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The Gut Feeling of the Joints: Celiac Disease and Rheumatoid Arthritis Are Related

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Abstract The "mosaic of autoimmunity" is a complex, multiple-faceted, challenging scientific enigma. Celiac disease and rheumatoid arthritis are part of the autoimmune bee hive and despite being separate entities, they share multiple aspects. The present review summarizes the epidemiological, clinical, serological, genetic, environmental, enteric eco-events and associated diseases shared by the two mechanistically similar though different antigenic entities.

Keywords: *celiac disease, rheumatoid arthritis, HLA, microbiome/dysbiome, leaky gut, post translational modification of proteins*

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1. Introduction

The incidence of multiple autoimmune diseases (AD) is surging in the last few decades [1,2] including celiac disease (CD) [3] and rheumatoid arthritis (RA) [4,5]. Both diseases fulfill the criteria for autoimmune condition. More and more scientific knowledge is constantly accumulating on the cross talks along the gut-joint axes. Not surprising is the fact that most of the ADs are related and share numerous epidemiological, gender, environmental, genetic and clinical aspects, constituting the "Mosaic of autoimmunity" [6], or termed polyautoimmunity [7]. In this regard, Mounir A et al. [8], should be congratulated for bringing the association of CD and RA in a Moroccan woman, thus adding to the increased reports coming from the North African continent [9].

The present review will update on the CD/RA interrelationships, highlighting the central place played by the intestinal eco-events that are driving systemic autoimmunity, including rheumatological diseases.

2. Epidemiological Similarities between CD and RA

Both entities share multiple epidemiological features. In both, North- West to South-East gradient exist and the incidences are similar, being 1% in the developed countries [4]. Their incidences are on a rise. In both, the female gender is predominant and they share several environmental factors that were described to either influence or predispose to the diseases. In CD and RA, infections, stress, change in composition and diversity of the microbiome, pregnancy and the postpartum period were suggested. Finally, microorganisms like EBV, HCV, CMV and *Mycobacterium tuberculosis* were reported in both of the entities [4,10-14].

3. Shared Clinical Presentations

3.1. Joint Manifestations in CD

Multiple case reports, case series and reviews described rheumatological signs and symptoms in CD patients. Arthralgia, arthritis, polyarthralgia, enthesopathy, early morning joint stiffness, subclinical synovitis, back pains and sacroiliitis were reported in CD patients [4,5]. Interestingly, lower education, elderly age and osteoporosis were significantly associated with joint inflammation in CD affected population [15]. When 200 adult CD patients were followed up, the prevalence of arthritis was 41% in naïve versus 26% on gluten withdrawal [16].

A totally different aspect is presented by the improvement or disappearance of the rheumatological manifestations in around 30% of CD patients that consume gluten free diet [4,15,16,17,18]. Intriguingly, dietary gluten was recently described as pro-inflammatory, pro-oxidative, anti-apoptotic and even an activator of the innate immune system with negative effect on the regulatory T cells [19]. Those actions might explain some of the anti-inflammatory effects of gluten withdrawal on the joint manifestations in CD. HLA-DQ 2/8 gluten selected T cells were shown to migrate from the inflamed CD mucosa to the extra intestinal blood vessels, upon gluten challenge, thus, providing an additional pathway involved in the pathological joint manifestations in naïve CD patients. Finally, most recently, "preclinical" rheumatoid arthritis

was described in active CD patients [20]. The authors concluded that CD patients should be considered a high-risk group for RA, when positive for rheumatoid factor/anti-CCP antibodies.

3.2. Intestinal Manifestations in RA

The majority of the enteric pathology in RA is due to drug side effects. However, gastrointestinal manifestations were described in naive RA patients [4]. Heartburn and dysphagia due to esophageal motility abnormalities, difficulties of mastication due to temporomandibular arthritis, intestinal vasculitis manifested as bowel ulcers, enteric infarctions/strictures, acute surgical abdomen, gut perforation, appendicitis, colitis, atrophic gastritis, malabsorption due to amyloidosis, protein losing enteropathy, bacterial overgrowth, intestinal pseudo-obstruction, were described in naive RA patients [4,21]. The liver is also involved in RA [4,21]. Transaminasemia, steatosis, necrotizing hepatic arteritis, nodular hyperplasia and primary biliary cirrhosis were described in RA patients [22]. The question, whether primary biliary cirrhosis in RA is a cause, consequence, or coincidence, is still open [23]. A very interesting subject is the response of RA patients to gluten elimination [19,24,25]. It appears that a subset of RA patients, mainly those positive to anti gliadin antibodies or other CD associated antibodies, might benefit from a gluten free diet. Gut-derived antigens, like the peptidyl arginine citrullinated peptides, are key initiators driving the immune abnormalities in RA. So, logically multiple diets were tried in RA nutritional therapies [26]. Gluten free diet is one of them. When submitted to gluten free vegan diet for 1 year, antibodies against β-lactoglobulin and gliadin and disease activity were significantly reduced in RA patients [27].

4. RA and CD Associated Antibodies and Diseases

CD and RA are ADs and as such are integral part of the mosaic of autoimmunity and the poly-autoimmune complexes, intriguing, but partially explored, syndromes. Following are rheumatic ADs associated with CD and vice versa.

4.1. Rheumatological Conditions and Serology Associated with CD

Several rheumatological or connective tissue diseases are associated with CD [4,28]. RA, juvenile rheumatoid arthritis or juvenile idiopathic arthritis, Sjogren's syndrome, systemic lupus erythematosus, ankyloses spondylitis, osteoarthritis, psoriatic arthritis, reactive arthritis, and adult-onset Still's disease, were reported as associated with CD.

CD sera might harbor multiple serological markers of rheumatological/connective tissue conditions [4,29,30]. IgM rheumatoid factor is an interesting one since its increased jejunal mucosal production is relayed to active CD. Other antibodies that were reported in CD, in relation to rheumatological/connective tissue entities are: anti-reticulin, anti- actin, anti-smooth muscle, anti-desmin, anti-calreticulin, anti-collagen, anti-bone, anti-single/double-stranded DNA, anti-extractable nuclear antigen, anti-Ro/SSA, anti-cardiolipin and anti-endomysial antibodies [4,29,30].

4.2. Enteric Conditions and serology associated with RA

The gastrointestinal symptomatology, signs and conditions that were reported in RA patients were detailed above, in sector 3.2. Increased incidence of gastrointestinal antibodies were reported in rheumatological/connective tissue entities: IgG anti-gliadin in anti-phospholipid syndrome, IgG anti-gliadin in RA, IgG anti tissue transglutaminase in anti-phospholipid syndrome and IgG anti ASCA in SLE [31]. The authors concluded that the findings suggest an association between gastrointestinal related-antibodies and a wide spectrum of ADs. The clinical implication of these findings is yet to be determined.

Subjects with RA had 3 fold increased prevalence in CD, compared to controls, (3%, 1%, respectively) [32]. When CD associated antibodies were studied in outpatients rheumatological clinics, 5.8% of Sjogren's syndrome, 4.8% of systemic sclerosis, 1.5% of RA and 2.85% of SLE patients, were positive, thus highlighting the importance of CD screening in elective rheumatological facilities [33].

5. Shared HLA and Non-HLA Genes

CD and RA are strongly associated with the HLA-DR/DQ locus. The strongest association in CD is to HLA-DQA1*05: 01 and HLA-DQB1*02: 01 haplotypes while RA is associated with the HLA-DRB1*04 alleles [4,34,35,36]. While the DQ2/8 test has an excellent negative predictive value of 95-99%, the RA haplotype analysis is neither included, nor recommended as a diagnostic tool by the current ACR/EULAR guidelines [34]. Being complex, polygenic and heterogeneous entities, both share multiple non-HLA susceptible genes. Using genome-wide association techniques and applying meta-analysis of immunochip data, 26 known and 5 new shared genetic loci were reported by Gutierrez-Achury J et al, in 2016 [36]. Interestingly, two of the shared loci showed opposite allelic effects, suggesting that the risk allele for one condition is in fact protective for the other. More recently, a meta-analysis of immunochip date of four ADs was published. [37] In total, 38 risk variants were shared by at least two of the analyzed ADs. Ten of them were shared between RA and CD. Pathophysiologically, pleiotropic variants acting by deregulating gene expression might act in various subsets of T cells, including specifically TH17 and regulatory T cells. The common molecular mechanistic pathways of RA and CD might detect new drug targets as a novel therapeutic strategy to combat the two ADs. It seems that CD and RA share similar mechanisms, different autoantigens and comparable environmental enteric eco-events [38-41].

6. Shared Intestinal Luminal Eco-events in RA and CD

The intestinal compartment and the luminal eco-events play a central role in remote organs ADs [42]. Under normal homeostasis, nutrients and their impact on the microbiome and the tight junction function, the microbiome/dysbiome/virome balance, post translational modifications of proteins, prokaryotic horizontal gene transfer of hostile genes, the intestinal permeability and the resulting leaky gut, are intermingling harmoniously, though, disturbed under pathological circumstances [43,44,45,46].

6.1. Microbiome/dysbiome Ratio

The place of the enteric microbiome/dysbiome balance as a driving factor in autoimmunogenesis is extensively explored, but cause and effect relationship are far from being established. In both diseases, in CD and RA, there seems to be a microbial imprint, where changes in composition and diversity were reported. In RA, a decreased gut microbial diversity, related to disease duration and autoantibody levels were described. A decreased abundance of *Bifidobacterium* and *Bacteroides* families and an abundance of *Prevotella copri*, were reported [4,5,47]. It should be stressed that strain-level *Prevotella copri* diversity is highly dependent on Western and non-Western diets and should be considered when examining host-microbe associations in RA [48]. In CD, however, an increase of Gram-negative bacteria and *Bacteroidetes* and a decrease in of Gram-positive bacteria numbers of *Bifidobacterium* and *Lactobacilli*, is observed [49,50]. The two entities share the decreased abundancy of *Bifidobacterium* and *Lactobacilli* strains.

6.2. Post Translational Modification of Naive Peptides

The microbial enzymatic machinery of the microbiome may modify naïve proteins to immunogenic ones. The changed spectrum of luminal bacterial enzymes involved in post-translational modification of naïve proteins contribute to generation of neo-epitopes in the modified proteins, thus generating autoimmune responses by the host, resulting generally in ADS, particularly, RA and CD [43]. An immune response against post-translationally modified protein antigens is a hallmark of both condition. In RA, peptidyl arginine deiminase citrullinates antigens, including vimentin, fibrinogen and α-enolase, thus breaking tolerance and inducing the anti-cyclic citrullinated peptide antibodies [4]. In CD, a comparable post translation modification of gliadin occurs, where the tissue transglutaminase deamidates or cross links the gliadins, resulting in neo-epitope deamidated or cross linked gliadin antigens presented by the predisposing HLA-DQ2/8 to the local immune systems [38,43]. The ensuing results are the CD associated antibody repertoire of anti deamidated gliadin and anti neo-epitope tissue transglutaminase antibodies [51,52,53]. It can be summarized that in both ADs, enzymatic post translational modification, of citrullinated proteins in RA and gliadin peptides in CD, are crucial intestinal steps in the disease initiation and progression. Microbial transglutaminase is a known cross linker of proteins, heavily used in the processed food industries and imitates functionally the endogenous tissue transglutaminase [54,55]. As a post translation modifier of peptides, it was recently shown to be immunogenic and potentially pathogenic in CD [56,56,57,58]. No studies are available, as yet, on its immunogenicity/pathogenicity in RA, despite the fact that the enzyme is secreted by the gut microbiome and dysbiome [44,45].

6.3. Enteric Luminal Horizontal Gene Transfer

The inheritance of mutated genes during human evolution is almost exclusively vertical, however, the main mechanism for microbial evolution is horizontal gene transfer [45]. It represents an indispensable survival mechanism of adaptation to extreme conditions, with the capacity to exchange genetic cargo in between prokaryotes and more seldom to eukaryotes. The inter-bacterially exchanged hostile genes may affect the human microbiome/dysbiome balance, induce post translational modification of naive proteins, compromise tight junction functional integrity and counteract the local immune protective mechanisms [45]. Altogether, it can represent a major pathway that drive the autoimmune cascade [45]. No studies were performed on the luminal extend of the horizontal gene exchange in CD or RA. However, since both are microbe and infection mediated, characterized by corresponding dysbiome, this prokaryotic gene transfer pathway might operate in each one of them. It is foreseeable that the new future dimension of gene therapy and tissue engineering of joint and cartilage pathologies might attenuate the horizontal hostile gene transfer consequences [59,60].

6.4. Intestinal Permeability and Leaky Gut

Impaired intestinal permeability is an intrinsic feature in multiple ADs [42]. Referred to as a 'leaky gut', its mechanistic impact on the pathogenesis of ADs remains obscure. Is it a cause, consequence or coevolutional phenomenon? [42,61,62,63]. Nutrients, allergens, toxins, pathobionts, carcinogens, dysbiotic microbes, stress, drugs and the lately described industrial processed food additives, can alter the tight junction functional integrity [12,13,14,19,42,46,54-58,61]. Notably, compromised tight junction function is a major defect in CD and gliadin/gluten are breachers of this tightly conserved mechanism [61,64]. Intestinal permeability is increased in various rheumatic ADs: ankylosing spondylitis, juvenile onset arthritis, psoriatic arthritis, Behçet's syndrome and rheumatoid arthritis [65]. It points to the potential involvement of the leaky gut in CD extra intestinal and RA extra articular manifestation evolvement. The end result of the passage of those non-self-peptides, from the luminal compartment to the internal ones, provoke the autoimmune cascade, contributing to peripheral organs' pathology in CD an RA [66,67].

6.5. Responsiveness to Gluten Withdrawal

No doubt that gluten elimination is the only and the most effective accepted therapy for gluten dependent conditions, CD being one of them. As mentioned above, gluten has numerous side effects that were shown in vitro, ex vivo and on animal models [12,19]. Being a universal food additive for multiple food processed industries, not only for the bakeries [68], gluten might affect non-celiac ADs. In fact, some of RA patients, mainly those with anti-gliadin/gluten antibodies, can benefit from gluten withdrawal [19,24,25,69,70]. The response of the CD rheumatological manifestations to gluten elimination reinforce the additional mechanism of articular pathology in CD that might benefit gluten-free diet.

7. Conclusions

CD and RA are two different ADs that share multiple aspects. Epidemiologic feature, clinical presentations outside of the target affected organs, luminal and intestinal events affected by nutrients, microbiome and lateral gene exchange, pathological pathways in terms of translational modification of the offending peptides and the leaky gut are some of the shared aspects. Activated immune cells, pro-inflammatory cytokines, microbial constituents, mobilome, and multiple molecules that escape the tight junction barrier present potential messengers that irradiate and spread the intestinal cargo to remote organs, in our case to the joints. Understanding those factors, cross talks and pathways might bring new therapeutic strategies to treat the two mechanistically similar though different antigenic entities.

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