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Role of "Western Diet" in Inflammatory Autoimmune Diseases

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Abstract

Developed societies, although having successfully reduced the burden of infectious disease, constitute an environment where metabolic, cardiovascular, and autoimmune diseases thrive. Living in westernized countries has not fundamentally changed the genetic basis on which these diseases emerge, but has strong impact on lifestyle and pathogen exposure. In particular, nutritional patterns collectively termed the "Western diet", including high-fat and cholesterol, high-protein, high-sugar, and excess salt intake, as well as frequent consumption of processed and 'fast foods', promote obesity, metabolic syndrome, and cardiovascular disease. These factors have also gained high interest as possible promoters of autoimmune diseases. Underlying metabolic and immunologic mechanisms are currently being intensively explored. This review discusses the current knowledge relative to the association of "Western diet" with autoimmunity, and highlights the role of T cells as central players linking dietary influences to autoimmune pathology.

Keywords

Western diet; Autoimmune diseases; Autoimmunity; Obesity; Sodium; Inflammatory; Gut microbiome; T cell regulation

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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Introduction

Autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), type 1 diabetes (T1D), and psoriasis (Ps) are a heterogeneous set of diseases that share common hallmarks including multifactorial aetiologies, involvement of T cell-mediated autoimmune pathomechanisms, and a chronic clinical course that often requires life-long disease management. Genetic factors clearly predispose to the development of inflammatory autoimmune diseases [1, 2], but a relatively low concordance rate for most of the diseases between monozygotic twins [3] suggests environmental factors as important triggers of disease. This view is corroborated by the striking increase of autoimmune diseases in recent decades, whereas the genetic basis in affected populations has remained arguably constant [4]. Notably, there is a high prevalence in Western societies and established market economies as opposed to a lower prevalence in the Eastern world and developing countries [4, 5]. It is of interest that there are also some high prevalence areas today that display a stable or even slightly declining occurrence of some autoimmune diseases [6, 7], while there is certainly a steep incline in former low prevalence regions [8–11]. The trend towards a higher prevalence often coincides with a high pace of socio-economic improvement and westernization in these countries [4, 5]. There are multiple explanations of how the “Western lifestyle” favors the development of autoimmunity. The hygiene hypothesis states that high standards of hygiene and good health care reduce the burden of infections, but can also limit exposure to pathogens that are potentially beneficial for proper function of the immune system [4, 5, 12]. Psychosocial stress generated by high demands on productivity, as well as smoking and alcohol consumption, may be additional lifestyle-associated risk and severity factors for autoimmune diseases [13–15]. Finally, lack of physical activity in combination with excess calorie intake and frequent consumption of ‘fast food’ causes a high prevalence of obesity in developed societies [16]. Obesity in turn predisposes to metabolic and cardiovascular disease [17], and it is becoming increasingly clear that the dietary habits in Western societies (“too much”, “too fatty”, “too salty”) and a high body mass index (BMI) also constitute risk factors for autoimmune diseases [18]. In this review, we briefly summarize the evidence provided by epidemiological and experimental studies linking nutrition to autoimmunity. Exploring possible mechanisms, we then discuss the nexus of nutrition, gut mucosal immunity, and systemic autoimmune responses. Here, T helper cells emerge as central players linking dietary perturbations to the modulation of autoimmune pathology.

Nutrients in the aetiology of autoimmune diseases

The association between diet and the risk of developing inflammatory autoimmune diseases was proposed as early as 50 years ago [19–21]. Diseases prominently influenced by nutrition comprise Crohn’s disease and ulcerative colitis (UC), generally grouped together as IBD, where the pathologically affected organ is the gut. Nevertheless, the exact role of diet as a risk factor in these conditions is less clear-cut. Numerous foods and food components including dietary milk, carbohydrates, fats, protein, fiber, fruit, and vegetables have been studied as potential aetiological factors in IBD, but the results from the majority of studies have been equivocal and do not yet support any of these macronutrients as causal factors

[20]. Recent systematic reviews note a possible predisposing role of a diet rich in animal protein and a protective effect of ω-3 polyunsaturated acids (n3-PUFA) in Crohn's disease and UC [22]. Similar to IBD, studies on the role of cow milk, fruit and berry juices [23], and n3-PUFA [24] in T1D risk yielded inconsistent results. Interestingly, early population-based studies in MS, a disease where the influence of nutrition seems less obvious than in IBD, consistently suggested dietary traits as risk factors. MS incidence may be positively associated with the consumption of milk [25], animal fat [26],and meat [27], as well as total energy intake and resulting obesity [28, 29]. In contrast, diets containing high amounts of certain polyunsaturated fatty acids and plant fiber may decrease MS risk [25, 30]. The same pattern of dietary risk factors was also suggested by studies in RA [21]. Yet, these epidemiological findings in MS and RA were not corroborated by the majority of more recent case-controlled studies [19]. Several studies have examined the relationship between nutrition and the risk of developing Ps, and beneficial effects were observed, for example, for fish oils [31] or for the intake of vegetables and fresh fruits [32].

In summary, the body of studies so far addressing nutrition as an aetiological factor in inflammatory autoimmune diseases has not firmly verified functional links between dietary macronutrients and a risk for developing disease. However, the inconclusive results of epidemiologic studies do not justify omitting nutrients as influential factors, but rather illustrate the challenge to detect these on the level of otherwise heterogeneous populations. Subjects prone to autoimmunity have complex individual risk profiles comprised of genetic and environmental determinants that make their response to nutritional cues diverse [33]. Research testing specific nutrients and dietary modifications in spontaneous animal models of autoimmune disease under standardized conditions and a careful stratification of persons-at-risk in human studies is therefore required to advance the efforts in identifying dietary risk factors in autoimmunity.

Obesity as a risk and severity factor in autoimmunity

Studying the aetiological role of obesity in autoimmunity has been more fruitful than exploring special diets or single nutrients as predisposing factors. Obesity is defined as abnormal or excessive fat accumulation that may impair health. The condition is fundamentally caused by excess calorie intake in relation to calorie expenditure, thus integrating energy intake changes, dietary composition changes and physical activity changes that typically occur in the wake of a convenient lifestyle [34]. According to the WHO, worldwide obesity has doubled since 1980. WHO global comparable estimates in 2010 document a mean prevalence of overweight (BMI > 25) or obesity (BMI > 30) in 46 % of the US population (aged 15+) as compared to a global mean of 17 % [35]. Obesity is often accompanied by a condition termed metabolic syndrome that is characterized by insulin resistance and high triglyceride and low high-density lipoprotein (HDL) levels, hypertension, and systemic inflammation [36].

Obesity and metabolic syndrome predispose individuals to a plethora of chronic diseases, including inflammatory autoimmune diseases. For instance, a recent large case-controlled [29] and a retrospective study [28] demonstrate that a high BMI and obesity before adulthood are associated with a higher risk of developing MS. A number of case-controlled

studies robustly also link obesity and metabolic syndrome to Ps [37] and RA [38]. In particular, the finding that metabolic syndrome is already present in early-diagnosed RA underscores its role as a risk factor [39]. IBD in turn is not convincingly linked to overweight, obesity, or metabolic syndrome on a population level, probably because the symptoms of the disease can severely compromise food intake [40]. However, the association of obesity and some inflammatory gut disorders is well documented [41], and alterations in adipose tissue are noted in Crohn's disease [42]. Since obesity and metabolic syndrome are arguably the most consistent predisposing factors across a large set of inflammatory autoimmune disease, it seems to be mandatory to prevent excessive fat accumulation in the first place. This again underscores the need to further investigate dietary factors of the "Western diet" that are associated with obesity, including animal-derived fats, refined grains, sugars, and salt.

Mechanisms linking Western diet to autoimmunity – Fat, obesity and T cell responses

A high-fat diet is a prominent factor promoting obesity, which leads to excessive accumulation of white adipose tissue (WAT) and systemic inflammation. WAT is not an inert tissue devoted solely to energy storage but is now regarded an "endocrine organ" releasing a plethora of pro-inflammatory mediators such as TNF-α, IL-6, leptin, resistin, and C-reactive protein [43]. These "adipokines" account for a chronic low-grade systemic inflammation in obese subjects. Of note, these chronic inflammatory signals can have a profound impact on $CD4^+$ T cell populations, and it has been shown in murine studies that diet-induced obesity can impact specific fat-resident regulatory T cells (Treg) and particularly promote a T_H17-biased immunity, partly dependent on IL-6 [44–47]. Moreover, a similar T_H17-biased immune profile in obese people was observed in a human study [48]. Although the role of IL-17 in obesity seems to be complex, diet-induced obesity can impact several autoimmune disease models [49]. It was shown that a high-fat diet can exacerbate IBD [50], collagen-induced arthritis (CIA) [51], trinitrobenzenesulfonic acid (TNBS)-induced colitis [44], and experimental autoimmune encephalomyelitis (EAE, an rodent model mimicking aspects of MS) [44, 52] (Table 1). Moreover, published data indicate that paracrine interactions occur between lymphocytes and WAT adjacent to lymphatic tissues [53]. Thus, it is conceivable that this relationship can influence autoimmune responses.

Animal studies established leptin, one of the most studied adipose-derived hormones, as an important link between calorie intake and autoimmune inflammation [54]. Leptin is critical in the regulation of energy balance and body weight, but additionally may co-stimulate T cell proliferation and polarise T_H1 responses via direct signaling through T cell-expressed leptin receptors [55]. Of interest, the levels of circulating leptin can be sharply reduced by fasting and a 48-h starvation can potently ameliorate severity of a relapsing-remitting form of EAE [56]. Taken together, the above findings demonstrate that, on a molecular level, WAT-derived adipokines and the resultant systemic inflammation can highly impact T cell responses and thus potentially have a direct influence on autoimmune diseases.

Mechanisms linking Western diet to autoimmunity – Sodium intake and T_H17 cells

Salt (sodium chloride, NaCl) intake varies vastly around the world, ranging from less than 1 g/day in some indigenous populations to more than 20 g/day in the Western world and Japan [57]. The sodium content of processed foods and 'fast food' preferentially consumed in the developed societies can be more than 100 times higher in comparison to similar homemade meals [57]. Excess dietary salt intake is already a well-studied culprit in the development of cardiovascular disease and stroke [58, 59]. Moreover, experimental studies in mice highlight a role for T cells as causal players in the genesis of hypertension and resulting target organ damage [60–62], suggesting similarities in the aetiology of hypertensive inflammatory autoimmune diseases.

Shapiro and Dinarello noted earlier that osmotic stress can induce the release of pro-inflammatory cytokines from human mononuclear cells in culture [63]. Accordingly, the clinical use of hypertonic saline for plasma expansion is associated with immune activation [64, 65]. Further investigation of potential mechanisms underlying this phenomenon demonstrated that elevated NaCl concentrations enhance T cell responses on a cellular level, and that p38/MAPK and the transcription factor nuclear factor of activated T cells 5 (NFAT5) play an integral part of the cellular response to hyperosmotic environments [66–68].

While the immune-enhancing effect of hypertonicity has been clearly demonstrated, it is only starting to be unravelled how dietary salt intake acts as a risk factor for cardiovascular and autoimmune disease in vivo. This concept involves major paradigm shifts in the understanding of the body's sodium and fluid regulation. Specifically, the steady-state concept of sodium homeostasis dictates that dietary sodium is quantitatively eliminated via urinary excretion, achieving isotonicity with constant sodium and water content throughout plasma and tissues. However, this concept was recently challenged by observations in laboratory animals and humans [69]. First, elevated sodium contents were measured in secondary lymphatic organs of mice and were proposed as a permissive environment for NFAT5 activation, which in turn is required for proper T cell functioning [66]. Second, high-salt diet in rodents could lead to salt accumulation in the skin-interstitium, which locally activates macrophages in a NFAT5-dependent manner. The activated macrophages in turn affect lymphatics by secretion of vascular endothelial growth factor-C (VEGFC) that can inhibit the development of salt-sensitive hypertension [70, 71]. Third, by changing salt intake under highly controlled conditions, daily sodium excretion revealed periodic sodium storage in humans [72]. All together, the classical concept of sodium-water balance has been challenged by the view that tissue sodium content is compartmentalized under physiological and pathophysiological conditions. Thus, the tissue sodium content seems to exert a surprising flexibility and can change in response to dietary intake and may impact immune function.

Based on these findings, effects of elevated NaCl were recently investigated in human T cells and murine EAE [73]. Elevated NaCl concentrations found locally under physiological conditions in vivo promoted the in vitro differentiation of murine and human T_H17 cells

with a highly pro-inflammatory phenotype. This process was dependent on the activation of the osmotic stress pathway including the serum/glucocorticoid-regulated kinase 1 (SGK1) [73]. Of note, mice on a high-salt diet developed a more severe course of EAE that was associated with a pronounced T_H17 response in vivo, in an SGK1- and IL-23R-dependent manner [73, 74]. However, the exact mechanism of how excess dietary salt intake affects $CD4^+$ T cell responses in vivo and whether other, indirect pathways contribute to this effect remains to be explored. Since the highest changes in IL-17-producing cells under non-inflammatory conditions could be detected in gut-associated tissues [74], salt-regulated pathways in the gut deserve major attention.

Mechanisms linking Western diet to autoimmunity: Gut microbiome and T cell regulation

The intestine is the primary absorption interface for nutrients, vitamins, and water, and therefore constitutes a premier site to investigate dietary influences in autoimmune disease. The digestion of proteins, lipids, and carbohydrates in the gut is facilitated by host enzymes as well as handling by commensal bacteria (the “gut microbiota”) colonizing the human gut [75]. It is conceivable that the nutritional value of food is influenced by the composition and operation of a consumer´s gut microbiome, and that dietary components in turn shape the composition and functional status of the microbial community [76]. For example, a high-fat diet alters the structure of the microbiome even in the absence of obesity [77]. The intestinal mucosal immune system has adapted to tolerate the vast numbers of commensal bacteria, a balance that involves an intricate two-way communication mediated by host-derived anti-microbial peptides and sensing of bacterial-derived molecular patterns [78].

New methods to probe the microbiome, including 16s rRNA gene pyrosequencing, have fueled research into the composition and perturbations of the intestinal communities [79]. Such studies have identified altered gut microbiomes in obesity [80], T1D [81], and IBD [82]. Gnotobiotic approaches (the rearing of animals under germ-free conditions, with or without subsequent exposure to a microbial species or species consortium) have provided a wealth of information about the functional significance of the gut microbiome in autoimmune responses. Mere presence of intestinal commensal bacteria is a prerequisite for the development of EAE and IBD in rodents [83, 84]. Furthermore, clinical signs of actively induced murine EAE can be ameliorated with the right mixture of orally delivered probiotic bacteria [85]. Depending on the particular species of gut bacteria, mono-colonization of germ-free mice can either enhance the differentiation of pro-inflammatory T_H17 cells [86] or foster the development of Treg [87, 88].

An important lesson learned from those studies is that the gut microbiome can profoundly modulate the extra intestinal immune responses, in particular the Treg/T_H17 balance, and can “imprint” functional phenotypes in T helper cells. For instance, the intestinal lamina propria is a site of effector T cell regulation where an excessive systemic T_H17 response can be locally disarmed by luminal disposal of T_H17 cells or their conversion into IL-10-producing T_H17 cells with a regulatory function [89]. Furthermore, altering the gut microbiota by supplementation of probiotic bacteria potently prevented diet-induced obesity and T_H17-biased immunity despite ad-libitum access to a high calorie “Western diet” in an

IL-10- and Treg-dependent manner. Strikingly, the transfer of $CD4^+$ T cells was sufficient to confer the same beneficial effect to recipient mice [45].

In summary, the gut microbiome is central to maintaining metabolic balance as well as self-tolerance, and constitutes a valuable target for dietary intervention and probiotic approaches. Although conclusive data based on studies in humans are still sparse, novel reports documenting a central role of T lymphocytes in integrating nutritional perturbations of the gut microbiota require further exploration. Here, dietary modulation of T helper cell phenotypes, immunologic memory, and T cell receptor repertoires are aspects of potential high interest.

Conclusions

Although no definite associations between dietary factors and autoimmune diseases have so far been firmly established, a large proportion of patients consider special diets or dietary supplements as alternative therapeutic measures [19]. While this is not yet backed by positive phase II or III interventional trials or consensus recommendations, some aspects may deserve special attention. First, symptoms of disease, such as fatigue in MS, pain and diarrhea in IBD, or the need of acute medication in T1D, may be considerably affected by food intake [40]. This may in turn compromise their nutritional status [90]. Furthermore, a number of immunomodulatory nutrients such as polyphenols and n3-PUFAs are part of diets traditionally associated with health benefits, including the “Mediterranean diet” [91]. Here, diverse foods and food supplements have been tested in interventional studies in various inflammatory autoimmune diseases. A collection of studies involving macronutrients in the management of inflammatory autoimmune disease models is presented in Table 1. Yet, in humans, large trials are sparse and the recent OFAMS-study failed to detect any influence n3-PUFA on the course of MS [92]. In general, it should be considered that the efficacy of dietary interventions in autoimmune diseases might crucially depend on how well pathology is controlled by immunomodulatory and anti-inflammatory treatments in first place. Nonetheless, numerous positive experimental results across different disease entities encourage further exploration of the cellular and molecular immunological basis underlying nutritional control of autoimmunity. It is current knowledge that nutrition, the intestinal microbiota, the gut mucosal immune system, and autoimmune pathology are deeply intertwined.

The development of further innovative therapies for gut microbial-dependent immune dysfunctions may also include a fresh, objective re-assessment of fecal microbial transplants that more recently have shown extraordinary efficacy in fighting *Clostridium difficile* infection [93]. Pyrosequencing could provide information about the exact microbial consortia in donor feces that are beneficial for a given condition, ultimately even eliminating the need for this aesthetically unpleasing procedure. Another unconventional approach could be helminth therapy, the deliberate infection with gut parasitic hookworms that exert immunomodulatory effects on the host [94]. Despite logistic challenges, this kind of treatment is currently already being tested in MS patients in a phase II trial (WIRMS study, results due in 2014).

In summary, the links between diet, gut microbiota, T cells, and autoimmunity are intriguing, and understanding the nexus of nutrition, metabolism, gut immunology, and systemic immune responses is key to explaining these interactions. Conceivably, effects of nutrition on the gut mucosal immune system, on sodium and fluid homeostasis, and on the metabolic state of the body could represent additive factors acting in concert with other (e.g., infectious) triggers in autoimmunity. In fact, the finding that sodium chloride promotes T_H17 responses and aggravates EAE illustrates that single nutritional components have the capability to potently modulate autoimmune responses and inflammation.

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Table 1

Studies testing dietary interventions in models of autoimmune diseases

Dietary factor	Disease model	Ref.	Overall effect	Putative mechanisms
Calorie restriction	EAE	[56]	Beneficial	Curtailment of leptin
Calorie restriction	EAE	[95]	Beneficial	Curtailment of leptin
PUFA	EAE	[96]	Beneficial	PPAR-γ induction
Olive oil and polyphenols	DIC	[97]	Beneficial	PPAR-γ induction
Fish-oil	CIA	[98]	Beneficial	Macrophage function
Green tea extract	EAE	[99]	Beneficial	NFκB inhibition
High-fat diet	IBD	[50]	Detrimental	Unknown
High-fat diet	CIA	[51]	Detrimental	T_H17 induction
High-fat diet	EAE, TNBS Colitis	[44]	Detrimental	T_H17 induction
High-salt diet	EAE	[74]	Detrimental	T_H17 induction
High-salt diet	EAE	[73]	Detrimental	T_H17 induction
Trans fatty acids	DIC	[100]	Detrimental	T_H17 induction

EAE Experimental autoimmune encephalomyelitis, *CIA* collagen-induced arthritis, *DIC* DSS-induced colitis, *PUFA* polyunsaturated fatty acid, *TNBS* trinitrobenzenesulfonic acid