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REVIEW

Dermatitis herpetiformis, celiac disease and their impact on women and their families

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ABSTRACT

Dermatitis herpetiformis (DH) is the specific cutaneous manifestation of celiac disease (CD), both of which require lifelong management. A comprehensive literature review was conducted to gather evidence on gender-related differences aiming at reducing healthcare inequalities. While women tend to be more symptomatic, the diagnosis is often delayed, leading to a reduced quality of life and an increased risk of long-term complications. This may be partly a consequence of the fact that they are more likely to present with seronegative forms. Moreover, in women, reproductive issues, known to be associated with DH and CD, along with osteopenia/osteoporosis, and anemia are particularly prevalent. It should be also noted that beyond personal diagnosis, DH and CD also affect women indirectly, as they often take on caregiving roles for affected family members. The lifelong adherence to a gluten-free diet, the only effective treatment for DH, imposes a substantial lifestyle and financial burden. Gluten-free diet is frequently perceived as both gendered and class-based, placing a disproportionate strain on women and lower-income households. In this regard, recent recommendations to prioritize naturally gluten-free foods rather than "gluten-free" products, may offer some relief. However, the responsibility for acquiring the skills necessary for such dietary choices often falls predominantly on women.

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KEY WORDS: Dermatitis herpetiformis; Celiac disease; Fertility; Gluten-free diet.

In 1884, Louis Adolphus Duhring coined the term dermatitis herpetiformis (DH) to describe a chronic, itchy skin condition.[1] Recognized as a distinct form of celiac disease (CD), it is characterized by subepidermal IgA deposits and gluten-sensitive enteropathy.[2] Both CD and DH are triggered by gluten in genetically susceptible individuals, presenting with skin lesions, positive celiac-related antibodies, and improvement on a gluten-free diet. Over the past 25 years, tissue transglutaminase (TG2, tTG) and epidermal transglutaminase (TG3, eTG) have been identified as the autoantigens involved in CD and DH, respectively.[3] DH primarily presents with intensely pruritic rashes on extensor surfaces, and diagnosis is confirmed by detecting IgA deposits at the dermo-epidermal junction *via* direct immunofluorescence microscopy on perilesional skin. Serologic testing also play a key role, revealing the presence of circulating anti-eTG, anti-tTG, anti-endomysium, and anti-deamidated synthetic gliadin-derived peptides.[4] Cutaneous morbidity includes, scratching, discomfort, and insomnia, as well as to the risk of superimposed infections. However, systemic complications may occur, primarily manifesting as symptoms of the associated gluten-sensitive enteropathy, now recognized to be present in nearly all patients with DH, though milder than those in clinically diagnosed CD. Accordingly, most exhibit only subclinical gastrointestinal issues.[5] In recent years, significant gen-

der-related differences have been observed regarding the clinical presentation, management, and complications of DH/CD,[6] mirroring patterns seen in many other diseases. Women, in particular, face distinct challenges including an increased risk of diagnostic delays, greater symptom burden, and a higher prevalence of seronegative cases. Additionally, DH/CD can profoundly affect female reproductive health, contributing to fertility issues, pregnancy complications, and heightened susceptibility to nutritional deficiencies.[7, 8] Beyond direct health implications, the impact of DH/CD on women and their families extends to daily life, with women often shouldering a disproportionate burden due to the lifestyle changes required – most notably, adherence to a strict gluten-free diet (GFD). In many households, women often bear a larger burden in this regard, as they are typically responsible for preparing meals and managing the dietary needs of family members. This role involves not only ensuring adherence to the GFD intensifying the physical, emotional, and financial strain of managing the disease. This added responsibility, coupled with the need to navigate long-term medical care, underscores the broader social and gender-based disparities associated with DH/CD.

Epidemiology

The rate of CD diagnoses has increased over time, with its incidence reported to have risen fivefold in the past 25 years.[9] However, a decrease of new CD diagnoses in the last decade has also been reported,[10] possibly related to a predictable decline after a period of an intensive search in at-risk groups. Concerning DH, its incidence seems to be in constant decrease. This difference may be explained with the increased awareness of CD leading to a wider prescription of screening tests and thus to an earlier identification of patients with latent or potential CD.[11] CD can present at any age in adults, with a bimodal peak in women (30s-40s) and men (40s-50s). A 22-year UK study found CD was twice as common in women, with rising incidence, particularly in young children and those over 50; DH incidence also increased with age.[12] Although males have been historically reported to have a higher overall prevalence of DH (male-to-female ratio of 3:2), females seem to be more commonly affected under the age of twenty (male-to-female ratio of 2:3).[2, 13] Data collected by the Italian Association of Celiac disease (AIC) show that two out of three people affected by CD in Italy, are women. Of these, it is esteemed that around 300,000 are still undiagnosed.[14] Studies reported that men and women with CD may present differences in the clinical presentation at the time of diagnosis. A forty-year analysis in an Italian referral center (Department of Internal Medicine, St. Orsola-Malpighi Hospital, Bologna, Italy) revealed that seropositive CD was predominant in both sexes, but seronegative CD patients were mainly females (68.4%), with a higher median age at the diagnosis (45 years) compared to seropositive CD (33 years), supporting the results of a previous study.[15] Moreover, a female preponderance was found in classical phenotype, characterized, according to the Oslo classification, by malabsorption syndrome (*i.e.*, diarrhea and weight loss regardless of extra-intestinal manifestations) (26.9% and 23.9% of females and males, respectively; $P<0.001$), non-classical forms with evidence of gastrointestinal symptoms, except from diarrhea, and extraintestinal manifestations (64.4% and 59.7% in females and males, respectively; $P<0.001$), and Marsh 3C histotype (46.1% *vs.* 37.9%, respectively; $P<0.05$). Among CD related manifestations, osteopenia was more frequent in females (64.3% *vs.* 46.2%; $P<0.001$). Also, long-term follow-up revealed statistically significant differences between females and males (11.97±7.95 years in females *vs.* 11.01±7.48 years in males, respectively; $P<0.05$), probably indicating a slightly elevated tendance in females to attend clinical visits.[10] Thus, as previously reported, generally women seem to be more symptomatic exhibiting more gastrointestinal issues than men.[16] Despite this, females have a delayed diagnosis significantly more often than males.[17] While the causes of delayed diagnosis are uncertain, it is well known that undiagnosed DH reduces the quality of life and predisposes to complications, such as lymphoma and low bone mineral density.[18-20] In particular, in women, clinical systemic manifestations of untreated CD frequently interest the reproductive system, the hematopoietic system, and the osteoarticular system.

Familial DH

Genomic typing and family studies have exposed the common genetic background of DH and CD in association with HLA-DQ2 and DQ8.[21] Due to the high negative predictive value but relatively low positive predictive value among the Caucasian population, HLA genotyping is applicable in certain cases requiring the exclusion of DH or CD.[2] Results from genetic studies fit well to a mendelian dominant mode of inheritance for DH and CD.[22-24] Gender may also be important because first-degree relatives affected with DH and CD are more often females. However, the reason why women seem to be more prone to get familial DH is

not known. Furthermore, the increased risk of celiac disease in first-degree relatives of patients with DH is indicative of serologic screening of family members even when minor symptoms are present.[25]

Gender-related differences in clinical manifestation of celiac patients at diagnosis

Studies suggest that women tend to exhibit more pronounced symptoms than men including poor appetite, nausea, weight loss, anxiety/depression, malaise, anemia, and thyroiditis. Moreover, it seems that women are more likely to have a short stature, both as a consequence of weight loss and of delay in CD diagnosis. However, there seem not to be differences in classical CD symptoms such as diarrhea, abdominal distension, and abdominal pain and men show a higher frequency of dermatitis herpetiformis.[2, 18, 26]

Concerning DH, no differences in clinical manifestations have been classically reported between the two sexes, although recently a few reports highlighted that a very unusual DH presentation, involving the face, seems to be slightly more prevalent in women (four cases in women among the overall six cases reported in the literature).[27-30]

Hormonal influences and fertility issues in DH and CD

It is known that hormonal factors play an important role in the progression and severity of autoimmune diseases. Accordingly, most autoimmune diseases affect women more often than men.[31] Besides, pregnancy seems to exacerbate some autoimmune conditions, such as systemic lupus erythematosus,[31] pemphigus,[32] and epidermolysis bullosa acquisita,[27] but to ameliorate the severity of others, including rheumatoid arthritis and linear IgA disease.[33] This suggests the important role and the profound effects of estrogens on the immune system supporting the hypothesis that estrogen is responsible for the observed "gender gap."[31] Several reports have shown a significantly increased prevalence of autoimmune diseases in patients with CD compared with controls, including autoimmune thyroiditis, type 1 diabetes, and systemic lupus erythematosus.[16, 26] However, as it is known that females exhibit a higher frequency of autoimmune diseases than males, these associations are yet to be confirmed. These data may be kept in mind when operating differential diagnosis between cutaneous manifestations in women. For example, cases of under-diagnosed CD and DH have been reported in women exhibiting chronic severe dermatitis with vasculitis' manifestations[34, 35] or with chronic vulvar erosions,[36] highlighting the need to include lichen sclerosus and other autoimmune dermatoses among the differential diagnosis of DH in women.

For the first time, Morris *et al.* linked CD with reproductive disorders in 1970.[37] Since then, many studies have pointed out the relationship between CD with obstetric disorders such as delayed menarche, early menopause, amenorrhea, reduced pregnancy rates, and adverse pregnancy outcomes,[38-41] which are more frequently observed in untreated celiac women than general population.[42, 43] It has been commonly accepted that CD is associated with infertility and recurrent abortions in women, as well as gonadal dysfunction and infertility in men, and that adherence to a gluten-free diet (GFD), can lead to the return of fertility in both men and women.[21, 44] A recent meta-analysis, however, indicates that CD is not more common in infertile women than in the general population.[45] Those findings differ from previous meta-analyses that indicate higher infertility rates among women with CD.[46, 47] Regardless of the exact prevalence and cause, CD-associated infertility has been treated successfully with GFD.[42, 48, 49] Accumulated data have suggested that women with unexplained reproductive disorders should be screened for CD by serologically testing for anti-tTG and anti-endomysium antibodies.[39] Interestingly, DH and CD share a common HLA genetic background and a higher proportion of DQ2 alleles are found in infertile and RSA (recurrent spontaneous abortion) women.[50] Furthermore, recent findings suggest that probiotics and micronutrient supplementation, in particular vitamin D, in addition to removal of gluten from the diet, may turn out to be an effective treatment for different reproductive disorders, associated with CD and DH.[39-50]

The exact mechanisms by which CD is related to fertility issues are unclear, but factors such as malnutrition, iron, folate, and zinc deficiencies have all been implicated. Anti-transglutaminase antibodies that activate transglutaminase in the trophoblastic cells, inducing apoptotic cell death and placental insufficiency,[51] may also contribute. Moreover, untreated celiac women suffer from iron malabsorption, which causes severe anemia during pregnancy when iron demand increase. Iron deficiency itself is a delayed fetal growth cause.[52] Intestinal malabsorption involves folic acid too, which intake is fundamental in order to prevent neural tube defects. Another possible explanation, though mostly presumed in men, is gonadal dysfunction. For instance, reduced conversion of testosterone to dihydrotestosterone caused by low levels of 5 alpha-reductase in CD

results in derangement of the hypothalamo-pituitary-gonadal axis, which is now well known to modulate immune function.[41] The occurrence of DH has been described in a 75-year-old man one month after the initiation of leuprolide acetate, a gonadotropin-releasing hormone analog used for androgen suppression in the treatment of prostate cancer.[53] The monthly premenstrual flare of DH lesions has been reported in a 29-year-old multipara woman.[54] Another case of DH has been described in a patient with panhypopituitarism due to a giant pituitary adenoma in whom the blistering disease disappeared after removal of the tumor and glucocorticoid replacement therapy.[55] Hyperprolactinemia is seen in 25% of coeliac patients, which causes impotence and loss of libido.[41] GFD and correction of deficient dietary elements can lead to a return of fertility both in men and women.

Osteopenia and osteoporosis

Osteopenia and osteoporosis are frequently associated to CD. In fact, celiac patients present anticipated spontaneous fractures more frequently than the general population and celiac disease is more frequent than expected in a cohort of patients with osteoporosis.[56] In women affected by CD, multiple mechanisms add on. These include the lack of the protective role of estrogens during menopause, intestinal malabsorption of calcium and vitamin D, and the production of anti osteoprotegerin antibodies that enable osteoprotegerin from working correctly.[57] In the end, the production of inflammatory cytokines leads to augmented reabsorption of calcium from bones. It has been demonstrated that a GFD, besides medical therapy and adequate lifestyles, is effective in reducing the risk of fractures and reducing bone rarefaction in celiac patients and that this intervention is much more effective if it is conducted at the earliest.[58]

Anemia

It has been reported that up to 50% of celiac patients present with anemia at diagnosis[59] and that celiac disease is responsible for the 6% of the cases of anemia without other causes.[58] Moreover, anemia is reported to be much more common among women affected by CD. In females with CD, multiple causes may add on including malabsorption of iron in the initial portion of the duodenum due to mucosal atrophy, menstrual cycles with monthly blood loss without adequate replacement,[26] and chronic inflammation. In fact, for what concerns the latter, celiac inflammation is known to lead to the production of inflammatory cytokines that induce hepcidin production and erythropoietin secretion.[60] This mechanism explains the reduced efficacy of martial therapy to correct iron deficiency anemia associated with celiac disease. The only therapy with efficacy is GFD that by stopping inflammation restore correct iron absorption thank to intestinal mucosa healing. Following the recommendations of the Italian Association of Celiac disease, the essay on anti-IgG/IgA transglutaminases must be prescribed in all cases of anemia without other causes.

Family burden due to GFD

The only known effective treatment of DH is a lifelong GFD.[2] However, limited data is available on the impact of family processes on adherence to a GFD.[61] It has been reported that women are significantly more knowledgeable about a GFD than men, probably as a result of their greater role in all aspects of food, both at home and away from home.[62-64] For the same reason, a larger percentage of women on a GFD may experience emotional distress than men, which might explain in part the greater burden of disease experienced by women.[63-65]

DH patients face the substantial expenses and economic burdens not only for buying gluten-free products (GFP) but also for direct and indirect medical costs. Studies have shown that GFP are considerably more expensive, unequally distributed, and less nutritious than their regular counterparts.[66-69] That is why GFD is considered a class-based diet. However, there is no clear consensus on the safe amount of daily gluten intake for CD patients.[70] Most health authorities, including the US FDA, define "gluten-free" products as containing less than 20 parts per million (ppm) gluten. While this is the lowest level that can be consistently detected in foods using valid scientific analytical tools, there are patients that are sensitive to such "gluten-free" levels. In fact, a health hazard assessment for gluten exposure conducted by the US FDA has concluded that "less than 1 ppm level of gluten in foods is the level of exposure for individuals with CD on a GFD that protects the most sensitive individuals with CD and thus, also protects the greatest number of individuals with CD from experiencing any detrimental health effects from extended to long-term exposure to gluten."[71] This data may be of help for lower-income families, already tending to rely more on naturally gluten-free foods and home-baked goods, which are cheaper than commercially prepared substitutes.

However, it must be said that in a few countries, patients suffering from CD and DH benefit from monthly vouchers

for bread and gluten-free products. In Italy, in particular, diagnosed celiac patients and patients suffering from DH receive vouchers to buy specifically produced gluten-free foods, up to 140 euros per month.[72] Lifelong GFD requires permanent lifestyle changes, and considerable time and money. Clinical status of disease, access to food, and mental health are most relevant in patients on GFD during the pandemic.[73] Poor adherence to GFD is linked to deteriorated mental health, which is mainly due to increased anxiety and depression during the pandemic. Furthermore, GFD households identified job losses, food shortage, increased prices, poor access to safe foods, and poor availability of medical help as relevant difficulties during the pandemic, which inevitably led to deteriorated quality of life. In regular households, women do more cooking and grocery shopping than men.[74] The process becomes even more gendered among families with GFD requirements, where careful planning is required. Furthermore, adult women rarely impose their GFD requirements but are willing to change the entire family's eating habits to better accommodate another family member.

Conclusions and recommendations

DH is a form of CD with specific cutaneous and gastrointestinal manifestations. Case finding strategy[75] remains the more adequate to highlight the great number of undiagnosed DH and CD cases, but it should be supported by the knowledge of the chameleonic modalities in which they both may manifest, particularly in women. In fact, although women have been reported to be more symptomatic, they experiment more often than men a delay in diagnosis. For this reason, the scientific board of the Italian Association of Celiac Disease recommends to perform the assay of the anti-transglutaminases IgA antibodies (or IgG in case of IgA deficiency) whether a patient presents with the following conditions: iron deficiency and anemia non-responding to iron supply, spontaneous fractures in pre-menopausal age, spontaneous recurrent miscarriage, low birth weight, intrauterine growth retardation, prematurity, pre-eclampsia and eclampsia, sterility/infertility, endometriosis, menarche retardation, early menopause, and amenorrhea (Figure 1). Along with disease-related events, it should be outlined that GFD intensifies gendered feeding work related to planning, grocery shopping and cooking as a proper GFD is complex, expensive and time-consuming and generally borne by women. Governments should consider proper financial measures and polices to assist families with GFD and to ensure the availability and adequate nutritional value of gluten-free products. At this regard, more evidence-based policies are needed to define proper "gluten-free" levels, which cannot be secured without adequate technology advancement.

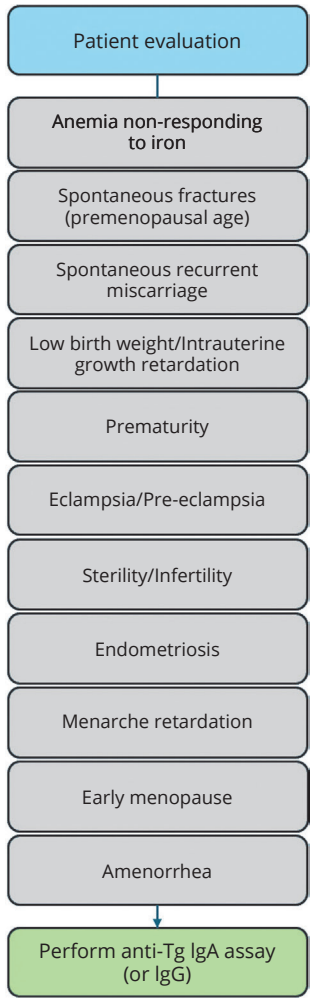

Figure 1.—Italian Celiac Disease Association recommendations to bridge the diagnostic gap between female and male patients.
Tg: transglutaminase.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Martin Shahid and Elena B. Mariotti share first authorship. Snejina Vassileva and Marzia Caproni have given substantial contributions to the conception of the manuscript. All authors have participated to drafting the manuscript, Martin Shahid and Elena B. Mariotti revised it critically. All authors read and approved the final version of the manuscript.

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