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Editorial

Dermatitis herpetiformis – What lies beneath the skin?

The prevalence of celiac disease (CD) has continuously increased in the last few years in such a way that 1-3 % of the European population is affected sometime during their lifetime (1). In parallel a change in clinical expression and a delay in diagnosis have been documented (2), with a high frequency of atypical manifestations and a low level of suspicion leading to a majority of undiagnosed celiac patients who will suffer from disease symptoms and remain exposed to the consequences of the condition for years. CD recognition is increasingly apparent in our society - "gluten-free" labels on multiple goods on supermarket shelves, and restaurants with posters publicizing gluten-free menus clearly underscore that the significance of CD has not gone unnoticed to the food industry. In contrast, CD recognition by healthcare providers is still in need of improvement in order to allow an early, accurate diagnosis; only 10 % of CD cases are diagnosed by primary care physicians (3), and diagnostic delays of up to 10 years from symptom onset have been reported (4,5).

Already in the 1980s a number of publications noted a change in the clinical picture of CD, with a greater predominance of mild to moderate manifestations and diagnoses in increasingly older individuals (6,7). The recent literature reveals that over one half of new CD diagnoses are made in the population older than 50 years of age (5,8). Therefore, now CD may no longer be considered a childhood disorder. Even like this, the real fact is that a host of undiagnosed celiac patients sit down every morning in the offices of specialists that still hold on to the classic notion of a celiac child with diarrhea where serologic testing will invariably reach a diagnosis. Serologic markers, particularly tissue transglutaminase IgA antibodies (tTGA), are useful CD markers to identify patients who should undergo intestinal biopsy. However, adult patients commonly exhibit a negative serology, which makes duodenal biopsy taking mandatory in all subjects with suspected CD (9). tTGA titers bear a linear correlation with the intestinal lesion's histological stage, and are most sensitive and specific in patients with villous atrophy or stage 3 according to the Marsh-Oberhuber classification (10-12); their usefulness is therefore limited to patients with no villous atrophy or Marsh stage 1. In fact, the differential diagnosis of CD in the presence of lymphocytic duodenosis often represents a difficult challenge, and some patients even remain without a definite diagnosis despite genetic tests, serology, flow cytometry, and tTGA immunostaining of duodenal biopsies (13).

To CD underdiagnosis contributes the "chameleonic" nature of the condition s clinical presentation, according to Dr. L. Rodrigo (14); digestive symptoms are frequently absent in many patients expressing disease characteristics such as low bone mineral density, which occurs in up to 75 % of celiac individuals in some series (15), and the skin lesions defining dermatitis herpetiformis (DH). The latter represents the most common, CD-specific skin manifestation, which is exclusively found in

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this condition. First described in 1884 by Dr. Louis Dühring (16), DH was not linked to CD until 1966 (17), and now represents the presentation form of CD in up to 10-25 % of patients (9), being more common in adult males but reported in both genders regardless of age.

The present issue of the *Revista Española de Enfermedades Digestivas* includes an original paper by Katalin Lorinczy et al. highlighting the transcendence of CD and DH beyond the intestinal and skin lesions themselves (18). The study of bone mineralization in adult patients with DH has been scarcely reported in the literature and results have been inconclusive so far - While some authors find no lower bone mineral density among patients with DH (19), nor an increased risk of fractures *versus* classic celiac individuals (20) despite the presence of intestinal disease, others have reported significant changes in bone mass in patients with DH, similar to the rest of celiacs, in association with poorer nutritional status (21). The present paper by Lorinczy et al. is therefore highly relevant as it sheds light on a yet unknown aspect of adult CD whence notable consequences will ensue, since CD is associated with an increased risk of bone fractures estimated to be 40 % higher than in the healthy general population (22). The authors recruited 53 adult patients with DH, 34 celiacs with no skin lesions, and 34 age- and sex-matched healthy controls who underwent dual-energy X-ray absoptiometry (DEXA) and were also tested for serum calcium, phosphorus, and albumin levels. It was found that lumbar spine bone mineral content was significantly lower in patients with DH as compared to healthy controls, but higher than in CD patients. In contrast, bone mineral density at the femoral neck and radius of patients with DH was similar to that of healthy controls, whereas subjects with CD also exhibited a significantly reduced bone density in both these sites (18).

Thus, bone involvement in DH is preferentially located in bones with a higher trabecular component, that is, the lumbar spine, analogous with what happens in adult CD although to a lesser degree. Recent studies have also shown demineralization predominant in the lumbar spine (4) that is directly associated with poorer nutritional status and higher grades of villous atrophy (4,23). This association is also described in the study by Lorinczy et al., where patients with CD have villous atrophy more often than those with DH, as well as higher serum calcium and albumin levels versus DH.

Research findings by Lorinczy are highly relevant for both dermatologists and gastroenterologists, and reminds them that DH is but the "cover letter" of true CD (14), and that we should forget all about the old-fashioned notion of DH as a "dermatologically active though gastrointestinally silent CD", based on the fact that only 20 % of patients with DH reported overt intestinal complaints (24) even though virtually 100 % have intestinal disease to varying extents (25).

According to the paper by Lorinczy, one third of patients with DH followed no gluten-free diet. Various therapies have been suggested for DH, and skin lesions in many patients may improve with corticoids or dapsone, which target their autoimmune background. However, only gluten-free diet clears both intestinal and skin lesions. Years ago Garioch et al., following their study of 133 patients with DH, showed that gluten-free diet reduces or eliminates medication needs, resolves enteropathy, provides a feeling of general well-being, and exerts an effect potentially protective against the development of intestinal lymphoma (26).

From Lorinczy paper implications two unavoidable questions arise: first, whether bone mineral status should be examined with DEXA in all celiac patients. While not all authors recommend universal screening (27,28), DEXA truly represents an accurate, harmless, non-invasive approach from which a supplementary regimen to gluten-free diet may be derived to prevent bone fractures and their sequels, including pain, dis-

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ability, and even increased mortality rates during the first year (29). In times of economic adjustments and reforms, should restrictions on DEXA procedures be required despite their relatively low cost and the fact that osteoporotic fractures are 3 to 6 times more expensive for healthcare systems than stroke or breast cancer (30), we believe them inescapable for celiac patients showing malnutrition (regarding which body mass index or serum prealbumin are more informative than serum albumin, as tested by Lorinczy) or duodenal villous atrophy at the time of diagnosis, as both parameters have been associated with a higher frequency of osteoporosis and osteopenia (4,23).

The second question posed to us relates to the need for CD screening among patients with idiopathic osteoporosis, a disease with characteristics similar to CD in terms of frequency and underdiagnosis. In fact, it has been posited that CD might well account for a relevant proportion of idiopathic osteoporosis cases (15,31). The frequency of CD among patients with osteoporosis is ten times more than expected, hence screening –at least using serology– also seems warranted in this scenario.

The association between CD, DH and low bone density is now better established based on the results of the original paper you may now read in this journal. However, the intimate mechanisms by which a primarily digestive disease eventually reduces bone mass remain to be elucidated; these likely are multifactorial and involve both deficient calcium and vitamin D absoption as a result of intestinal villous atrophy (4), and an impact of chronic inflammation on bone turnover (32). In any case, an absolute, permanent exclusion of gluten from the diet remains the most effective therapy for these conditions - an apparently simple measure that becomes really complex in an industrial society where manufactured products abound, and cross contamination leaves gluten traces in up to 70 % of them (33). Let us trust that the new drugs for CD now under development (34,35) will at least minimize the impact of said contamination or smaller dietary transgressions, even if the need for a gluten-free diet remains.

Despite the fact that CD has accompanied human societies ever since the beginning of our time, many aspects of this condition remain greatly unknown. The paper by Lorinczy et al. represents one further step in the understanding of CD, and goes deeper in the knowledge of another disease, osteoporosis itself, allowing to make out an etiologic therapy beyond mere symptom relief.

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