogens such as Enterobacteriaceae and Escherichia coli [4,11].
In Europe, we have been witnessing a growing demand for gluten-free bakery products in the past few years and it is still expected to rise during the forecast period 2024-2029 [12]. This trend demonstrates the increasing popularity of the GFD.
With the growing variety and accessibility of gluten-free products, concerns regarding the healthfulness of a gluten-free diet cannot be overlooked [1].

3. Gluten-related disorders

Gluten-related disorders(GRD) encompass a spectrum of conditions evoked by ingestion of gluten, that include celiac disease (CD), non-celiac gluten/wheat sensitivity, wheat allergy, dermatitis herpetiformis and gluten ataxia [13,14,15,16,17]. The effectiveness of the GFD has been extensively studied and lifelong adherence is the optimal treatment for individuals with CD to achieve clinical and histological remission [18]. Patients with other GRD should avoid most gluten-containing cereals, but some may tolerate certain grains [4,15].

4. Autoimmune thyroiditis

Autoimmune thyroiditis (AIT), also known as chronic lymphocytic thyroiditis or Hashimoto's thyroiditis (HT), is a chronic inflammation of the thyroid gland, whose exact cause is not fully understood. It is the most common autoimmune disease and endocrine disorder, and the leading cause of hypothyroidism in iodine-sufficient countries. The incidence of HT is on the rise. Diagnosis is based on positive circulating thyroid autoantibodies, anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb), and imaging tests showing hypoechogenic inhomogeneous thyroid structure. Pathogenesis involves intrathyroidal infiltration of T and B cells, leading to chronic inflammation, fibrosis, and thyroid tissue atrophy. This can result in various thyroid functional states, ranging from euthyroid to overt hypothyroidism, characterized by increased TSH and decreased free thyroid hormone levels.
HT can negatively affect quality of life due to its impact on basal metabolism, carbohydrate, protein, fat metabolism, and thermogenesis. Clinical symptoms vary widely but can include concentration problems, chronic fatigue, weakness, dry skin, changes in body weight,

constipation, mood disorders, and anxiety. The exact mechanisms underlying its pathogenesis involve a complex interplay of genetic and environmental factors, including iodine intake, infections, certain medications, smoking, alcohol consumption, and stress.

Treatment involves lifelong oral administration of synthetic thyroid hormone levothyroxine to maintain normal TSH levels. Additionally, it has been proven that supplementation of selenium may help decrease TPOAb levels and vitamin D positively impacts the course of the disease [19].

Several studies have investigated whether introducing a gluten-free diet (GFD) could benefit patients with autoimmune thyroiditis (AIT).

In a pilot study involving 34 women with HT, Krysiak et al. observed that in the study group(n=16), the gluten-free diet led to a reduction in serum titers of TPOAb and TgAb and a slight increase in 25(OH)D levels. The TPOAb level correlated with 25(OH)D concentration. However, there were no changes in TSH, fT3, and fT4 levels after following the gluten-free diet [20].

Pobłocki et al., in a 62 caucasian women study during a 12-month follow-up between the control group and the gluten-free diet group, found no differences in anti-TPO and TGAb, fT3 or fT4 levels, except for a significant decrease in TSH levels in the GFD group. Additionally, they performed statistical analysis separately for both groups that showed a constant reduction of anti-TG levels and a slight decrease in TSH concentration after 12 months in the group eliminating gluten [21].

In another study, a group of researchers examined the effect of selenium supplementation paired with a gluten-free diet in drug-naive women with autoimmune thyroiditis in a state of subclinical hypothyroidism (SH) compared to exclusive supplementation of selenium and no dietary treatment in a control group. By the end of the study that lasted 6 months, euthyroidism was achieved in 37 out of 50 participants (74%) in the study group and in 28 out of 48 participants (58.3%) in the control group. TSH, TPOAb and TgAb levels were significantly diminished in both groups, although serum TPOAb level in the GFD group was significantly more reduced (by 49%) than in those who supplemented selenium only (by 34%). Thus, these results suggest that selenium supplementation paired with a gluten-free diet is more effective in reducing levels of TSH, TPOAb and TgAb in Hashimoto women with SH than supplementing selenium alone [22].

When it comes to clinical manifestation, there is no evidence to suggest that adhering to a gluten-free diet alleviates other symptoms of autoimmune thyroid disease [23].

In an overview, Mikulska et al. concluded that the evidence to support a gluten-free diet for all HT patients is insufficient [19].

5. Type 1 diabetes mellitus

Type 1 diabetes (T1D) is an autoimmune disease marked by the destruction of pancreatic beta cells within the islets of Langerhans due to autoantibodies. The primary autoantibodies used as indicators include glutamic acid decarboxylase, insulinoma antigen-2, insulin, and zinc transporter 8. However, the destruction of B cells is a gradual process preceded by a prodromal phase that is marked by the infiltration of CD4 and CD8 T cells into the pancreatic islets, resulting in insulin deficiency, persistent hyperglycemia and subsequent symptoms of polyuria, polydipsia, weight loss, and diabetic ketoacidosis. In many patients, the diagnosis of diabetes and the initiation of treatment is followed by a partial regeneration of β-cells and a decreased need for exogenous insulin, which is referred to as clinical remission. Remission usually begins between the third and sixth month of diabetes. It is characterized by a low insulin requirement with simultaneously normal blood glucose levels. Other criteria considered when assessing remission include a decrease in C-peptide levels and the IDAA1C (insulin dose-adjusted A1c) index [24]. Its increasing incidence remains unexplained and cannot be solely attributed to genetic factors. Instead, changes in exposure to environmental triggers play a significant role in the disease's development. The occurrence of T1D differs across regions, influenced by both genetic and environmental agents. In South American and Asian countries, the incidence ranges from one to three cases per year, while in the United States (US) and South European countries, it is higher, ranging from 10 to 20 cases per 100,000 people annually [25].

When it comes to genetic predisposition, type 1 diabetes and celiac disease share the predisposing HLA-DQ2/DQ8 genotype, which can partially explain their frequent comorbidity. Moreover, among patients with type 1 diabetes, the prevalence of celiac disease ranges between 5-10%. Whereas, if celiac disease is diagnosed first, type 1 diabetes seldom develops, possibly as a result of adherence to a GFD [26].

Already 25 years ago, gluten-free diet has been shown to delay onset and diminish occurrence of autoimmune diabetes in non-obese diabetic (NOD) mice [27].

The protective potential of a GFD is currently being studied. There is also available data that suggests that a gluten-free diet attenuates the development of type 1 diabetes through the gut microbiota composition [28] as well as in a microbiota-independent manner [29]. It has been shown to upregulate markers for regulatory T cells and T helper 2 cells in the pancreas of the GF-fed mice which alleviates T1D [28]. The abnormal functional integrity of the intestine, along with its effects on the immune system, may also contribute to the development of the disease through activation and proliferation of islet-specific T cells, particularly diabetogenic CD8+ T cells, promoting insulitis [30]. However the precise mechanisms of developing autoimmune diabetes still remain unclear.

Due to comorbidity of celiac disease in type 1 diabetes, Haupt-Jorgensen et al. hypothesized that GFD during pregnancy ameliorates autoimmune diabetes in NOD mouse offspring. In their research a GFD compared to a standard (STD) diet in utero led to decreased insulitis and both systemic and local inflammation [26].

In another study they observed that in NOD mice, a lifelong GFD reduces insulitis and inflammation in the pancreatic islets, possibly by lowering VEGFR2 (vascular endothelial growth factor receptor 2) levels [31]. However, in the latest attempt to clarify possible mechanisms, researchers did not replicate the diabetes alleviating effect of a maternal GFD in its offspring. The dietary intervention did not lead to a reduction in the incidence of autoimmune diabetes, the degree of insulitis, glucose or insulin tolerance, nor plasma insulin autoantibody levels [32].

In a National Danish prospective cohort study on humans, high gluten consumption by mothers during pregnancy has been linked to a higher risk of their children developing T1D. However, the researchers claim that these findings need to be confirmed in further research [33].

Apart from the possible preventive effect of eliminating gluten, there is also emerging evidence indicating its alleviating effect post-diagnosis, a prolonged partial remission period, and better glycemic control.

Söderström et al. found that children on a GFD had a significantly lower HbA1c level at 6 months compared to those on a regular diet, and better glycemic control in the GFD group after 6 and 12 months [34].

Svensson et al. examined 15 newly diagnosed children with T1D in another 12-month pilot study. One year post onset, in GFD group three times as many children were still in partial remission based on IDAA1c, HbA1c levels were significantly 21% lower and IDAA1c was

over 1 unit lower in the cohort on a gluten-free diet compared to the two previous cohorts. They found no significant difference in stimulated C-peptide levels [35].

On a bigger sample of 45 non-coeliac children with recently diagnosed type 1 diabetes, C-peptide decline, insulin dose, IDAA1c, HbA1c and quality of life (QoL) were assessed. At 12 months they observed that C-peptide declined more slowly in the GFD group than in controls. The GFD group had a significantly lower IDAA1c and mean HbA1c and marginally lower insulin dose. There was no prominent difference in the QoL between the groups according to the patients as well as their parents/caregivers [36].

In summary, a body of research using animal models of T1D suggests that the development of autoimmune disease can be altered by factors affecting the gut immune system, providing a foundation for exploring similar questions in humans. Prenatal and early-life interventions that alter the intestinal microbiota and permeability can impact the risk of type 1 diabetes.

Further research is needed as this provides a compelling basis for developing new therapeutic strategies for at-risk individuals to prevent the onset of T1D.

In patients already diagnosed with T1D who maintained a gluten-free diet during the first year after diagnosis, there was an association with lower HbA1c levels and a prolonged partial remission period. There was also an indication of a slower decline in C-peptide, although the association is not strong enough to draw definitive conclusions.

6. Psoriasis

Psoriasis is a chronic, immune-mediated skin disease that presents in various forms, with plaque psoriasis being the most common. It is characterized by well-defined, scaly, red plaques that are typically symmetrical and found on the knees, elbows, lower back, and scalp. The Psoriasis Area and Severity Index (PASI) is commonly used to assess the severity of the condition by measuring the extent and intensity of psoriasis in four regions: head-neck, arms, body, and legs, evaluating redness, infiltration, and scaling. Treatment involves local therapies, with systemic medications reserved for cases where local treatments are ineffective. It is influenced by both genetic predisposition and environmental factors. It involves a dysregulated interaction between the innate and adaptive immune responses, driven mainly by antigen-presenting cells and T helper cell-17 in skin lesions. Environmental triggers for these immune responses include infections, medications, skin trauma, and psychosocial stress. Psoriasis is most prevalent in high-income countries, where modern lifestyles characterized by sedentary behavior, high-calorie diets, and obesity significantly contribute to its incidence.

The effect of diet on psoriasis has not been thoroughly researched, but it is of significant interest to many patients [37].

There are several studies that demonstrate GFD to alleviate psoriasis symptoms, showing an improvement in their PASI score. However, their limitations include an absence of randomization, small control groups, and the potential influence of the placebo effect. [38]

In a recent cohort studies among 85,185 women, the amount of gluten intake has been unambiguously ruled out as a risk factor for psoriasis. [39] In a survey with patient-reported skin outcomes in response to GFD, 53.4% of them declared improvement in their disease[40]. In a different sample, 52.22% followers of a GFD did not observe any effect on psoriasis manifestation, and 3.33% claimed that gluten aggravated their symptoms [41]. These findings are contradictory and subjective, thus they cannot lead to a definitive conclusion.

However, in a number of studies involving patients seropositive with gluten-related antibodies, implementing a GFD entailed major improvements in their PASI scores and even total clearance of their lesions, compared to no changes in seronegative patients [42].

In psoriasis patients without concomitant CD, current guidelines weakly recommend GFD only in patients who test positive for serologic markers of gluten sensitivity to evaluate whether it may improve skin symptoms [43].

7. Metabolic syndrome and cardiovascular risk

Cardiovascular diseases (CVD) are a leading cause of disability and the primary cause of death globally. They encompass conditions affecting the heart and blood vessels, such as acute coronary and cerebrovascular events. Their main risk factors include type 2 diabetes, high blood pressure, abdominal obesity and dyslipidemia. They often occur together as a result of negative lifestyle choices (i.e. lack of physical activity, unbalanced diet) along with genetic predisposition. Metabolic syndrome (MES) is defined by the coexistence of at least 3 out of 5 criteria: elevated waist circumference (WC) depending on sex and race, type 2 diabetes or high fasting serum glucose (>100 mg/dL), high blood pressure (systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥ 85 mmHg), elevated triglycerides (>150 mg/dL), and low HDL cholesterol (<40 mg/dL).

In a preliminary randomized trial of 45 subjects with MES, a comparison of the GFD and control diet after 8-week adherence showed no effect on LDL cholesterol, total cholesterol, fasting insulin, HOMA-IR, systolic and diastolic blood pressure levels, but the GFD significantly reduced fasting blood glucose, WC and serum triglyceride levels compared with

the control diet. The reduction in waist circumference, without a significant decrease in body weight, may suggest a preferential loss of abdominal fat [44]. In a cross-sectional study Kim et al. revealed that individuals with no CVD following a GFD have a reduced risk of obesity, metabolic syndrome, and cardiovascular disorders. However, this study cannot conclusively link these effects to the GFD, as it is possible that individuals adhering to a GFD also follow a generally healthy diet, and these effects may be attributable to it [45].

A different review, predominantly based on observational studies, indicates little or no association between gluten intake and cardiovascular mortality or non-fatal myocardial infarction. Additionally, lower gluten intake may be associated with a slightly increased risk of developing type 2 diabetes, a significant cardiovascular risk factor. For other cardiovascular risk factors, it remains unclear if there are differences between a gluten-free and a regular diet. Nevertheless, these conclusions are based on limited findings and therefore the evidence is of a very low certainty [46].

So far, a gluten-free diet has not been shown to be unequivocally beneficial for individuals without celiac disease. In non-celiac patients, a gluten-free diet may slightly improve overall cardiac risk factors. However, its use without a gluten-related disease requires larger studies with a more clearly defined dietary composition. Therefore, a gluten-free diet should not be considered for promoting weight loss or improving lipidemic profile in non-celiac patients [47].

Discussion

The paper only discussed studies that excluded patients with diagnosed gluten-related diseases. However, in the majority of the studies a small intestine biopsy was not performed and therefore, we cannot completely rule out the possibility of a latent or asymptomatic CD. The duration of adhering to the diet varied between studies, which could cause inconsistencies in the results. Moreover, the exact composition and eliminated products were usually not specified and compliance was not always objectively verified.

It should also be remembered that GFD despite its potential benefits, also carries certain risks and can cause negative side effects, e.g. vitamins and multiple micronutrients deficiencies that were not assessed in most of the studies and in the long term could aggravate.

Furthermore, most of the included research compared the GFD to a 'standard' or 'regular' diet, while the discussed conditions often have specific nutritional guidelines. To evaluate the

definitive efficacy of a GFD, it should also be compared with tailored dietary recommendations for each disease.

Conclusion

In conclusion, based on the aforementioned research results, adhering to a gluten-free diet may be favorable for patients with AIT and T1D even after ruling out gluten-related disorders. However, to date, the improvement is not significant enough to recommend it to all patients. There is no evidence that GFD alleviates symptoms of AIT or T1D. Further research is needed to determine whether prenatal and early-life interventions may affect the risk of developing T1D and if adhering to a GFD post diagnosis can prolong partial remission period. In psoriasis, a GFD can be recommended in patients that are seropositive with gluten-related antibodies, as it may mitigate skin lesions or even clear them completely. No benefits were observed in seronegative for gluten-related markers psoriasis patients.

The data concerning GFD's impact on cardiovascular disease is contradictory, and therefore it cannot be considered reliable.

Studies conducted so far do not support the claim that patients with diseases other than gluten-related disorders absolutely should eliminate gluten from their diet.

Disclosure

Author's Contribution Statement

Conceptualization, Dominika Zaliwska and Adrianna Kraszkiewicz; methodology, Natalia Paduszyńska; software, Anna Dąbrowska; check, Marta Justyna Gonciarz, and Monika Anna Kamińska; formal analysis, Agnieszka Aleksandra Strojny, Dominika Karolina Adamiec; investigation, Adrianna Kraszkiewicz; resources, Monika Kienanh Do, Magdalena Czach; data curation, Anna Dąbrowska, Dominika Zaliwska; writing - rough preparation, Dominika Zaliwska, Magdalena Czach, Agnieszka Aleksandra Strojny; writing - review and editing, Monika Kienanh Do, Monika Anna Kamińska; visualization, Dominika Karolina Adamiec; supervision, Natalia Paduszyńska; project administration, Marta Justyna Gonciarz;

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