Association between celiac disease and vitiligo: A review of the literature

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Abstract

Celiac disease (CD) is an autoimmune intestinal disease caused by the intake of gluten-containing cereals and their products by individuals with genetic susceptibility genes. Vitiligo is a commonly acquired depigmentation of the skin; its clinical manifestation are skin patches caused by localized or generalized melanin deficiency. Both diseases have similar global incidence rates (approximately 1%) and are associated to similar diseases, including autoimmune bullous disease, inflammatory bowel disease, autoimmune thyroiditis, autoimmune gastritis, and type 1 diabetes. The relationship between CD and vitiligo has been reported in several studies, but their conclusions are inconsistent. Further, it has also been reported that a gluten-free diet (GFD) can improve the symptoms of immune-related skin diseases such as vitiligo. In this mini-review, we summarize and review the literature on the relationship between CD and vitiligo, assess the therapeutic significance of GFD for patients with vitiligo, and explore their possible physiopathology. We are hopeful that the information summarized here will assist physicians who treat patients with CD or vitiligo, thereby improving the prognosis.

Key Words: Celiac disease; Gluten-free diet; Vitiligo; Dermatitis herpetiformis

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Celiac disease (CD) is an autoimmune intestinal disease caused by the intake of gluten-protein containing cereals and its products by individuals with genetic susceptibility genes. The disease can lead to intestinal mucosal damage, mainly manifested as abdominal pain, diarrhea, and other gastrointestinal symptoms. It can also lead to extraintestinal symptoms caused by secondary malnutrition and is associated with an increase in mortality[1]. The global prevalence of CD is approximately 1.4%, and it is gradually increasing[2]. The detection of anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA), anti-endomysial antibody (EMA), and anti-gliadin antibody plays an important role in the diagnosis of CD[3-5]. Anti-tTG IgA is considered the first choice for the serological examination of CD. However, duodenal mucosal biopsy remains the gold standard for the diagnosis of CD[6].

Vitiligo is a commonly acquired depigmentation of the skin that clinically manifests as skin patch caused by localized or generalized melanin deficiency[7]. It is considered an autoimmune disease, although its pathogenesis is not clear and is affected by multiple factors, including autoimmunity, oxidative stress, and genetic susceptibility[8,9]. The incidence rate of vitiligo worldwide is 0.5%–2.0%[10].

Many studies have confirmed that CD and vitiligo are associated with a variety of autoimmune diseases, including autoimmune bullous disease, inflammatory bowel disease, autoimmune thyroiditis, autoimmune gastritis, and type 1 diabetes[11-17]. The relationship between CD and some immune-related skin diseases has been studied and confirmed, but its relationship with vitiligo is controversial. For example, some studies have shown that the incidence of vitiligo in patients with CD is higher than that in patients without CD[18,19]. However, the study by Volta et al[20] did not find any correlation between these two immune diseases[20]. Further, a gluten-free diet (GFD) has been reported to improve the symptoms of patients with immune-related skin diseases, such as dermatitis herpetiformis (DH), psoriasis, and vitiligo, who are seropositive for CD-related autoantibodies[21-23]. The purpose of this mini-review was to explore the relationship between CD and vitiligo, assess the therapeutic significance of GFD for patients with vitiligo, and investigate the underlying mechanisms.

LITERATURE ANALYSIS

We reviewed the literature on the role of CD and gluten in vitiligo. We searched the PubMed, Ovid, Web of Science and Cochrane databases for published articles from their inception to February 2021. The search terms used were "celiac disease" or "gluten-free diet" and "vitiligo." We first screened the titles and abstracts to select potential studies and, then, performed a full-text review. We also reviewed the references in the selected articles to identify any other relevant studies. We included cohort studies, cross-sectional studies, case-control studies, reviews, and case reports that studied the relationship between vitiligo and CD. The duplicates were then removed. If the article lacked clinical relevance or the full text was not available, it was
excluded. There was no restriction based on language.

CLINICAL CHARACTERISTICS

Study characteristics
After a literature search, 878 studies were included, of which 102 duplicates were excluded. The titles and abstracts of 776 studies were screened. After reviewing the selected articles and their references, 15 eligible studies were included. Four studies examined the relationship between vitiligo and the incidence of CD (Table 1), and seven studies reported a relationship between CD and incidence of vitiligo (Table 2). In four studies, the relationship between GFD and vitiligo was studied (Table 3).

Vitiligo and the incidence of CD
Four studies, including two case-control and two cross-sectional studies, investigated the incidence of CD in patients with vitiligo. One cross-sectional study investigated the incidence of CD in 176 patients with vitiligo; five (2.8%) of these patients were diagnosed with CD [24]. Further, in a case-control study, Seyhan et al. [25] assessed serum anti-endomysial IgA antibody in 61 patients with vitiligo (21 children) and 60 controls. Eleven patients with vitiligo and one control were positive, and among these seropositive patients, five were younger than 18 years of age. The seroprevalence rates for children and adults were 23.8% and 15%, respectively. Seropositive patients underwent endoscopic duodenal biopsy of the upper gastrointestinal tract, and the prevalence of CD confirmed by biopsy was 3.2% [25]. The second case-control study by Shahmoradi et al. [16] assessed EMA and anti-tTG IgA in 64 patients with vitiligo and 64 controls; each group included 41 (64.1%) women and 23 (35.9%) men. Among the patients with vitiligo, autoantibody tests were positive in two (3.1%) women. No one in the control group has positive results for autoantibodies [16]. However, the other cross-sectional study investigated the incidence of CD in 198 patients with vitiligo and found no positive CD serology in any of the participants [20].

CD and incidence of vitiligo
The incidence of vitiligo among CD patients was examined in six cross-sectional studies and one population-based cohort study. Ertekin et al. [18] reported on 140 children with CD, of whom 3 (2.1%) had vitiligo [18], while Lancaster-Smith et al. [26] found that 1 (1.8%) out of 57 patients with CD had vitiligo [26]. Further, Seyhan et al. [19] studied 55 cases of children and adolescents with CD and found that 45 children (81.8%) had gastrointestinal symptoms; 5 of them were subsequently diagnosed with vitiligo, with an incidence rate of 9.1% [19]. A Swedish population-based cohort study, in which each CD patient was matched with five control patients, demonstrated that among 43300 patients with CD, 106 cases (0.2%) were affected by vitiligo. Moreover, in a population of 198532 patients, vitiligo was diagnosed in 261 cases (0.1%), and the incidence of vitiligo was statistically significant [27]. In a study in Italy, 1 of 82 patients with CD had vitiligo (incidence rate of 1.2%) [28]; another report including 1010 patients with CD in Spain found that only 4 children (0.4%) had vitiligo [29]. However, surprisingly, Reunala et al. [30] did not report the onset of vitiligo in 383 patients with CD who received GFD [30]. GFD may reduce the risk of vitiligo.

GFD and vitiligo
Only a few cases of GFD and vitiligo have been reported in the literature. Our literature review identified two case reports describing the recoloring of vitiligo lesions after the onset of a GFD. One case reported a 9-year-old child with both CD and vitiligo who developed extensive repigmentation after following a GFD for 1 year [21]. The second report describes a 22-year-old female patient with vitiligo, who received a 2-year treatment including dapsone with no significant response but began to recover after 1 mo of GFD [31]. These cases suggest that elimination of gluten in the early stages of disease may have the potential to encourage and improve the disease.

Additionally, there are some reports on the coexistence of DH and vitiligo. Two case reports describe this relationship: in both, the DH lesions were significantly improved after the patients began a GFD; however, the vitiligo lesions remained unchanged or further aggravated. One report described a 53-year-old woman with vitiligo and DH. The patient began a GFD, and DH was completely relieved after 5 mo, but vitiligo did not subside and further increased [32]; she did not undergo a CD-related examination. The second case report described a 21-year-old patient with vitiligo and DH who was
Table 1 Summary of studies reporting prevalence of celiac disease in vitiligo

| Ref.       | Country    | Study design        | Setting       | Vitiligo, n (%) | CD prevalence (V + CD) | Vitiligo diagnosis | CD diagnosis     |
|------------|------------|---------------------|---------------|-----------------|------------------------|--------------------|------------------|
| Shahmoradi et al[16], 2013 | Iran       | Case-control study  | Hospital      | 64              | 3.1% (n = 2)            | Medical records    | Serology         |
| Volta et al[20], 1997     | Italy      | Cross-sectional study | Hospital      | 198             | 0                      | NA                 | Serology and histology |
| Henker and Hartmann[24], 2019 | Germany   | Cross-sectional study | Hospital      | 176             | 2.8% (n = 5)            | Medical records    | Serology and histology |
| Seyhan et al[25], 2011    | Turkey     | Case-control study  | Hospital      | 61              | 3.2% (n = 2)            | NA                 | Serology and histology |

CD: Celiac disease; NA: Not applicable.

Table 2 Summary of studies reporting prevalence of vitiligo in celiac disease

| Ref.       | Country    | Study design        | Setting       | CD, n (%) | Vitiligo prevalence (V + CD) | Vitiligo diagnosis | Celiac disease diagnosis     |
|------------|------------|---------------------|---------------|-----------|-----------------------------|--------------------|-------------------------------|
| Reunala et al[30], 1997 | Finland    | Cross-sectional study | Hospital      | 383       | 0                           | Medical records    | Histology                     |
| Ertekin et al[16], 2009 | Turkey     | Cross-sectional study | Hospital      | 140       | 2.1% (n = 3)                | Medical records    | Serology and histology        |
| Lancaster-Smith et al[26], 1974 | United Kingdom | Cross-sectional study | Hospital      | 57        | 1.8% (n = 1)                | Medical records    | Serology and histology        |
| Seyhan et al[19], 2007   | Turkey     | Cross-sectional study | Hospital      | 55        | 9.1% (n = 5)                | Medical records    | Serology and histology        |
| Lebwohl et al[27], 2020  | Sweden     | Population-Based cohort study | Database      | 43300     | 0.24% (n = 106)              | Medical records    | Histology                     |
| Catassi et al[28], 1996  | Italy      | Cross-sectional study | School        | 82        | 1.2% (n = 1)                | Questionnaire survey | Serology and histology        |
| Polanco[29], 2008        | Spain      | Cross-sectional study | Hospital      | 1010      | 0.4% (n = 4)                | Medical records    | Serology and histology        |

CD: Celiac disease; V: Vitiligo.

Table 3 Summary of the effect of gluten-free diet on vitiligo

| Ref.       | Country    | Evidence type | Celiac disease diagnosis | Accompanied diseases | Measure of improvement | Time to dermatologic improvement |
|------------|------------|---------------|--------------------------|----------------------|------------------------|---------------------------------|
| Rodriguez-Garcia et al[21], 2011 | Spain       | Case report    | Diagnosis, method not described | None                  | Repigmentation of skin lesions | 1 yr, continuous improvement for 3 yr |
| Khandalavala et al[31], 2014    | United States | Case report    | Serology and histology not done | None                  | Repigmentation of skin lesions | 1 mo, continuous improvement for 3 mo |
| Amato et al[32], 2000          | Italy       | Case report    | Serology                  | Dermatitis herpetiform | No response             | NA                             |
| Karabudak et al[33], 2007      | Turkey      | Case report    | Histology                 | Dermatitis herpetiform | No response             | NA                             |

NA: Not applicable

diagnosed with CD after gastrointestinal endoscopy. He was prescribed strict GFD and topical steroids, after which DH significantly improved, although his vitiligo remained unchanged[33].
Discussion of CD

CD is a chronic autoimmune disease caused by improper absorption of wheat gluten and related cereal peptides by the small intestine, and this causes the human body to lose its ability to absorb nutrients through the villi. The disease may affect patients of any age, with a peak in early childhood and the 4th and 5th decade[34]. The gastrointestinal symptoms of CD include abdominal distension, abdominal pain, chronic diarrhea, steatosis, anorexia, weight loss, and nutritional deficiency. Further, an increasing number of related diseases and parenteral manifestations have been reported[35]. Vitiligo is also associated with a variety of gastrointestinal comorbidities, including autoimmune liver disease, autoimmune atrophic gastritis, inflammatory bowel disease, and intestinal flora dysfunction[13,36-38]. Furthermore, the incidence of some autoimmune diseases (pernicious anemia, inflammatory bowel disease, systemic lupus erythematosus, Addison’s disease, and autoimmune thyroid disease) in patients with vitiligo is significantly increased[39]. These associations indicate that vitiligo has a common genetic etiology with other autoimmune diseases. Studies have found that patients with multiple autoimmune syndromes may have CD and/or vitiligo. In addition to well-defined polygenic syndromes, there may be a positive correlation between CD and vitiligo[40].

There is no published research explaining the pathophysiological relationship between CD and vitiligo; both are T cell-mediated disorders in which gamma-delta T cells, T-helper 1, and T-helper 17 play important roles[41-44]. CD has been found to be highly correlated with interleukin (IL)-2, IL-6, IL-17, and IL-21[45-47] which have been proven to play important roles in the pathogenesis of vitiligo[48,49]. The shared immunogenic mechanisms between the two conditions could explain their association. The incidence rate of autoimmune diseases is increased in patients with prolonged gluten exposure, due to the intestinal barrier dysfunction associated with CD and increased permeability to immunogenic triggers[50]. CD patients exposed to gluten can show triggering of the CD4 + T cell responses, causing the production of high levels of interferon-gamma; this has been related to the severity of psoriasis[51,52]. A similar mechanism may be involved in the pathogenesis of vitiligo. On the other hand, in vitiligo, nuclear factor-erythroid 2-related factor 2 activation decreased in keratinocytes with impaired phosphoinositide 3-kinase phosphorylation, increasing the susceptibility to reactive oxygen species (ROS), leading to chemically induced apoptosis[53]. Moreover, IL-15 and CD4 + T cytokines (TNF, IL-2, IL-21) increased the phosphorylation of activators of transcription (STAT) 5 and protein kinase b, as well as the transcription of B-cell lymphoma-extra-large (BCL-xL) protein. Further, TNF, IL-2, and IL-21 synergistically trigger the proliferation of Lin(-) intraepithelial lymphocytes (IELs) and CD3-CD56 + IELs in duodenal biopsy specimens of refractory CD type II (RCDD), while CD4 + T cytokines are involved in its pathogenesis[54]. Additionally, another possible mechanism linking vitiligo and CD is vitamin D deficiency in CD patients due to intestinal malabsorption[55]. Vitamin D deficiency can make susceptible individuals develop vitiligo[56]. However, this mechanism may not be important as it has been previously reported that patients with vitiligo have significant recoloring after a GFD. Large population-based studies in the future may provide better insight into the role of GFD in vitiligo.

Furthermore, CD is closely related to DH. Sulfasalazine, a commonly used treatment for DH, may induce vitiligo in patients with CD and DH[57] as it can consume glutathione, leading to a large amount of ROS accumulation, resulting in melanocyte damage[58,59]. Further, sulfasalazine is an inhibitor of the thioredoxin pathway[60], and reduced thioredoxin participates in the inhibition of tyrosinase, which is the rate-limiting enzyme in melanin biosynthesis and inhibits melanogenesis[61,62]. Moreover, sulfasalazine may reduce the level of cofactor tetrahydrobiopterin (BH4) by inhibiting the squid reductase that plays a crucial role in melanin production[63]; BH4 can also lead to the production of ROS, leading to the disruption of melanin biosynthesis[64].

CONCLUSION

The analysis based on a review of existing evidence supports the association between CD and vitiligo. In the treatment of vitiligo patients, this information is particularly important because the intestinal symptoms are usually non-specific and are often ignored by doctors and patients. Further, patients with vitiligo may benefit from CD screening, while early diagnosis of vitiligo in CD patients may be beneficial because GFD may improve both conditions. However, large-scale, long-term follow-up studies are needed.
are needed to further endorse these findings.

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