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EDITORIAL

Rheumatologic manifestations in celiac disease: what should we remember?

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Dear Editor,

Data regarding celiac disease (CD) have advanced greatly in the past years. Described initially as a gastroenterological entity with rare occurrence, we now admit for CD a prevalence of 1% and systemic involvement [1–4]. However, CD remains still an underdiagnosed disease [3, 4] and awareness should be raised especially for its non-digestive, non-classical clinical presentation [2, 5]. Therefore, we aim to shortly review here the musculoskeletal involvements described in or associated with adult CD, useful for internal medicine practice.

CD has some specific features: it is an immune (anti-deamidated gliadin antibodies – DGP) and autoimmune (anti-endomysial antibodies – EMA, anti-tissue transglutaminase antibodies – tTG) condition that occurs in genetic susceptible individuals (90–95% HLA-DQ2 and for the rest HLA-DQ8) [1, 3]. The main pathogenic process is developing in the intestinal mucosa by lymphocytic infiltration with subsequent destruction of the intestinal villi architecture. CD diagnosis should be confirmed by intestinal biopsy in patients with positive serology before initiating the gluten-free diet (GFD). The GFD is easily accessible and has good rates of response for the CD symptoms [3, 4].

When the intestinal histology features suggestive for CD are found in seronegative patients, differential diagnosis should include also other autoimmune diseases that might mimics CD, like autoimmune enteropathy, Graves or Hashimoto disease, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome or type I diabetes [4].

During the last years, the systemic involvement in CD was more studied and musculoskeletal manifestations were also described. Jericho *et al*. identified extra-intestinal manifestations in 62% adults and 60% children known with CD (interestingly, 9% adults and 18% children presented only extra-intestinal CD manifestations) [6]. In the same study, an important number of adult patients presented musculoskeletal manifestations: arthralgia (16%), arthritis (15%), and myalgia (8%). After the introduction of the GFD, the rates of clinical response were important: 69% for arthritis, 54% for arthralgia, and 50% for myalgia [6]. In a recent meta-analysis that comprised data up to August 2016, Daron *et al*. found cumulative incidence of 18.3 (4.7–38.1)% for osteomalacia, 22.1 (7.9–40.9)% for arthritis, 30.3 (19.2–42.8)% for arthralgia, and 6.1 (0.5–17.0)% for bone pain [7]. Moreover, they showed higher cumulative incidence in CD when compared to controls of 16.6% *vs*. 9.9%, 9.8% *vs*. 4.2%, and 18.1% *vs*. 5.0% for unspecified site, femoral, and spinal osteoporosis, respectively [7]. The relative risk of any site osteoporosis in CD patients when compared to controls was 2.7 (1.9–4.0) [7]. Results of meta-analysis showed that there is an association between CD and bone fracture [8,9]: 30% (CI 1.1–1.5) for any site and 69% (CI 1.1–2.6) increase in risk for the hip fracture [9].

Furthermore, in middle-aged women, the tTG-IgA positivity was associated with bone mass density loss and osteoporosis; fractures were more prevalent in cases with high tTG-IgA levels [10]. Nuti *et al*. included in their research only women with osteoporosis and identified significant lower serum vitamin D in patients with positive AGA and tTG: 17.8 *vs*. 55.1 nmol/L [11].

The pathogenic mechanisms involved in osteopenia/ osteoporosis in CD are mainly related to vitamin D and calcium malabsorption due to villous atrophy. These are added to secondary hyperparathyroidism in patients with hypocalcemia, systemic inflammation with high serum levels of proinflammatory cytokines (IL-1, IL-6, TNF-alpha) as well as to hypogonadism and sexual hormones metabolism disturbances that also have impact on the bone turnover [1]. However, the risk of osteoporosis seems to be equal for both women and

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men and so the impact of sexual hormones might not be important [12]. The bone mass density is improving under GFD, mostly during the first year (5%), but rests however lower than expected [12].

Vilppula *et al*. showed that the introduction of GFD in CD screen-detected patients older than 50 years is followed not only by the diminution of the lymphocytic infiltrate and amelioration of the villous height, but also by a significant higher serum vitamin D level (64 *vs*. 45 nmol/L) [13]. At diagnosis, searching for vitamin D deficiency could be so considered [3], but there is only low evidence for GFD benefits in osteoporosis prevention [4]. Moreover, there is not strong evidence for the benefits of calcium supplementation either [4].

The relative risk of associating one or more autoimmune pathologies is approximately three times higher in CD patients when compared to general population [14] and 30% of the CD patients have also another immune pathology [15]. Together with the musculoskeletal involvement, the female gender, DGP positivity, vitamin D deficiency and antinuclear antibody positivity were associated with polyautoimmunity in CD patients [15]. The following mechanisms might explain the increased autoimmunity expression in CD: similar genetic features, common triggers, or the disturbed intestinal permeability [16]. In this regard, the association of type I diabetes, autoimmune thyroiditis, and Sjögren's syndrome was established [1, 14]. There are also other autoimmune diseases like primary biliary cirrhosis, Addison's disease, juvenile idiopathic arthritis [1], or psoriasis [14] for which there are some arguments for an association with CD.

In such cases with polyautoimmunity, the bone impairment is multifactorial: endocrine and nutritional consequence, but also immune osteoclast imbalanced [17]. Moreover, specific treatments used in other immune conditions (e.g. rituximab) might improve also CD symptomatology [18, 19].

Patients with symptomatology of irritable bowel disease might have undiagnosed CD and there is also an association between irritable bowel disease and fibromyalgia syndrome [20]. In patients with both diseases, CD could be searched. When positive diagnosis, the dietary therapy might improve not only the CD digestive symptoms, but also those related to fibromyalgia; however, data are still scarce [20]. There are also no data of an association, other than sporadic, between CD and fibromyalgia syndrome [21].

In some autoimmune diseases, such as SLE, there was supposed a relation with CD due to DGP positivity. The use of more specific antibodies (EMA, tTG) showed that this association is not frequent but more likely similar to general population [22]. Back pain and sacroiliitis in long-standing CD were also reported [23]. Further, in RA, inflammatory bowel disease, autoimmune hepatitis, SLE, autoimmune hepatitis, vasculitis, polymyositis or myasthenia, might be only random association of CD [1], but research is still needed for achieving final conclusions [16].

Therefore, we think that screening for CD should be proposed in selected patients with osteoporosis, osteopenia, or osteomalacia of unknown cause. There is also need of rheumatologic follow-up in some CD patients [23].

In terms of treatment, the GFD is started also without having CD or without a medical recommendation, with the hope of a better outcome in healthy or in pathologies not-related to CD (e.g. inflammatory bowel disease, SLE). Until now, there are no consistent results for the GFD utility in other pathologies than CD, wheat allergy or non-celiac gluten sensitivity [24]. Moreover, a GFD might have negative effects on the gut health when the GFD is followed in the absence of gluten intolerance and further researches are needed to clarify the general impact of gluten alimentary discharge [24]. One question that remains open is related to the possible usefulness of GFD in patients with other immune diseases than CD and persistent AGA or DGP positivity. However, the value of a GFD in patients with other immune pathologies than those directly related to gluten exposure has not been yet observed.

In conclusion, arthralgia and myalgia are encountered in CD patients and may respond to GFD. There is also an increased risk of vitamin D deficiency and osteoporosis in these patients. Evaluation of vitamin D status is indicated at CD diagnosis and, when needed, its supplementation might be useful for the bone mass loss prevention. And finally, CD patients associate more frequently than general population other autoimmune diseases, some of which might have also musculoskeletal involvement (e.g. Sjögren's syndrome, psoriasis).

Abbreviations:

AGA: anti-gliadin antibodies
CD: celiac disease
DGP: anti-deamidated gliadin antibodies
EMA: anti-endomysial antibodies
GFD: gluten-free diet
tTG: anti-tissue transglutaminase antibodies

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