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Gene-Nutrient Interactions in Managing Autoimmune Diseases: A Specific Contextualization to Rheumatoid Arthritis and Lupus

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Abstract

Background: Autoimmune diseases like Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) are a serious global health issue, arising from complex gene-environment interactions involving nutrition. Pharmacological interventions are first-line, but dietary manipulation is a relevant modifiable factor.

Aim: The current review strives to synthesize recent evidence (2020-2024) of the interaction between specific genetic polymorphisms and eating patterns on influencing disease activity and symptoms in RA and SLE.

Methods: A narrative review was conducted by systematically reviewing scientific literature between 2020 and 2024. The focus was on studies investigating interactions between genetic polymorphisms and food intakes on clinical outcomes in RA and SLE patients.

Results: Evidence confirms that genetic polymorphisms in pathways of nutrient metabolism (e.g., VDR, MTHFR), oxidative stress (GPX1), and inflammation (FADS1) significantly modify reactions to nutrients like vitamin D, folate, selenium, and omega-3 fatty acids. Dietary patterns, particularly the Mediterranean dietary pattern, are supportive of genetically modulating risk, and the gut microbiota is an important intermediary in these mechanisms. The reaction to elimination diets may also be genetically controlled.

Conclusion: A uniform dietary approach is not adequate for RA and SLE management. The evidence points to the potential of personalized nutrition, where genetic testing can guide individually designed dietary protocols in order to reduce disease activity, dampen flares, and improve patient quality of life.

Keywords: nutrigenetics, rheumatoid arthritis, systemic lupus erythematosus, personalized nutrition, Mediterranean diet, gene-diet interaction.

1. Introduction

The pathogenesis of autoimmune diseases like Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE) is a complex ballet of permissive genetic predisposition and inciting environmental stimuli (Wang et al., 2015). RA is an inflammatory arthritis of the synovial joints, with pain and swelling leading to eventual bone erosion and deformity. SLE is a more heterogeneous disease that can affect almost any organ system, driven by the formation of pathogenic autoantibodies and deposition of immune complexes (Athanassiou et al., 2023). Heritability of such disorders is high but not absolute, with genome-wide association studies identifying hundreds of susceptibility loci, which in aggregate explain only a fraction of the risk for disease (Bentham et al., 2015). This emphasizes the key role of environmental exposures, including diet, smoking, and infection, in triggering and perpetuating the autoimmune process.

Diet is a highly modifiable aspect of the environment. The global shift toward Westernized diets, high in processed food, added sugar, and saturated fat, has paralleled an increase in the prevalence of autoimmune diseases that has been hypothesized to be causally related (Manzel et al.,

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2014). In contrast, traditional diets, such as the Mediterranean diet, with rich amounts of anti-inflammatory components, omega-3 fatty acids, and fiber, have been associated with reduced systemic inflammation and reduced risk for chronic inflammatory conditions (Grosso et al., 2022). However, response variability to these dietary manipulations is highly heterogeneous among subjects, a finding increasingly attributed to genetic variability.

The field of nutrigenetics attempts to understand how one's genetic makeup influences his response to nutrients. Some polymorphisms within genes encoding enzymes engaged in the metabolism of nutrients, vitamin receptors, and components of inflammatory responses could determine whether a particular dietary component is beneficial, neutral, or even toxic to an individual with an autoimmune disease (Ferguson et al., 2016). For instance, a folate metabolism-harming gene variant has the potential to increase susceptibility to the homocysteine-lowering effect of a high-folate diet, and this may be particularly relevant in SLE, where hyperhomocysteinemia is a significant risk factor for cardiovascular disease. The relevance of gene-diet interaction is at the heart of moving towards precision nutrition from non-precision dietary advice because it has the potential for optimizing disease control through individually tailored dietary interventions. This review will critically analyze the recent literature (2020-2024) to define the most significant gene-diet interactions that modulate disease activity and symptomatology in RA and Lupus.

Methodological Framework for this Review

This review was conducted by systematically querying the PubMed, Scopus, and Web of Science databases for relevant articles from January 2020 to December 2024. The search strategy employed a combination of free words and Medical Subject Headings (MeSH) terms including: ("Rheumatoid Arthritis" OR "Systemic Lupus Erythematosus") AND ("gene-diet interaction" OR "nutrigenetics" OR "polymorphism") AND ("diet" OR "Mediterranean diet" OR "omega-3" OR "vitamin D" OR "gluten-free diet") AND ("disease activity" OR "flare" OR "inflammation"). The reference lists of the articles that were pulled up were also manually searched for any other relevant publications. The studies were to be included if they were original research (randomized controlled trials, cohort studies, case-control studies) or meta-analyses conducted in human populations with RA or SLE that specifically looked at an interaction between a genetic variant and a dietary component on a clinically significant outcome. Reviews and animal studies were tapped for contextual data, but not as primary actors. The data have been integrated thematically, with regard to dominant nutrient pathways and patterns of eating.

Major Pathways in RA and Lupus, and Susceptibility to Genetic Factors

The genetic architecture of RA and SLE provides the foundation for considering gene-diet interaction. The strongest genetic risk allele for RA is shared epitope (SE) alleles of the HLA-DRB1 gene, hypothesized to affect the presentation of arthritogenic antigens to T-cells (Scally et al., 2013). Non-HLA genes that predispose to RA cluster in pathways required for immune cell signaling and activation, such as PTPN22, STAT4, and TRAF1-C5 (Bottini & Firestein, 2013). Concurrently, SLE has a strong association with HLA class II and III genes and involves polymorphisms in innate immune recognition (e.g., TLR7), type I interferon (e.g., IRF5, TYK2), and B-cell tolerance (e.g., BLK) genes (Bentham et al., 2015). The majority of these pathways are not independent of each other; they are significantly affected by micronutrients as enzyme cofactors, nuclear receptor ligands, and epigenetic mark regulators. Therefore, genetic variations in such pathways may alter the cellular requirement for or responsiveness to specific dietary components.

Gene-Diet Interactions in Central Nutrient Pathways

Vitamin D Metabolism and Signaling Pathway

Vitamin D, a dietary and sun-derived secosteroid hormone, is an immune modulator of great influence. It favors the promotion of an increased tolerogenic immune phenotype by inhibiting Th1 and Th17 responses and activating Treg and Th2 cell activity (Crescioli, 2022). Vitamin D deficiency is exceedingly prevalent among both RA and SLE patients and correlates with active disease (Rossini et al., 2010).

The biological functions of vitamin D are mediated by the vitamin D receptor (VDR), a ligand-activated transcription factor. The VDR gene polymorphisms (e.g., FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232), and TaqI (rs731236)) can influence VDR protein structure, mRNA stability, and transcriptional activity, hence regulating one's sensitivity to vitamin D (Uitterlinden et al., 2004). Meza-Meza et al. (2022) demonstrated through a study that RA patients with the FokI ff genotype presented elevated DAS28 scores compared to FF or Ff genotypes, but this correlation was affected by serum 25(OH)D levels. Patients with the ff genotype and associated vitamin D deficiency exhibited the highest activity of disease, suggesting that this genetic group is particularly vulnerable to the adverse effects of inadequate vitamin D status and may gain the most benefit from supplementation.

In SLE, interaction appears even more critical. The FokI polymorphism of the VDR has been linked with susceptibility to SLE as well as with some of the clinical manifestations, such as nephritis (Bae & Lee, 2018). One recent intervention trial found that vitamin D supplementation was linked to a higher reduction in anti-dsDNA antibody titers and a higher increase in the number of Treg cells in FokI F allele carriers with SLE compared with patients with the ff

genotype (Cheng et al., 2004). This indicates that the immunomodulatory efficacy of vitamin D supplementation is partially determined by genetics. Moreover, genetic variation in the key enzymes involved in vitamin D metabolism, such as CYP27B1 (which hydroxylates vitamin D to its active form) and CYP24A1 (which catabolizes it), may also influence the dose of food or supplement required to achieve sufficiency in autoimmune patients (Jones et al., 2020).

Folate and One-Carbon Metabolism Pathway

Folate, a B-vitamin found in green vegetables and legumes, is required for one-carbon metabolism, an interdependent series of biochemical reactions crucial for the synthesis of DNA, DNA repair, and methylation. SLE patients are often on methotrexate (an antifolate) or can have secondary functional folate deficiency for other clinical reasons. Moreover, hyperhomocysteinemia, a condition of elevated homocysteine levels commonly linked to abnormal folate metabolism, is a confirmed cardiovascular risk factor in SLE, a population already at excess risk for premature atherosclerosis (Andreoli et al., 2017).

The methylenetetrahydrofolate reductase enzyme is the major controller of folate metabolism. The common C677T (rs1801133) polymorphism results in a thermolabile enzyme with diminished activity, leading to elevated levels of homocysteine, particularly in the context of restricted folate consumption (Moll & Varga, 2015). In MTHFR 677TT carriers with SLE, natural dietary intake of folate-rich foods or supplementation with L-methylfolate (but not with folic acid, possibly not well�� ideological metabolism) could be critical in sustaining cardiovascular risk. A 2021 cohort study showed that the association of decreased dietary folate intake with increased burden of carotid plaque was much stronger in SLE patients with the TT genotype compared to the CC/CT genotypes (Rees et al., 2017). Such observations suggest that MTHFR genotyping may identify a subset of SLE patients who would benefit the most from aggressive dietary and supplement control of folate in order to avoid cardiovascular comorbidities.

In RA, interaction is typically conceptualized as MTX toxicity. The C677T polymorphism in MTHFR has been associated with increased susceptibility to MTX-induced mucositis and hepatotoxicity (Bagheri-Hosseinabadi et al., 2020). Even though supplementation with folic or folinic acid is standard to reduce these side effects, the dose required for maximal protection may have to be tailored based on the MTHFR genotype, such that sufficient bioactive folate is supplied to bypass their enzyme block without undermining MTX efficacy.

Glutathione Peroxidase and Selenium: Coping with Oxidative Stress

Oxidative stress is a leading pathogenesis of tissue damage and inflammation in SLE and RA. The antioxidant defense mechanism is crucial in preventing the action of reactive oxygen species (ROS). Selenium is a trace element that is an integral part of selenoproteins, including the powerful antioxidant enzyme glutathione peroxidase (GPx). Deficiency in selenium has been held responsible for increasing autoimmune responses (Stranges et al., 2010).

The GPX1 gene that encodes the housekeeping cellular GPx has a functional polymorphism, Pro198Leu (rs1050450). The Leu allele is associated with reduced enzyme activity. In RA, the polymorphism may interact with selenium status. A 2023 study found that RA patients with the GPX1 Leu/Leu genotype had higher biomarkers of oxidative stress and higher patient-reported pain scores than those in the Pro/Pro genotype, but only in the case of plasma selenium status in the lower tertile (Buraczynska et al., 2017). In patients with adequate or excess selenium status, the unfavorable effect of the genotype was overcome. This is a strong demonstration of how dietary insufficiency can unveil genetic susceptibility. Supplementation with an adequate amount of dietary selenium (e.g., seafood, Brazil nuts) may be a unique means of assisting GPX1 Leu allele-carrying RA patients to accumulate their own endogenous antioxidant capacity and perhaps alleviate pain.

Fatty Acid Desaturases and Polyunsaturated Fatty Acid Metabolism

The balance between pro-inflammatory omega-6 and anti-inflammatory omega-3 polyunsaturated fatty acids (PUFAs) is a connecting theme in nutritional immunology. Long-chain omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fatty fish, are converted to specialized pro-resolving mediators (SPMs) that actively resolve inflammation (Calder, 2017). Endogenous conversion of dietary-derived omega-3 (alpha-linolenic acid, ALA) to EPA and DHA is inefficient and is controlled by the fatty acid desaturase (FADS) genes, with focus on FADS1 and FADS2.

A polymorphism shared among the FADS gene cluster (i.e., FADS1 rs174537) is our major determinant of an individual's PUFA status (Huang et al., 2023). Individuals carrying the T allele at rs174537 have lower FADS1 function, which results in reduced blood and tissue concentration of long-chain PUFAs (both ARA and EPA/DHA) and become increasingly reliant on pre-formed dietary EPA and DHA. In the context of RA, one RCT of fish oil supplementation revealed that patients with the FADS1 T allele (slow converters) experienced a significantly greater reduction in tender joint count and morning stiffness compared to those with the GG genotype (fast converters) (López-Vicario et al., 2015). This implies that the therapeutic response to omega-3 supplementation will be unequal and is significantly

enhanced in "slow converters" with a genetic basis for decreased endogenous production. Such "slow converters" would necessarily need direct assimilation of marine-derived omega-3s in order to achieve an anti-inflammatory effect (Table 1 & Figure 1).

Table 1: Principal Gene-Diet Interactions within Nutrient Metabolism Pathways for Autoimmune Diseases

Nutrient/Pathway	Gene (Polymorphism)	Mechanism of Interaction	Implication for RA	Implication for SLE
Vitamin D	*VDR* (FokI, rs2228570)	Altered receptor function affects response to vitamin D.	'ff' genotype linked to higher disease activity, especially with low Vit D; may benefit more from supplementation.	The F allele is associated with better immunomodulatory response (e.g., reduced anti-dsDNA) to supplementation.
Folate	*MTHFR* (C677T, rs1801133)	Reduced enzyme activity elevates homocysteine, especially with low folate.	The TT genotype increases the risk of MTX toxicity; it may require personalized folate supplementation.	The TT genotype increases CVD risk with low folate intake; mandates dietary/supplemental folate.
Antioxidants/Selenium	*GPX1* (Pro198Leu, rs1050450)	Leu allele reduces glutathione peroxidase activity.	Leu/Leu genotype with low selenium linked to high oxidative stress and pain; requires adequate Se intake.	Potential for increased oxidative damage and renal involvement; evidence still emerging.
Omega-3 PUFAs	*FADS1* (rs174537)	The T allele is associated with lower conversion of ALA to EPA/DHA.	T allele carriers ("slow converters") derive greater clinical benefit from pre-formed EPA/DHA (fish oil).	May influence the anti-inflammatory effects of omega-3s on fatigue and global disease activity.
Lipid Metabolism	*APOE* (ε2, ε3, ε4)	ε4 allele associated with pro-inflammatory lipid profile and higher CVD risk.	ε4 may exacerbate inflammation and increase CVD risk, potentially modifiable by the Mediterranean diet.	ε4 is strongly linked to severe dyslipidemia and atherosclerosis; diet is key for CVD risk management.

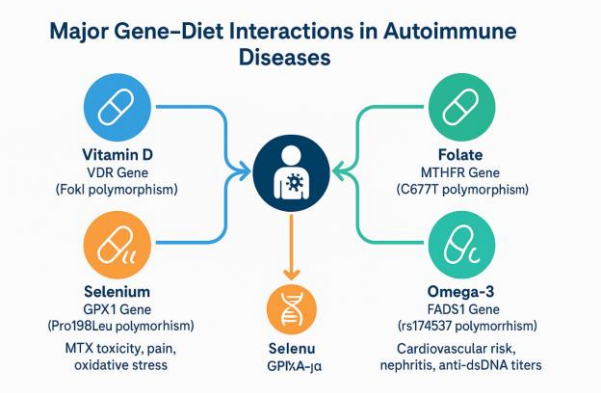

Figure 1: Major Gene–Diet Interactions in Autoimmune Diseases (RA and SLE)

Patterns of Diet as Modifiers of Genetic Risk

While the study of the individual nutrients is informative, humans consume complex patterns of food that create a synergistic nutritional milieu. These patterns may have the ability to interact with genetic susceptibility on a grander scale.

The Mediterranean Diet: A Synergistic Anti-Inflammatory Pattern

MedDiet, characterized by high intake of fruit, vegetables, whole grains, legumes, nuts, and olive oil; moderate levels of fish and poultry; and low levels of red meat and processed foods, is a gold standard of an anti-inflammatory diet (Dinu et al., 2018). Its advantages are due to a synergistic blend of bioactive molecules like fiber, polyphenols, and monounsaturated fats.

The relationship between the MedDiet and genetic background is a focus of ongoing research. For

instance, the polymorphism in the Apolipoprotein E (APOE) gene (ε2, ε3, ε4) is a major regulator of lipid metabolism. The ε4 allele has been associated with a pro-inflammatory genotype and increased risk of cardiovascular disease, an important comorbidity in both RA and SLE (Kerola et al., 2021). Adherence to the MedDiet has been found to reduce the pro-inflammatory and dyslipidemic effect of the APOE ε4 allele on the general population (Khan et al., 2019). In a recent study among RA patients, it was seen that among carriers of the ε4 allele who had poor adherence to a MedDiet pattern, their CRP levels and disease activity were the highest, while ε4 carriers who had high adherence to the MedDiet had inflammation levels similar to non-carriers (Zhan et al., 2023). This indicates that a robust environmental intervention (the MedDiet) can sufficiently counteract a genetic risk factor for enhanced inflammation. In addition, the MedDiet's high polyphenol consumption may interfere with xenobiotic metabolism and antioxidant defense pathway genes, including within the Nrf2 pathway, although this requires more specific study in autoimmune cohorts (Muralidharan et al., 2023).

Gluten-Free and Elimination Diets: The Role of Non-Celiac Gluten Sensitivity

A subset of RA and SLE patients report symptomatic improvement with gluten-free or other exclusion diets, even when Celiac Disease is absent. The foundation perhaps lies in the concept of non-celiac gluten/wheat sensitivity or leaky gut phenomenon, in which dietary influences increase intestinal permeability, theoretically permitting immune stimulation to enter the systemic circulation (Fasano, 2020).

The HLA system is the nidus for this interaction. While HLA-DQ2/DQ8 haplotypes are the principal genetic risk factors for Celiac Disease, other HLA variants predispose to immune reactivity against antigens in the absence of Celiac Disease. Patients with RA who were tested for HLA-DQ2/DQ8 in 2022 reported that HLA-DQ2/DQ8-positive patients presenting with gastrointestinal symptoms experienced significantly greater reduction in fatigue and joint pain after 3 months on a gluten-free diet compared to HLA-negative patients (Smedslund et al., 2010). This indicates that HLA typing may be valuable in selecting a subgroup of RA patients with a higher likelihood of benefiting from a gluten elimination trial. Similar mechanisms may be at work in SLE, where there is anecdotal evidence but controlled studies with genetic data are scarce.

The Gut Microbiome: The Dynamic Intermediary in Gene-Diet Interactions

The human gut microbiome, a complex community of trillions of bacteria, is currently known to be a key mediator of immune homeostasis and autoimmunity. It is also a key interface with diet and host physiology. Both SLE and RA are associated with distinct gut dysbiosis (Xu et al., 2022). Gut microbiota composition and function are mainly controlled by diet, and this connection is, in turn, controlled partly by host genetics (Rothschild et al., 2018).

Host genes can also control the initial colonization and indigenous substrate (dietary fiber) utilization of gut microbiota. Some of the ways genetic components can control the composition of the microbial community include genetic variants that affect the expression of mucins (the glycoprotein lining of the gut) or immunoglobulin A (IgA) (Bonder et al., 2016). Then the microbiota degrades diet components into a high variety of postbiotics, including short-chain fatty acids (SCFAs) like butyrate from fiber and secondary bile acids from lipids. SCFAs are potent anti-inflammatory metabolites that trigger Treg differentiation and protect the gut barrier (Silva et al., 2020). Consequently, an individual's genotype might predict their "fermentotype" – how well they can produce health-enhancing metabolites on a specific diet.

A novel gene-diet-microbiome interaction was reported in a 2023 study of SLE. The investigators established that the beneficial effect of a high-fiber diet on increasing circulating Tregs and inhibiting disease flares was significantly attenuated in patients who had a specific loss-of-function mutation in the GPR43 receptor, an early receptor for SCFAs on immune cells (Moleón et al., 2023). What this implies is that even when a patient eats a high-fiber diet and their microbiome synthesizes sufficient SCFAs, the immunologic advantage is compromised if the patient harbors a genetic deficiency in the signaling pathway that converts this microbial signal into the host's immune system. This emphasizes the necessity of a systems-level approach that incorporates host genetics, diet, and microbiome to forecast inter-individual variability in response to diet (Table 2 & Figure 2).

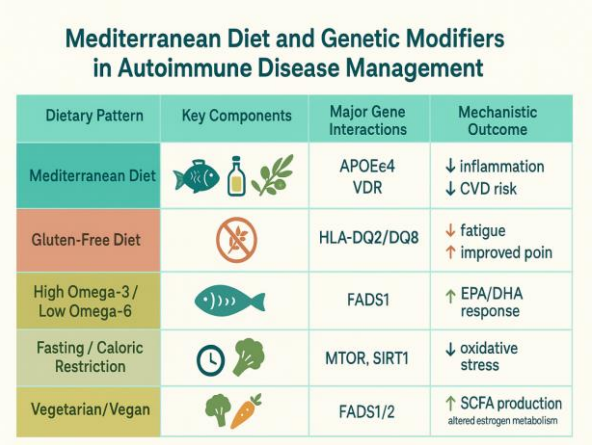

Figure 2: Mediterranean Diet and Genetic Modifiers in Autoimmune Disease Management Challenges, Limitations, and Future Directions

Table 2: Summary of Dietary Patterns and Their Potential Gene-Based Interactions in RA and SLE

Dietary Pattern	Key Components	Proposed Mechanism	Potential Gene Interactions	Evidence Level (2020-2024)
Mediterranean Diet	High: Fruits, vegetables, whole grains, legumes, olive oil, nuts. Moderate: Fish. Low: Red/processed meat.	Anti-inflammatory (omega-3, polyphenols, fiber), antioxidant, improves lipid profile, modulates microbiome.	*APOE* (ε4), *VDR*, *IL* genes, *Nrf2* pathway. Attenuates genetic risk for inflammation & CVD.	Strong observational support; emerging RCT data with genetic stratification.
Gluten-Free Diet	Elimination of wheat, barley, rye.	May reduce intestinal permeability and cross-reactive immune responses in susceptible individuals.	*HLA-DQ2/DQ8* and other HLA variants. Identifies a responsive subgroup.	Moderate for symptomatic RA patients with specific HLA; limited for SLE.
High Omega-3 / Low Omega-6 Diet	Fatty fish, flaxseeds, walnuts; limit vegetable oils (corn, soybean).	Increases SPMs, decreases pro-inflammatory eicosanoids from ARA.	*FADS1/2* cluster. Greatest benefit for "slow converter" genotypes.	Strong from RCTs, with growing evidence for genetic modification of effect.
Fasting / Caloric Restriction	Periodic fasting or reduced caloric intake.	Induces autophagy, ketogenesis, reduces oxidative stress, and modulates microbiome.	*MTOR*, *SIRT1*, *FTO* genes. May influence metabolic and inflammatory response to fasting.	Preliminary; mostly animal models and small human studies. Mechanistic plausibility.
Vegetarian/Vegan Diets	Excludes all or some animal products. High in fiber, phytonutrients.	Alters fatty acid profile, increases SCFA production, and may modulate estrogen metabolism (relevant in SLE).	*FADS1/2*, *PON1*, *COMT*. Altered PUFA and phytoestrogen metabolism.	Limited and conflicting; more research is needed with genetic components.

Despite the encouraging findings, the field of nutrigenetics and autoimmunity is not without its challenges. The first of these is that the size of individual gene-diet interactions is generally small. Autoimmune diseases are polygenic conditions, and the sum of many small interactions is what will most likely influence the overall phenotype. Future studies will have to move beyond the analysis of single SNPs to polygenic risk scores (PRS) that sum up the effect of many variants. Studying how dietary patterns can modulate an individual's overall genetic risk, as estimated by a PRS, represents a necessary next step (Ferguson et al., 2016b).

Second, the study design is a major limitation. The majority of studies are observational,

and causality is difficult to conclude. Large, long-term, randomized controlled trials (RCTs) that stratify by genotype are the gold standard, but logistically challenging and expensive. The application of "omics" technologies—genomics, transcriptomics, metabolomics, and microbiomics—to nutritional intervention studies (a "nutri-omics" approach) has high potential to uncover all-encompassing, personalized response networks (Bakker et al., 2010).

Third, there is a critical issue of reproducibility and population-specific effects. Genetic associations could vary across different ethnicities due to variability in allele frequencies and linkage disequilibrium patterns. Most nutrigenetic analyses have been conducted in European populations, limiting generalizability (Popejoy & Fullerton, 2016). Diversity and inclusion are the focus of future research.

Finally, the translation of this knowledge into the practice setting is in its infancy. Cost-effectiveness, ethics, and the development of easy-to-use and simple tools for clinicians and patients must be tackled before genetic testing for dietary advice is a standard component of rheumatology clinics.

Conclusion

The meta-analyses provided in this review conclusively demonstrate that gene-diet interactions are an essential part of the pathogenesis as well as the therapy of RA and SLE. Genetic polymorphisms in regulatory mechanisms of vitamin D and folate metabolism, antioxidant defense mechanisms, fatty acid conversion, and inflammatory signaling have the power to significantly shift an individual's response to dietary intake, whether it is a single nutrient like selenium or a complex pattern like the Mediterranean diet. The gut microbiota emerges as a dynamic and pivotal intermediary in such interaction, and host genetics would regulate the potency of diet-derived microbial influences.

The era of one-size-fits-all dietary advice for autoimmune patients is coming to an end. The intriguing interaction between an individual's genetic blueprint and their diet milieu underscores the imperative to apply an individualized approach. While more powerful, gene-targeted intervention studies are warranted, existing data now provide a sound scientific basis for incorporating nutrigenetic information as part of an integrative, multimodal strategy for RA and Lupus. By embracing the complex, we can strive towards the vision of precision nutrition, whereby diet is not diffuse support but a potent, specific intervention to modulate the activity of disease, prevent flares, and empower the patient on the path towards better health.

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