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Risk Factors and Autoimmunity in Diet- A Narrative Review of Literature

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Abstract

Introduction

The role of dietary factors in modulating immune function and influencing the risk and progression of autoimmune diseases has recently gained increasing attention. Western-style dietary factors, rich in processed foods, saturated fatty acids, and refined sugars, have been implicated in promoting systemic low-grade inflammation and contributing to gut dysbiosis, while anti-inflammatory diets may offer protective benefits. Better understanding of diet and its impact on the immune system may offer new therapeutic avenues to explore in the near future.

Materials and Methods

A literature review was performed using four major scientific databases: PubMed, Elsevier, Web of Science, and Scopus. A total of 72 research and review articles relevant to the topic were selected based on predefined inclusion criteria. The selection criteria were based upon key words: autoimmune diseases, diet, inflammation, gut microbiota, micronutrients, Western diet, Mediterranean diet, omega-3 fatty acids.

Basic Results

Diets high in processed foods, saturated fatty acids, and high-glycemic index foods contribute to the development and maintenance of chronic inflammation, oxidative stress, and gut microbiota dysbiosis. Conversely, diets rich in polyphenols, flavonoids, fibers, and omega-3 fatty acids, promote immune tolerance and maintain the balance between anty- and proinflammatory factors.

Conclusions

Nutritional interventions may serve as supportive strategies for prevention and management of autoimmune diseases. Understanding dietary risk factors and implementing targeted nutritional modifications in the future could improve patients' outcomes.

Key words: autoimmune diseases, diet, gut microbiota, micronutrients, Western diet, Mediterranean diet, omega-3 fatty acids

Introduction

Autoimmune diseases are a heterogeneous group of diseases in which the body's immune system mistakes its own healthy tissues as foreign, precipitating immune response with subsequent chronic inflammation and damage to the organ. Diseases like rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and Hashimoto's thyroiditis create a huge impact on the affected ones as well as on the health care systems across the globe. Although the genetic background is known to be an important risk factor, recent data show the importance of environmental factors, in particular dietary habits, in shaping immune responses and disease risk. (1,2).

Western-dietary patterns, typically high in processed food, saturated fat, refined sugar but low in dietary fiber, are linked to chronic low-grade inflammation and an altered homeostasis of gut microbiota. These dietary habits help create a pro-inflammatory environment that can provoke or drive autoimmune reactions (1,3). In contrast, diets rich in fruits, vegetables, whole grains, and other anti-inflammatory nutrients appear to support immunological balance and lower the risk of autoimmunity. Several key nutritional components also have direct immunomodulatory effects. Vitamin D, for example, modulates innate and adaptive immune cells via specific receptors and can alter cytokine production and T-cell differentiation; low vitamin D has been associated with a higher prevalence of autoimmune disease (3). Similarly, omega-3 fatty acids possess potent anti-inflammatory properties that counteract pro-inflammatory mediators implicated in autoimmune pathogenesis (4).

Moreover, the emerging concept of the gut–immune axis underscores the role of dietary components in shaping the gut microbiota—a key regulator of immune tolerance. Dysbiosis, or an imbalance in the microbial community, has been linked to the development and progression of autoimmune disorders (5). Dietary interventions aimed at restoring a healthy gut microbiome may help re-establish mucosal integrity and promote immune tolerance, offering a promising adjunct to conventional therapies (6). Numerous studies further reinforce these associations. For instance, a recent meta-analysis reported that higher dietary inflammatory index scores are significantly associated with an increased risk of multiple sclerosis and other demyelinating disorders (7). In addition, emerging evidence suggests that targeted supplementation with vitamin, antioxidant, and micronutrient formulations may modulate the risk of developing autoimmune diseases (8), while epidemiological data indicate that specific dietary factors can influence the onset of rheumatoid arthritis (9). Given the rising prevalence and profound impact of autoimmune disorders, a clear understanding of dietary risk factors is urgently needed to inform effective prevention and intervention strategies.

Dietary Risk Factors in Autoimmunity

Dietary components can either trigger or protect against autoimmunity by influencing inflammation, oxidative stress, gut barrier function, microbial composition, and even epigenetic regulation. Therefore individual's dietary patterns are currently thought of as a viable component contributing to the risk and development of autoimmune conditions.

Dietary Patterns

Recent studies have demonstrated that chronic consumption of a Western-style diet contributes to immune dysregulation through multiple mechanisms. Excess intake of saturated fats and refined carbohydrates not only promotes oxidative stress but also leads to the

formation of advanced glycation end-products (AGEs). These AGEs exacerbate inflammation by further stimulating reactive oxygen species production and disrupting normal cellular signaling pathways (10). In parallel, processed meats are rich in nitrites and additional AGEs, which have been implicated in altering immune cell functions and promoting a persistent proinflammatory state (11). Moreover, the Western diet is closely associated with gut dysbiosis- a reduction in microbial diversity coupled with increased intestinal permeability. This altered gut environment facilitates the translocation of bacterial endotoxins, thereby triggering innate immune responses that may precipitate autoimmune phenomena (12).

High dietary salt intake, another hallmark of this dietary pattern, has been shown to modify the gut microbiota composition and promote the expansion of proinflammatory bacterial strains. This effect, in turn, augments Th17 cell responses, which are critical in the development of several autoimmune diseases (13). In addition, an imbalanced intake of omega-6 versus omega-3 PUFAs not only skews immune responses toward a Th17 phenotype but may also interfere with the production of anti-inflammatory eicosanoids, further compounding the risk of autoimmunity (2). The obesity often observed in individuals following Western dietary habits further compounds this risk. Adipose tissue, far from being an inert energy store, functions as an active endocrine organ. It secretes proinflammatory cytokines- such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)- which sustain chronic low-grade inflammation and may trigger autoimmune processes in genetically predisposed individuals (14). Additionally, the combination of saturated fats, refined sugars, and high salt intake may disrupt immune tolerance mechanisms and promote the generation of autoantibodies, which are central to the pathogenesis of disorders such as rheumatoid arthritis and multiple sclerosis (15).

In stark contrast, the Mediterranean diet offers a protective effect against autoimmune disorders through several interrelated pathways. This diet is abundant in bioactive compounds, including polyphenols, which exert potent antioxidant and anti-inflammatory effects. For example, oleocanthal- a phenolic compound in extra-virgin olive oil- has been shown to inhibit cyclooxygenase activity and modulate NF-κB signaling, thereby reducing inflammation (16). In addition, the high fiber content inherent to this diet promotes the growth of beneficial gut bacteria and leads to increased production of short-chain fatty acids (SCFAs) such as butyrate. SCFAs not only support intestinal barrier integrity but also exert systemic immunoregulatory effects by modulating cytokine production and T-cell differentiation (17). Emerging research in the field of nutrigenomics suggests that the Mediterranean diet may also influence immune function through epigenetic modifications. Bioactive food components can alter DNA methylation patterns and histone acetylation states, thereby regulating the expression of genes involved in immune responses. Such epigenetic modifications are thought to contribute to the observed reduction in autoimmune risk among adherents of the Mediterranean diet (18,19). These dietary-induced changes may recalibrate the balance between proinflammatory and anti-inflammatory pathways, offering a mechanistic explanation for the lower prevalence and severity of autoimmune conditions observed in populations consuming this diet (20,21).

Macronutrient Composition

Excessive consumption of animal proteins, particularly red meat, has been associated with autoimmune thyroid disorders and rheumatoid arthritis (22,23). Such diets generate proinflammatory metabolites, including AGEs, which may damage tissues and further activate immune responses (22). Dietary saturated and trans fats activate toll-like receptors (TLRs) on

immune cells, triggering the release of proinflammatory cytokines (24). Animal studies indicate that high-fat diets can drive a Th17-biased immune profile, exacerbating models of autoimmunity (25). Foods with a high glycemic index cause rapid spikes in blood glucose and insulin, resulting in increased production of reactive oxygen species (ROS) and inflammatory cytokines, potentially initiating or worsening autoimmune reactions (26). Furthermore, recent investigations have expanded our understanding of the impact of red meat and animal protein consumption on autoimmune processes. Epidemiological studies indicate that diets rich in red meat not only elevate systemic inflammatory markers but may also compromise intestinal barrier integrity, allowing bacterial endotoxins to enter circulation and intensify immune activation (27). Concurrently, high intake of dietary fats—especially saturated and trans fats—has been linked to modifications in lipid raft composition within immune cells, thereby enhancing TLR-mediated signalling and fostering a persistent inflammatory environment (24).

Emerging evidence also highlights the role of high glycemic index foods in autoimmunity. Rapid postprandial hyperglycemia can lead to oxidative stress and endothelial dysfunction, which are known to exacerbate inflammatory responses and may trigger autoimmune phenomena in genetically predisposed individuals (28,29). In contrast, diets that emphasize a low glycemic load—with an abundance of complex carbohydrates and dietary fibres—have been associated with improved glycemic control and a reduction in proinflammatory cytokine secretion (30). Table I. summarizes the known dietary risk factors thought to contributing to the development of autoimmune diseases, with emphasis on the potential contributing pathomechanisms.

Category	Known Risk Factor	Mechanism
Dietary Patterns	Western dietary pattern	Promotes oxidative stress; excessive AGEs, salt, saturated and trans fatty acids intake
	Processed meat products' intake	Nitrites promotes oxidative stress; AGEs exacerbate systemic inflammation, may lead to the formation of defective antigens, triggering autoimmune response
	High salt intake	Modifies intestinal microbiota microenvironment; promotes Th17 cells differentiation and turnover
	Omega-6 vs. Omega-3 fatty acids imbalance	Directs immune response toward auto aggressive Th17; increases proinflammatory eicosanoids production
	Excessive caloric intake	Adipose tissue secretes proinflammatory cytokines; dysregulation of Th cells differentiation and turnover
Macronutrients' Composition	High animal protein diet; red meat intake	Increases systemic inflammatory state; impairs intestinal barrier
	High saturated and trans fatty acids intake	Activates TLRs; increase systemic inflammatory state; dysregulates Th cells' differentiation
	High glycemic index food intake	Rapid glucose spikes induce oxidative stress; promotes production of proinflammatory cytokines
Micronutrients and Immunomodulation	Vitamin D deficiency	Regulates T-cell differentiation, reduces Th1/Th17
	Selenium deficiency	Direct antioxidant function; regulation of thyroid hormones production and turnover

	Iron, Zinc, B1, B2, B5, B6 Vitamins deficiencies	Deficiencies impair Th cell differentiation and turnover; increase oxidative stress and ROS production
	Gut microbiota imbalance	Disrupts intestinal barrier, triggers systemic immune response; molecular mimicry
	Vitamin A deficiency	Required for maintaining mucosal integrity, promotes autoinflammatory Treg cells proliferation
	Omega-3 fatty acids intake	Reduces inflammatory cytokines' production; modulates Th17 cell differentiation, inhibits autoreactive Th17 cells
	Vitamin C deficiency	Direct antioxidant function; modulates response to autoantigens

Table I. Summary of known dietary risk factors in autoimmunity with accompanying potential patomechanisms contributing to the dysregulation of inflammatory and immune responses. Based on (11,13,14,15,22,24,25,27,28,32,35,38,39,42,45,47).

Micronutrients and Immunomodulation

Low serum vitamin D levels are commonly observed in autoimmune conditions such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (31). Vitamin D modulates immunity by promoting regulatory T cell (Treg) differentiation and dampening Th1/Th17 responses (3). Although supplementation outcomes are variable (32,33), recent mechanistic studies have further delineated vitamin D's role in immune regulation and autoimmunity (34). Selenium is an essential trace element incorporated into selenoproteins that function as antioxidants and are critical for thyroid hormone metabolism. Deficiencies are linked to autoimmune thyroiditis (35,36). Both iodine deficiency and excess may disrupt thyroid homeostasis, with imbalances increasing the risk for autoimmune thyroid disorders (37). Deficiencies or imbalances in iron, zinc, and B vitamins can impair immune cell function and promote oxidative stress, further predisposing individuals to autoimmunity (38–41).

Modern diets high in ultra-processed foods and synthetic additives may damage the intestinal barrier and alter the composition of gut microbiota. This "leaky gut" permits the translocation of luminal antigens and bacterial products, thereby triggering systemic immune activation and inflammation (42,43). In contrast, diets high in fibres and polyphenols encourage the growth of beneficial commensals that produce SCFAs with immunoregulatory properties. Recent multiomics studies also highlight that diet-induced shifts in microbiota and their metabolites can modulate systemic immunity—an effect further demonstrated by emerging data on the ketogenic diet reducing Th17 activation via increased β-hydroxybutyrate and beneficial gut bacteria (44). Vitamin A and its active metabolite, retinoic acid, are critical for maintaining mucosal integrity and modulating T-cell differentiation by promoting Treg development and suppressing pro-inflammatory Th17 responses (45). Dietary omega-3 polyunsaturated fatty acids, abundant in fish oils, have been shown to suppress inflammatory cytokine production and may reduce the incidence or severity of autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease (28). In addition, vitamin C acts as a potent antioxidant that protects immune cells from oxidative damage and helps regenerate other antioxidants, thereby contributing to the maintenance of immune homeostasis (46).

Nutritional Interventions in Autoimmune Diseases

Nutritional Interventions in Autoimmune Disorders- Overall Considerations

Vitamin D has been extensively investigated in the context of autoimmunity due to its immunomodulatory effects on both innate and adaptive responses. Its receptor is expressed on T cells, B cells, and antigen-presenting cells, and experimental data indicate that vitamin D can suppress proinflammatory cytokines while enhancing regulatory T-cell differentiation. Although observational studies consistently report an association between low serum vitamin D and increased autoimmunity risk (47,48), randomized controlled trials in conditions such as multiple sclerosis and rheumatoid arthritis have yielded mixed results regarding clinical efficacy (49,50). Recent meta-analyses, however, suggest that appropriate dosing may improve inflammatory markers in rheumatoid arthritis (50) and similar trials continue to refine optimal dosing strategies (49).

Omega-3 polyunsaturated fatty acids primarily from marine sources, exert anti-inflammatory effects by inhibiting proinflammatory eicosanoids and cytokines while promoting the synthesis of specialized pro-resolving mediators. Results of recent literature meta-analysis indicate that supplementation with omega-3 fatty acids can reduce clinical symptoms in rheumatoid arthritis and may diminish inflammatory activity in inflammatory bowel disease (28,51). More recent systematic reviews have further underscored their potential to lower disease activity indices in demyelinating conditions (7) and to complement standard therapies in autoimmune disorders (52).

Antioxidants such as vitamin E and selenium play a critical role in mitigating oxidative stress, a contributor to chronic inflammation. Deficiencies in these micronutrients may impair the capacity to neutralize free radicals, thereby exacerbating inflammatory cascades (35,51). Updated evidence suggests that targeted antioxidant supplementation may reduce inflammatory markers in autoimmune conditions (53), although clinical outcomes remain variable and warrant further investigation.

Comprehensive dietary patterns emphasizing whole grains, fruits, vegetables, lean proteins, and healthy fats—exemplified by the Mediterranean diet—are increasingly recognized for their anti-inflammatory properties. Such diets have been associated with lower systemic inflammation and improved clinical outcomes in inflammatory bowel disease, rheumatoid arthritis, and even multiple sclerosis (54,55). In pediatric Crohn's disease, exclusive enteral nutrition (EEN) is used as a first-line strategy to induce remission; recent controlled trials have reinforced the benefits of a Mediterranean-style diet in reducing relapse rates and enhancing mucosal healing (56).

The gut microbiome exerts a profound influence on systemic immunity. Dietary components, including prebiotics (non-digestible fibers that promote beneficial bacterial growth) and probiotics (live microorganisms with immunomodulatory properties), can restore gut barrier integrity and recalibrate immune homeostasis. Several recent randomized trials suggest that modulation of gut microbiota via probiotic supplementation may attenuate mucosal inflammation in inflammatory bowel disease and have broader immunoregulatory benefits in autoimmune settings (56).

Autoimmune Disorders- Specific Nutritional Considerations

Low vitamin D status is a well-established risk factor for multiple sclerosis. Observational studies consistently report an inverse correlation between serum 25-hydroxyvitamin D levels and MS risk (47). Diets enriched in omega-3 fatty acids and low in

saturated fats may help reduce inflammatory demyelination. Although intervention trials of vitamin D supplementation have not uniformly demonstrated disease-modifying benefits, emerging data from recent meta-analyses support the inclusion of vitamin D as part of a multimodal management strategy (49). In rheumatoid arthritis, high consumption of red meat and low antioxidant intake may exacerbate joint inflammation. Nutritional interventions, including omega-3 supplementation and adherence to anti-inflammatory diets, have been shown to reduce joint pain and stiffness while decreasing reliance on nonsteroidal anti-inflammatory drugs (28,51). New evidence also points to the adjunctive benefits of plant-based dietary approaches and potassium-rich supplements in ameliorating pain and functional status in RA patients (52)

Both undernutrition and specific dietary triggers contribute to inflammatory bowel disease activity. Exclusive enteral nutrition remains a cornerstone for inducing remission in pediatric Crohn's disease, and adherence to a Mediterranean diet has been linked to lower relapse rates and improved mucosal healing in adults (54). Recent systematic reviews have further supported the role of vitamin D supplementation in improving clinical and biochemical indices in IBD (56,57). Nutritional patterns that influence gut permeability and microbial composition have been implicated in type 1 diabetes pathogenesis. Early-life nutritional interventions (including breastfeeding and low glycemic-index foods) may delay or modify the risk of autoimmunity in genetically predisposed individuals. A recent systematic review highlights the need for further investigation into early dietary exposures and their long-term impact on beta-cell autoimmunity (58).

In autoimmune thyroid disorders, selenium supplementation has been associated with reductions in thyroid peroxidase antibodies, although clinical benefits remain inconsistent (48,59). Vitamin D supplementation and dietary modifications aimed at reducing inflammatory triggers (e.g., gluten avoidance in susceptible individuals) are under active investigation, with recent meta-analyses suggesting modest immunomodulatory effects (60). The definitive treatment for celiac disease is a strict, lifelong gluten-free diet. Nutritional counseling is critical to ensure that patients maintain balanced intake of energy, macronutrients, and micronutrients despite dietary restrictions. Recent studies have focused on optimizing the nutritional quality of gluten-free products and enhancing adherence, particularly among pediatric populations (55,61)

Controversies and Issues Requiring Further Research

Dietary Patterns and Their Controversies

The impact of overall dietary patterns on autoimmunity remains an area of active debate. The Western diet, characterized by high intakes of red and processed meats, saturated and trans fats, refined sugars, and salt—with low consumption of fruits, vegetables, and whole grains- has been implicated in generating oxidative stress and activating inflammatory pathways (2). However, its direct role in precipitating autoimmunity is controversial; some authors argue that observed associations may be confounded by lifestyle factors such as sedentary behaviour and socioeconomic status, with high saturated fat and refined carbohydrate intakes possibly requiring additional environmental stressors to trigger disease (25). In contrast, the Mediterranean diet, rich in fruits, vegetables, legumes, whole grains, and monounsaturated fatty acids, is associated with anti-inflammatory effects. Numerous epidemiological studies report inverse correlations between adherence to this diet and systemic inflammatory markers as well as autoimmune risk (21,62). Despite these promising associations, issues persist regarding how "adherence" is defined and measured-varying by food quality, regional customs, and study design- and whether modulation of the gut

microbiota (a proposed central protective mechanism) is causative remains to be conclusively established (63,64).

Macronutrients and Micronutrients: Balancing Risks and Benefits

High animal protein intake, particularly from red and processed meats, has been linked observationally to an increased risk of autoimmune thyroid disorders and rheumatoid arthritis, although these associations might reflect broader unhealthy lifestyle styles rather than a direct pathogenic role (65,66). Similarly, clinical studies yield variable results, implying that the pro-inflammatory potential of these fats may depend on dosage, dietary patterns, and overall quality of other nutrients in the diet (33,67).

Furthermore, an imbalanced dietary ratio of omega-6 to omega-3 fatty acids—favouring a high omega-6 intake- is thought to promote proinflammatory eicosanoid production and Th17 lymphocytes differentiation and proliferation. Although a balanced dietary ratio of omega-6 to omega-3 fatty acids is thought to lower inflammatory potential and overall autoimmune risk (21,25), the differences in dietary sources and bioavailability have made it difficult to reach clear international nutritional recommendations (68). High intakes of refined carbohydrates and high glycemic foods are also under further investigation; these may induce rapid glycemic fluctuations and oxidative stress, triggering the release of pro-inflammatory cytokines. However, their independent impact on the inflammatory state is difficult to tell apart from the associated factors and complications such as obesity and insulin resistance (69,70).

Several micronutrients play pivotal roles in immune regulation, yet controversies persist regarding optimal supplementation levels. Low serum level of vitamin D is common in multiple autoimmune disorders, and while its immunomodulatory effects are well established, interventive clinical trials have yielded mixed outcomes. Some clinical studies suggest benefits at supplementation levels of 600–800 IU/day, but differences in the environmental factors, associated dietary factors, baseline vitamin D metabolic rate and genetic polymorphisms in various enzymes involved in the vitamin metabolism complicate the establishment of universal international guidelines (47,71). Selenium, essential for antioxidant selenoproteins, appears protective in thyroid autoimmunity; however, conflicting outcomes and geographic intake differences call for more precise supplementation recommendations to avoid the inherent side effects and complications of both selenium deficiency and excess (2). Iodine intake illustrates a dual challenge: while its necessary for thyroid hormone synthesis, excessive iodine can enhance the immunogenicity of thyroglobulin and promote autoimmune thyroiditis, thereby complicating public health initiatives such as salt iodization (2). Other micronutrients like iron, zinc, and vitamin B6 exhibit similar selenium associations, where both deficiencies and excesses can disrupt immune homeostasis, highlighting significant gaps in defining safe supplementation ranges (2,72).

Food Processing, Additives, and Gut Microbiota Implications

The role of food additives and processing in autoimmunity is another area marked by uncertainty. The increased consumption of ultra-processed foods, which are high in synthetic additives, preservatives, and emulsifiers, has been associated with impaired gut barrier integrity and dysbiosis (21). However, most studies are associative, and isolating the effects of specific additives from the overall dietary pattern remains challenging . Diet is a key determinant of gut microbiota diversity, and emerging evidence links dysbiosis with the pathogenesis of autoimmune disorders. Although dietary fibres and polyphenols appear to

foster beneficial bacterial populations and enhance short-chain fatty acid production, it remains unresolved whether these microbial changes are a cause or consequence of autoimmune inflammation and whether targeted dietary interventions can yield lasting clinical benefits (63).

Autoimmune Disorders: Disorder-Specific Dietary Controversies

Consumption of animal products such as red meat and dairy has been associated with increased oxidative stress and inflammatory markers, yet some studies report no significant dietary differences between patients and controls, leaving the direct contribution of these factors uncertain (2,25). While red meat and saturated fat intake have been implicated in rheumatoid arthritis, confounding factors like smoking and overall lifestyle complicate these associations. Diets enriched with omega-3 fatty acids show some anti-inflammatory promise, but the modest clinical effect sizes raise questions about the efficacy of dietary modifications alone (66). MS has been linked to vitamin D deficiency and high-fat diets that may foster proinflammatory Th17 responses. Intervention studies with vitamin D and omega-3 supplementation have yielded inconclusive results, suggesting that dietary changes might best serve as adjuncts to conventional therapies. Emerging research also hints that ketogenic diets could favourably modulate gut microbiota and reduce symptom severity, although human trials remain pending (21). In IBD, diets high in refined sugars, animal proteins, and food additives are associated with intestinal dysbiosis and increased gut permeability. Disentangling these dietary effects from intrinsic disease processes and medication use remains challenging, underscoring the need for rigorously designed prospective studies (62).

Conclusions

The role of diet in autoimmune disorders is increasingly recognized as a significant factor influencing disease onset and progression. While Western dietary patterns rich in processed foods and unhealthy fats exacerbate inflammation and immune dysregulation, Mediterranean-style diets and nutrient-rich foods appear protective. Key micronutrients such as vitamin D, omega-3 fatty acids, and antioxidants play vital roles in modulating immune responses. Future research should focus on refining dietary recommendations and exploring personalized nutritional interventions to complement standard therapies for autoimmune diseases.

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