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Review Article

Should Rheumatoid Arthritis Patients go on a Gluten-Free Diet?

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Abstract

Rheumatoid arthritis and celiac disease are autoimmune inflammatory diseases that share multiple aspects. The only established therapy for celiac disease is the gluten-free diet. The current therapy for rheumatic arthritis patients is mainly pharmaceutical and physiotherapy. The nutritional therapy is in its first steps, while several diets were suggested. A gluten-free diet was preliminarily assessed with some beneficial effects; however, no guidelines exist in the rheumatic, nutritional, nor in autoimmune literature. The present review expends on rheumatoid arthritis - celiac disease relationship, on the gut-joint axis, on the enteric luminal and mucosal eco events in rheumatoid arthritis patients. Various aspects of Gluten-free diet are reported, guidelines for gluten withdrawal are suggested and the beneficial aspects of Gluten-free-Mediterranean diet are described.

Keywords: Rheumatoid arthritis; Gluten-free diet; Celiac disease; Non-celiac autoimmune diseases; Dietary therapy; Tissue transglutaminase

Abbreviations: Ads: Autoimmune Diseases; RA: Rheumatoid Arthritis; CD: Celiac Disease; GFD: Gluten-Free Diet; MD: Mediterranean Diet; SCFA: Short-Chain Fatty Acids; tTG: Tissue Transglutaminase

Introduction

A wide discrepancy exists between the worldwide increased wheat consumption and its popularity and between the scientific observations on the side effects of gluten, the major protein in wheat [1–4]. The human being first encountered the wheat approximately 15000 years ago in the Fertile Crescent of the Middle East [5]. Due to evolutionary environmental pressures and human breeding, nitrogen fertilizers and pesticides usage, wheat has undergone many phenotypic and genetic changes [6]. Compared to the old wheat, the contemporary one contains 8-folds more gluten and the protein is more immunogenic and more toxic [2,4]. Despite it, wheat is the most popular staple prolamin, representing a major caloric and protein source for most of the world's population [2,3], while its annual consumption is steadily increasing [1]. Interestingly, efforts are continuously made, aiming to develop low-gluten, non-transgenic wheat variety [7–9].

Alongside to the last decades' increased incidences of Autoimmune Diseases (ADs) [10,11], the major gluten-dependent autoimmune condition, namely Celiac Disease (CD) is also increasing [11,12]. Interestingly, the list of gluten-dependent diseases is expanding: gluten ataxia, dermatitis herpetiformis, non-celiac gluten/wheat sensitivity and gluten/wheat allergy are on the list [13]. On the other hand, gluten itself has recently been described as a potential contributor to the development of neurodegenerative diseases [14–16]. In addition, the beneficial effects of gluten withdrawal in AD are increasingly reported [1,2,4,17–19], not excluded are various rheumatic conditions [2,4,17–19]. The present narrative review will concentrate on rheumatoid arthritis aiming to answer the question, should rheumatoid arthritis patients go on a Gluten-Free Diet (GFD)?

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Rheumatoid Arthritis in a Nutshell

Rheumatoid Arthritis (RA) is a chronic, inflammatory, multi-factorial and progressive AD that primarily affects joints [20,21]. Its estimated prevalence is 1% in Europe and USA. The most frequently affected joints are the hands and wrists, where the joints are swollen, warm and painful, in a symmetrical presentation. It may affect extra-articular organs or tissues, hence present as a multi-organ systemic disease. The disease affects mainly the female gender and presents more frequently above the age of 50 years. The underlining causes are not clear and as with the other ADs, environmental and genetic factors determine RA susceptibility. The systemic and local immune systems attack the involved joints resulting in arthritis and joint's capsule thickness, bone erosion and cartilage damage. Many other ADs can be associated, including CD [1,2,4,17–19]. Multiple old modes of therapies exist like NSAIDs, steroids, disease-modifying Anti-Rheumatic Drugs and biologicals but new pharmacological agents are upcoming [22]. They can suppress the inflammation, prevent structural damage and improve the patient's quality of life. However, all those pharma therapies do not lack side effects, which accelerated the attempts to explore various nutritional therapies.

Dietary Therapy for Rheumatoid Arthritis

An increasing number of reports suggested that various nutrients and selected diets might impact induction, maintenance, behavior and progression in RA patients. The increasing knowledge on pro- and anti-inflammatory or antioxidative food components allow designing diets that are protective and fulfill the desire of targeting the inflammatory joints [23–25]. Recently, such beneficial or harmful nutrients were extensively summarized and their mechanism and potential pathways, starting from the enteric lumen to impact peripheral organs, were listed [1,26–28]. Nutrients, food additives, bugs and we can affect the composition and the diversity of the microbiome, switching the balance towards a dysbiome or to a pathobiome [29–31]. Gut eco-events are pivotal for homeostasis, hence, can orchestrate and drive a plethora of pathogenic mechanisms resulting in metabolic as well as autoimmune chronic diseases [26–31], RA is one of those long-term conditions [2,4,17–19,27,28].

Dietary components can affect gut functions. Nutrients can induce dysbiome, change post-translational modification of naïve peptides in the lumen, affect intestinal permeability and induce a leaky gut, impact digestion, absorption and even gut motility. All those events might operate in the gut-joint axes and induce arthritis when dysfunctional or failed [1,2,33–36,4,16,18,19,27,29,30,32]. Zooming on dietary trails on RA patients, several had some beneficial effects. Reports suggested that caloric restriction and fasting produce therapeutic anti-inflammatory effects in RA [37–40]. Plant-based foods were shown to improve gut microbiome in RA patients, resulting in reduced inflammatory arthritis and joint pain [37]. Comparable beneficial effects were reported on low-fat vegan [41–43] and on gluten-free vegan diets [43]. Anti-inflammatory nutraceuticals had good effects on the inflamed joints [44] and finally, the Mediterranean Diet (MD) can lower the risk for RA [45] and protect disease activity and microbiota composition in RA patients [46]. More so, a systemic review concluded that the MD reduces pain and increases physical activity in RA patients. However, there is not sufficient evidence for a widespread recommendation to follow the diet [47]. On the contrary, a recent study concluded that MD does not affect RA indices [48]. So, the jury is not there yet. The complex cross-talks between ADs in general and dietary therapy is "Well Begun, Is Half-Done" [49].

The Detrimental Effect of Gluten

The side effects of gluten were recently summarized [2,4,16,18,32]. The topic is applicable to all gluten-dependent diseases, but also might be of concern to other chronic diseases like non-celiac ADs and even to some parts of the normal population. The reported incidences of the classical gluten-dependent conditions are: CD-1-2%, gluten ataxia- 0-6%, wheat allergy- 0.5-1%, nonceliac wheat/gluten sensitivity- 0.6-13% and dermatitis herpetiformis-0.4-2.6 per 100000 people [50]. It appears that the adverse effects of gluten are present on the systemic, as well as on the local or organ levels. On the systemic levels, gluten is pro-inflammatory, pro-oxidative and impacts epigenetics. On the intestinal level, it breaches tight junction functional integrity thus enhancing gut permeability and inducing dysbiosis. On the cellular level it suppresses viability, it is pro-apoptotic, and decreases cell differentiation and DNA, RNA and glycoprotein synthesis. Gluten affects multiple immune functions. It increases immunogenicity, cytotoxicity, Th-17 activity, neutrophil's migration, NKG2D expression and TLR4 signalling pathway. Furthermore, it impacts the innate and adaptive immune systems' functions and Treg phenotype and behavior [2]. It should be stressed that most of the studies were performed on animals and on cell lines and not in vivo on humans. The proof of concept is presented by the numerous non-celiac ADs that might benefit gluten withdrawal, thus curtailing gluten adverse effects [2,4,15,18,19,28,30,50–52]. Intriguingly, even some patients with irritable bowel syndrome, metabolic syndrome, obesity, cardiac conditions and inflammatory bowel diseases might benefit from gluten withdrawal [53–60]. All the above-mentioned dark side of gluten intake might explain the impact of GFD in RA. And now some warnings on the popularity of GFD adaption in unproven, non-gluten-dependent conditions.

The Fashionista of Gluten-Free Diet

Before discussing GFD in RA, a word of caution should be forward due to the fashionista of GFD [3]. Facing the surge of non-infectious human chronic conditions like allergies, ADs, metabolic syndrome and cancer [10] and the surge in popular alternative medicine approaches, GFD has been rising, on a large scale, over the last decades. We are witnessing an uncontrolled, increasingly questioned and criticized by the scientific community contemporary phenomenon [3,61–64]. Despite it, the opponents of gluten consumption reach the center of the popular stage by reinforcing gluten avoidance. "Going gluten-free" became mainstream in the Western world and is an actual fashion trend [3,65–67]. Facing this fashion are the unwanted side effects of gluten avoidance. Indeed, Iron, calcium, sodium, Vitamin D, C, A, E, B12, thiamin, riboflavin and niacin, Folate, trace elements like zinc, magnesium, Selenium, fibers like oligo-fructose, inulin, fructans, HDL, Apo A1, essential amino acids and arachidonic acid abnormalities/deficiencies were described in gluten avoiding patients [3,68–70]. Key inadequacies of currently available GF products are low protein and complex carbohydrate fiber and high fat, simple sugars and salt contents [3,64,69,71]. Furthermore, unfavorable body composition changes might be observed. In celiac patients, after 1-year of GFD, increased fat mass is evident compared to their baseline [72].

An unsupervised GFD is associated with increased consumption of rice- or maize-based products. Those products might contain heavy metals such as copper, arsenic, lead and cadmium

or mycotoxins that risk [3]. Maize and its products may contain mycotoxins (fumonisins), which are hepatotoxic, nephrotoxic, hepatocarcinogenic and cytotoxic [43]. However, GF products have also health benefits [73].

Another aspect of the GFD is the adherence difficulties. Applying a GFD is a tough alley and the effort to follow and adhere to gluten withdrawal, represents nowadays also a torrid time [74]. The real-life scenarios of the gluten-dependent affected patients are tough [75] and full of daily challenges [76]. Finally, popular GFD contains several misconceptions that were summarized lately [50]. It is not a healthier option and many will not lose weight.

Rheumatoid Arthritis and Celiac Disease Relationship

Both ADs, despite being separated defined conditions, are related and share many aspects [36,77–81]. Both are autoimmune HLA-dependent diseases that share several non-HLA loci with comparable environmental factors and rising incidences. In both conditions, post-translational modification of naïve peptides is operating [29,36]. Citrullination by the peptidyl arginine deiminase in RA and deamidation and cross-linking by Tissue Transglutaminase (tTG) [36,82]. Clinically, rheumatoid extra-intestinal manifestations exist in CD, while extra-articular gastrointestinal involvement occurs in RA. Notably, enteric inflammation and hepatic damage were reported in rheumatoid patients, even before any joint damage [83,84]. In both conditions, dysbiosis and increased intestinal permeability are major pathophysiological players [29,30,85–88]. Celiac is a typical gluten-induced disease that responds to GFD; hence, parts of RA patients respond to gluten avoidance [2,4,18,19]. Interestingly, Non-celiac Gluten Sensitivity was reported to be associated with fibromyalgia, spondyloarthritis, and refractory RA [89]. Further exploring those shared similarities in the gut-joint axes might improve our knowledge of the mosaic of autoimmunity [90].

GFD in Rheumatoid Arthritis

Many aspects are shared between RA and CD [36,77–81]. GFD will help in gluten-dependent conditions; however, the question of GFD benefit for the RA patients is the topic of the current review. Screening the PubMed for RA and GFD reviles a surge in publications in the last years. Between 1964-2017 the average of publications was much less than 1 per year. It substantially increased to 3.5 per year in the last 4 years. When investigated, GFD alone, or combined with other dietary restrictions, was beneficial in many of them [2,4,94–96,18,19,42,43,82,91–93]. To our knowledge, only one study was negative [97]. Reviewing the literature, some studies explored GFD alone and some others, combined or elimination diets like GF vegan diet [42,43,92], high protein GFD [91] and excluding meat, gluten and lactose [95].

Potential Mechanisms and Pathways for the Beneficial Effect of GFD in RA

Gluten withdrawal might help RA patients in several ways. Some of them are connected to the suggested RA triad: "diet, Microbiota, and Gut Permeability" [32] and are schematically presented in (Figure 1). Following are some of those mechanisms and gut-joint pathways:

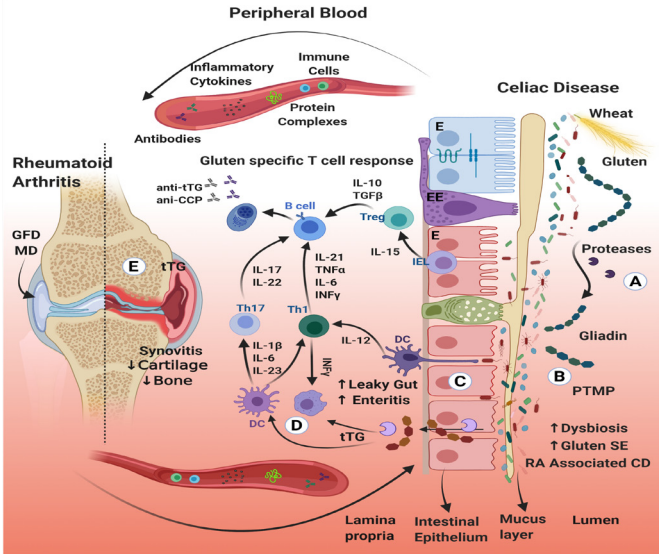

Figure 1: A schematic presentation of the Gut-Joints axis and the relationship between rheumatoid arthritis, gluten-free diet and celiac disease.

(A) Oral consumption of gluten-containing wheat. Gluten is ingested and digested, reaching the gut lumen as gliadin peptides. (B) Gliadins are rich in glutamine and proline, thus are a prime substrate for deamidation and cross-linking by luminal and mucosal transglutaminases, thus, turning those naïve molecules into immunogenic ones. Transglutaminase capacity to deamidate or transamidate results in an increase in post-translation modified proteins (PTMP). Luminal digestive peptidases cannot further break down those bonds, hence, inducing gut inflammation, mucus disruption and intestinal epithelial damage. This affects the microbiome/dysbiome ratio, resulting in the proinflammatory metabolome, pathobionts proliferation, maldigestion, malabsorption and even gut dysmotility. (C) Gluten increases intestinal permeability by binding to epithelial CXCR3 receptors, resulting in zonulin release. Gliadin-transglutaminase transformed peptides can potentially infiltrate through the open junctions or trans-enterocytically into the lamina propria. A breach in the epithelial barrier exposes the highly immunoreactive sub-epithelium to luminal foreign antigens, stimulating the local immune system. Enteritis and leaky gut are major contributors to the local and the articular inflammation in both diseases. (D) In the lamina propria, gliadin-transglutaminase cross-linked complexes induce pro-inflammatory cytokines. Two types of DC are present, sub-epithelial DCs that send protrusions into the lumen and sense the gut microbiota, and the lamina propria DCs that migrate to lymph nodes, where they present antigens to activate T cells. Th1 lymphocytes secrete IFNγ that activates macrophages. Th17 lymphocytes secrete IL-17 and IL-22 which activate B cells. The latter secret autoantibodies against tTG (anti-tTG) or against citrullinated peptides (anti-CCP), both, circulate in the blood. (E) Mucosal immune cells, immunogenic modify peptides, proinflammatory cytokines, autoantibodies and small particles that escaped the immune system enter the blood vessels. They can eventually reach the joints and trigger an autoimmune response, enhancing arthritis, cartilage damage and bone destruction. Local tTG may drive synovitis and bone erosion in RA. Finally, GFD and MD can potentially attenuate RA inflammatory activity in some of the patients.

As gluten have multiple adverse effects [2]. Its avoidance might prevent and curtail those harmful effects, thus lowering the joint inflammation and RA disease activity.

One of the main intestinal contributions to RA evolvement is the leaky gut. Tight junction functional integrity is pivotal for the local and systemic physiological homeostasis. Maintaining tolerance and avoiding autoimmunity are essential for human health [29,30]. A plethora of nutrients enhances or decreases gut permeability [26,32,98]. Since gluten is a major disruptor of the enteric permeability [2], its avoidance might protect the body from unwanted immune reactions on their way to target the joints [1,2,19,27,36,81,99,100].

Gut microbiota, a huge symbiotic prokaryote community inhabiting the human enteric lumen [101–103]. Upon microbiome/dysbiome ratio decrease, chronic diseases ranging from metabolic, cancerous and autoimmune are emerging [29–31,104] and RA is not an exception [2,4,18,19,27,36,85]. Gluten intake perturbates the microbiome balance and changes the composition and the diversity of the normal inhabitants [105–107]. As a result, GFD might partially reverse the abnormality towards a more physiological gut microbial community [108]. Interestingly enough, the effects may be due to the increased consumption of undigested fiber rather than to the gluten withdrawal [109].

Gluten/wheat withdrawal is associated with increased intake of undigested polysaccharides. Higher fiber consumption results in short-chain fatty acid (SCFA,) production and represent the main bacterial fermentation mobilome in the human gut luminal. SCFAs as multiple beneficial effects on the local as well as on the systemic homeostasis [110–112]. Notably, after one year of GFD, SCFA's excretion and the gut microbiome normalized in CD patients [113]. In addition, the MD is rich in fiber and the RA patients that consume it excrete higher SCFA levels [45–47,114,115], thus, exerting anti-inflammatory and immunomodulatory effects for the patient's benefit. It seems logical to suggest a combination of GF MD might help the RA patients [116].

Depression and behavioural problems are known to exist in RA patients [117,118]. Tryptophan deficiency is associated with serotonergic dysfunction, which plays a role in several depressive, affective and behavioural symptoms. In addition, tryptophan metabolism might represent a marker for disease activity and bone destruction in RA patients [119]. It appears that GFD might be beneficial for those behavioural disorders, though, the mechanism is not known [120,121].

Secretory IgA is a major luminal immune protective barrier; however, selective IgA efficiency is associated with ADs, including RA [122]. Its level and functions are microbiome, SCFAs and diet-dependent [123,124]. It is suggested that a GFD that induces a healthier microbiome and higher SCFA production will enhance luminal IgA levels in the gut of the RA patients.

Cross-reactive antibodies between wheat, gluten\gliadin peptides and many human antigens were reported [16,26,27,125–129]. More so, the intestinal fluid of many RA patients contains IgG, IgM and IgA antibodies' activity that react with specific food components, including against gliadin [130]. Of note, an increased serological antibody biomarker positivity exists in RA and wheat-related disorders [131]. Likewise, multiple anti-rheumatic and anti-connective tissue autoantibodies exist in the serum of gluten-depended conditions [36,81,132,133]. Taken together, GFD might suppress those cross-reactive antibodies, thus alleviating the inflammatory activity in their joints.

The tissue transglutaminase is the only proofed autoantigen in CD [82,134]. The enzyme deamidates or cross-link gluten\gliadin peptide, thus, breaking gluten tolerance in CD patients. Tissue transglutaminase exists in normal, as well, in the inflamed joints in RA. This transglutaminase is driving synovitis and bone erosion in RA and osteoarthritis [135–138]. Since gluten/gliadin peptides are the preferred substrate for the enzyme [28,134,139], GFD might deprive tTG of its gluten substrate, thus, preventing or attenuating the articular damage.

In (Table 1), each of these mechanisms is detailed for the beneficial effects of GFD in RA patients.

Table 1: Potential mechanisms for the beneficial effects of GFD in RA patients.

Mechanisms	Adverse effects of Gluten consumption	GFD effect on RA
Tight junction functional integrity maintains tolerance and avoids autoimmunity [29,30].	A major disruptor of the enteric permeability [2,26,32,98].	Might protect from immune reactions on the joints, lowering inflammation and RA disease activity [1,2,19,27,36,81,99,100].
A healthy gut microbiota composition has implications in preventing chronic conditions ranging from metabolic, cancerous and AD [29–31,101–104].	Perturbates microbiome/dysbiome ratio, change composition and diversity of the normal inhabitants [105–107].	Might partially reverse the abnormality towards a more physiological gut microbial community [108].
Physiologic Microbiome is important for homeostasis [2,4,18,19,27,36,85].	Increased dysbiota and pathobiota [105,106].	The effects may be due to the increased consumption of undigested fiber, rather than to the gluten withdrawal [109].
SCFAs have beneficial effects on local and systemic homeostasis, including anti-inflammatory and immunomodulatory effects [110–112].	Gluten/wheat withdrawal is associated with increased intake of higher fiber consumption which results in a higher SCFA production [113].	RA patients that consume MD excrete higher SCFA levels; GF MD might help RA patients [45–47,114,115].
Tryptophan deficiency is associated with serotonergic dysfunction leading to depression and behavioral problems and is a marker for disease activity and bone destruction in RA patients [117–119].	By its pro-inflammatory activity, gluten might decrease tryptophan absorption [1,2].	Might be beneficial for those behavioral disorders, though, the mechanism is not known [120,121].
IgA is a luminal immune protective barrier; its efficiency depends on microbiome, SCFAs and diet [122–124].	Selective IgA efficiency is associated with several ADs, including RA and CD [81,122].	A healthier microbiome and higher SCFA production might enhance luminal IgA levels of RA patients [123].

Cross-reactive antibodies against specific food components, including gliadin, in RA patients. Positive serological antibody biomarker in RA and wheat-related disorders [36,81,130–133].	Gluten might stimulate cross-reactive antibodies between wheat, gluten\gliadin peptides and human antigens, including joint components reported [16,26,27,125–129].	Might suppress cross-reactive antibodies, alleviating inflammatory activity in RA joints [154].
tTG exists in normal and inflamed joints. It drives synovitis and bone erosion in RA and osteoarthritis [135–138].	tTG is the autoantigen that breaks gluten tolerance in CD patients. Gluten/gliadin peptides are preferred substrate for the enzyme [28,82,134,139].	Might deprive tTG of its gluten substrate, preventing or attenuating the articular damage [82,134].

Should Rheumatoid Arthritis Patients go on Gluten-Free Diet?

The answer is not clear-cut and is highly debatable. Many publications are positive for gluten withdrawal [2,4,94–96,18,19,42,43,82,91–93] and only one study found no effect of GFD in RA [9]. We are not endorsing all the RA patients to try GFD. The RA patients should not join the popular GFD "fashionista" in a blind and sweeping way.

It should be remembered that gluten restriction has many limitations [3,43,68–70,72], long-term adherence is difficult and problematic [50,74–76], and should be done under a dietician's supervision. Based on all of the above, we suggest some guidelines and conditions that will apply to only part of the RA patients to go on a GFD:

A. Gastrointestinal complaints such as abdominal pains, bloating, soft or diarrheal stools, significant burps/belches, etc.

B. Positive CD serology like anti-gluten, anti-endomysial, anti-tTG, anti-deamidated gliadin, anti-neo-epitope tTG antibodies [140–147]

In case the RA patient meets these conditions, they should be referred to a gastroenterologist in order to rule out gluten-dependent conditions, mainly CD. It is suggested that an occasional GFD trail is not sufficient for a long-term gluten withdrawal. Upon applying to the above two clinical and laboratory conditions and after the GI consultation, going on gluten-free Mediterranean diets might represent the most appropriate diet. Since many RA patients, mainly females, are suffering from irritable bowel syndrome and since gluten can cause them GI symptoms, it is suggested that they will follow the above-mentioned work up, before adapting GFD [148].

Finally, it is highly recommended that the rheumatologic/ nutritional/ gastrointestinal communities will explore the GFD in RA, applying a well-designed, double-blind, cross-over study. As recommended, GF-MD should be investigated on RA patients.

Conclusions

Gluten is an autoimmunogenic nutrient [149] and imbeds multiple adverse effects [2,19]. Rheumatoid arthritis and CD share many aspects [36]; both conditions are ADs and are frequent members of the polyautoimmunity syndrome [150] as a part of the mosaic of autoimmunity [90]. The topic of nutritional therapy in RA is expanding towards a more personal approach [23,24,40–49,25,151,32–35,37–39]. There are many reports on the beneficial effects of GFD in RA patients, including amelioration of symptoms, disease activity and quality of life [42,91–96]. However, there are no accepted or established guidelines for GFD application in RA. The present narrative review suggests a few screening conditions, one clinical and the other laboratory. However, those guidelines should be scientifically reassessed for the long-term benefits of RA patients.

Since the compliance to GFD is poor, at least in CD [74–76,152,153] and gluten avoidance has several adverse effects [3,65–72], patients should consult the nutritional teams. It is hoped that targeting the inflamed joints, the enteric barrier functions and the dysbiome by specific dietary means will open new therapeutic strategies to modulate RA evolvement.

Take Home Messages

- GFD might be beneficial in RA patients by ameliorating symptoms, decreasing disease activity and improving quality of life.
- Clinical and serological guidelines for GFD in RA patients should be applied.

Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

AL- screened the literature, designed and wrote the manuscript, CB- screened the literature, edited and revised the manuscript, designed the figure with BioRender.com permission. The two authors agreed to the published version of the manuscript.

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