

Rheumatic diseases and IgG-mediated food intolerance

Rheumatism or rheumatic disorders are conditions causing chronic, often intermittent pain affecting the joints, tendons, ligaments, bones, muscles and connective tissue. This disorder includes about 200 different conditions and it is becoming clear that a chronic inflammatory response, also induced by gut dysbiosis, can critically contribute to the development of rheumatic diseases^{1,2}. They share inflammatory processes affecting joints, tendons, ligaments, bones and muscles, cause chronic, often intermittent pain, are difficult to treat and are very common. Among the most common ones are rheumatoid arthritis (RA), spondyloarthropathies (ankylosing spondylitis and psoriatic arthritis), juvenile idiopathic arthritis, osteoarthritis, rheumatic polymyalgia, Sjogren's syndrome, lupus, gout, scleroderma or infectious arthritis.

Patients with rheumatic diseases often feel that there is an association between food intake and symptom severity. In a survey, 300 subjects with rheumatoid arthritis (RA) were asked about consumption of 20 foods that make their RA symptoms better, worse, or unchanged. Almost a quarter of respondents stated that foods do affect their symptoms, being blueberries and spinach most often reported to improve RA symptoms. Soda with sugar and desserts were most often reported to worsen RA symptoms³. Another survey found that rheumatic disease was affected by diet among 60% of respondents, whereby a positive effect was attributed to groats and oily fish (39% and 32% of the respondents, respectively)⁴.

However, when patients seek advice from their rheumatologists regarding dietary modifications, they are told that there is limited scientific proof regarding the effectiveness of a dietary approach. But current data often provide rather conclusive answers to the question about recommended nutrition for RA patients⁵⁻⁸. Contrarily, the EULAR (European League Against Rheumatism) recommendations for treatment of early RA considered that none of the existing studies

has unequivocally proved an advantageous influence of specific diets on the course of the disease, but agreed that a vegetarian diet has positive influence on pain and disease activity indicators⁹. It was also shown that fasting for 7–10 days induces anti-inflammatory effects, and fasting is recommended¹⁰⁻¹⁴, also prior to going on a vegetarian diet. Diet and intestinal microbiota are modifying factors that may influence intestinal barrier strength, functional integrity and permeability regulation. Intestinal microbiota may play a crucial role in RA pathogenesis, but up to now, no solid data have clarified a mechanistic relationship between gut microbiota and the development of RA. Gut microbiota regulate the T cell-mediated immunity and seem to have a role in RA development, while gut dysbiosis contributes to the occurrence or development of a range of rheumatic diseases^{1,2}. In this reasoning, we can assume that diet can not only exert anti-inflammatory effects, but has also an influence on the gut bacteria and hence disease activity^{15,16}.

Systemic inflammation can be triggered by food. Proteins or protein-derived compounds that occur in food may modulate the immune response of the body. The immune system takes food proteins or derived compounds as immunogens that generate food specific IgG antibodies, which are combined with food particles and then induce inflammatory response, presented as symptoms or diseases. Continuous and repeated consumption of the same foods that trigger IgG-mediated hypersensitivity reactions may thus promote and maintain silent inflammations. IgG-mediated food hypersensitivity can therefore be a trigger factor for the development of diseases where inflammatory pathways are involved, such as rheumatic diseases. Following, we summarize data regarding the involvement of IgG antibodies against food antigens in several rheumatic diseases.

Rheumatoid arthritis

To investigate the immunological link between gut immunity and rheumatoid arthritis (RA), antibodies (IgG, IgA, and IgM) to dietary antigens (cow's milk (alpha-lactalbumin, beta-lactoglobulin, casein), cereals, hen's egg (ovalbumin), cod fish and pork meat) were measured in the serum and jejunal fluid of 14 RA patients and 20 healthy subjects. The results showed that jejunal IgA, IgG, and IgM activities to nearly all food antigens were highly or moderately increased in RA patients when compared with healthy individuals. Gliadin- and casein-specific IgG antibodies in the jejunum of RA patients were 12 times higher, and a 4-8 fold increase was measured for other food or food constituents, compared to healthy persons. Five RA patients were then treated with sulfasalazine



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(an anti-inflammatory drug used for patients with Crohn's disease, ulcerative colitis and RA) for 16 weeks. The increased food antibody level strongly decreased in two patients, suggesting that sulfasalazine had an immunosuppressive effect on intestinal immune responses. This points towards a connection between mucosal immune activation and the pathogenesis of RA, at least in some patients. Their food related problems probably reflect the additive effect of multiple hypersensitivity reactions that are mediated by immune complexes, which then predispose the joints for auto-immune tissue destructive reactions¹⁷.

Another study with experimental animals investigated whether the pathogenesis of RA can be related to a food allergy and which antigens might be relevant. In Wistar rats with arthritis, plasma concentrations of food-specific IgG and IgE levels and circulating immune complexes were determined. Concentrations of proinflammatory cytokines (tumor necrosis factor-alpha (TNF- α) IL-1, IL-6, IL-17) were also measured. Wistar rats with arthritis had increased circulating immune complexes and high amounts of the cytokines TNF- α , IL-1, IL-6, IL-17. The titers of milk or egg specific IgG and IgE antibodies were remarkably high. Accordingly, the pathogenesis of RA seems to be closely associated with elevated egg or milk specific antibodies¹⁸.

Rheumatoid arthritis in patients with Sjögren's syndrome

Sjögren's syndrome is a long-term autoimmune disease that affects the body's moisture-producing glands. Primary symptoms are a dry mouth and dry eyes, but this condition is often accompanied by other immune system disorders, such as rheumatoid arthritis and lupus. Certain immune cells attack the salivary and lacrimal glands in particular, which can lead to inflammatory changes in the internal organs and the central nervous system. Patients with Sjögren's syndrome (SS) often suffer from irritable bowel syndrome (IBS), and occasionally from celiac disease.

A study was conducted to investigate possible food intolerance in patients with SS and IBS. IgG-based food tests were performed in ten patients, and multiple food intolerances were detected in all cases. Nine of ten patients were found to be intolerant to wheat and dairy products. Most patients had antibodies indicating gastrointestinal inflammation. Eight of ten patients adhered consistently to an IgG-specific elimination diet for a period of six months. The changed diet led to a complete elimination of abdominal pain, flatulence, diarrhea and joint pain. Two patients excluded only wheat and milk prod-

ucts from their diet and also experienced an improvement, but not a complete elimination of the symptoms. As soon as wheat or dairy products were consumed, the symptoms returned. Over time, some of the patients were able to tolerate some foods (such as tomatoes, pork or rice) without an increased symptom burden. Fatigue and exhaustion were also an essential part of the symptoms of all patients. The elimination diet improved the symptoms, but not by 100%. Fatigue was improved by dietary supplements for the treatment of metabolic mitochondrial dysfunctions such as CoQ10, carnitine, folic acid and alpha lipoic acid. This study showed that hypersensitivity to food was involved in the symptoms of SS, being wheat and dairy intolerance the most relevant antigens. The authors of this study conclude that patients with SS who suffer from IBS should always be tested for food intolerance. These simple and inexpensive interventions have helped all patients and significantly improved their quality of life¹⁹.

Juvenile idiopathic arthritis

In juvenile idiopathic arthritis (JIA), a rheumatic disease affecting children, it is assumed that environmental factors impacting the composition of the microbiota (such as delivery mode and early exposure to antibiotics) affect the risk of this chronic inflammatory disease. In addition, numerous genes are involved in JIA predisposition. Cow's milk contains more than 25 different proteins, whereby children are most allergic to α -lactalbumin. IgG antibodies against cow's milk antigens are produced in the plasma cells of the intestinal tract, but the role of these antibodies in the pathogenesis of JIA is still unclear. At the European Congress for Rheumatology 2018, a study was presented which demonstrated the connection between an altered gastrointestinal immunological status and the pathogenesis of juvenile idiopathic arthritis. The aim of this study was to evaluate antibodies against cow's milk antigens in children with JIA and compare the results with antibody levels in healthy children. IgG antibodies against β -lactoglobulin, α -lactalbumin and casein were tested in the serum of 65 children with high and low disease activity and compared with the corresponding values of 30 healthy children. The disease activity was determined by calprotectin analysis. The results showed a significantly higher concentration of IgG antibodies (total IgG) against all three milk antigens at high disease activity compared to low disease activity. However, there was no difference in the concentration of IgG4 β -lactoglobulin between high and low disease activity. Children with high disease activity in JIA had the same degree of antibody-production against milk antigens in serum as healthy children, but the levels were significantly decreased in children with lower disease activity. These results support the influence on the gastrointestinal immune system on the disease activity and possibly also the treatment in JIA²⁰.

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Ankylosing spondylitis (AS)

This is a type of long-term inflammatory arthritis that affects typically the joints where the spine joins the pelvis, but other joints such as the shoulders or hips can also be involved. Stiffness of the affected joints generally worsens over time and back pain is a characteristic symptom of AS. The causes of this disease seem to lie in an immunological disorder. The tumor necrosis factor α (TNF- α) apparently plays a central role and occurs more frequently in the inflamed sacroiliac joint, together with T helper cells (CD4+ T lymphocytes), cytotoxic T cells (CD8+ T lymphocytes) and macrophages. In addition, it has been shown that misregulation of IL-6, IL-10, IL-17, TNF- α and IFN- γ contributes to the pathogenesis and progression of AS²¹. It is known that around 40% of patients with AS have subclinical bowel inflammation, suggesting that the origin of the disease could be in the gut²², and there is increased evidence of intestinal microbial pathogenesis²²⁻²⁴. IgE-mediated type I allergic reactions do not seem to play a significant role in AS. In contrast, IgG antibodies are considered to be delayed exposure responses to various food antigens.

A recent study questioned the significance of IgG-mediated food allergies in patients with AS. IgG tests (against 14 foods: wheat, egg, mushrooms, milk, pork, chicken, beef, crabs, cod, corn, soybeans, tomatoes, shrimps and rice) were performed in 75 patients with AS and 78 healthy volunteers. In addition, the CRP value was determined in all study participants as an inflammatory indicator of the disease severity. AS patients had significantly higher IgG serum levels against beef, crab and pork compared to healthy subjects. In addition, serum levels of pork-specific IgG were significantly and positively correlated with CRP. These results suggest that α -Gal, the predominant natural antigen in red meat, may play a potential role in the pathogenesis of AS. The authors therefore recommend the avoidance of beef and pork in AS patients²⁵. Studies on the importance of a personalized IgG elimination diet in AS patients have not yet been carried out, but would be very promising given the results to date.

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