

Dietary modifications for refractory chronic rhinosinusitis? Manipulating diet for the modulation of inflammation

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ABSTRACT

Background: An endotype of chronic rhinosinusitis (CRS) refractory to medical and surgical management is characterized by persistent T-helper 1/T-helper 17 inflammation of the sinus mucosa, which potentially facilitates colonization with dysbiotic microbial flora. Dietary interventions that target reduction of systemic inflammation are increasingly recommended as adjuncts to ongoing medical therapy in chronic disorders with a strong inflammatory component, such as cardiac disease, diabetes, and metabolic syndrome. Inflammation-reducing dietary modifications may thus be of benefit in patients with refractory CRS (RCRS).

Objective: To identify nonpharmacologic approaches that implicate modification of dietary factors, potentially reducing systemic level of inflammation in RCRS.

Methods: A systematic review of the literature was undertaken to identify dietary strategies for reducing inflammation in metabolic syndrome, diabetes, and cardiac disease. Mechanistic-based strategies for reducing systemic inflammation were identified and categorized to identify potential therapeutic avenues, which would be applicable to RCRS.

Results: Principal mechanisms for altering inflammation at the systemic level via dietary manipulation center around (1) increased consumption of foods with anti-inflammatory properties, and (2) modulation of the gut microbiome to reduce short-chain fatty acid secretion by dysbiotic gut flora. Recommended dietary modifications to reduce systemic markers of inflammation or to improve RCRS include alteration of macronutrient intake, alterations in consumption of meat and fats, consumption of prebiotics and probiotics, and a low-salicylate diet in the context of aspirin-exacerbated respiratory disease.

Conclusion: Dietary modifications may offer a potential nonpharmacologic means of reducing inflammation in patients with RCRS and hence may represent a complementary adjunct to existing medical therapies. Additional prospective studies are required to further validate the concept of dietary modifications in patients with RCRS to support the findings.

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Refractory chronic rhinosinusitis (RCRS) is characterized by frequent exacerbations of facial pain or pressure and nasal discharge. Maximal medical therapy often fails in patients with RCRS, and these patients may require multiple antibiotic treatments or revision sinus surgeries. Existing research has thus far proven insufficient in determining the underlying cause of RCRS and has centered around bacterial, constitutional, and immune system–related components.¹ Strong associations exist between chronic rhinosinusitis (CRS), asthma, aspirin intolerance, and atopy.^{2,3}

RCRS is primarily characterized by persistent inflammation of the sinus mucosa, which may play a role in both developing inflammatory-induced dysfunction of sinus mucosa and facilitating colonization with dysbiotic flora, which results in an abnormal microbiome.⁴ Currently, management strategies to treat CRS aim to reduce inflammation, bacterial colonization, and infection through pharmacologic means. Increasingly, nonpharmacologic therapies have been shown to be important adjuncts to standard medical therapies in several disease processes. In particular, dietary interventions that target reduction of systemic inflammation are increasingly recommended as complements to medical therapy in inflammatory disorders, such as cardiac disease, diabetes, and metabolic syndrome, and thus may be beneficial in the management of CRS. The objective of this review was

to identify dietary factors, which may be manipulated to reduce the systemic level of inflammation in CRS.

MOLECULAR MECHANISMS IN CRS

Different clinical phenotypes and endotypes of CRS have been described based on cytokine profile and inflammatory cell patterns.⁵ One of the proposed pathogenesis of CRS has been an imbalance of T-helper (Th) 1 and Th2 functions.⁶ Certain patients with CRS may be hyperresponsive to normal sinus flora or, alternatively, have reduced bacterial diversity.^{7,8} The resultant immune response manifests at both local and systemic levels.

In addition to its barrier function, the airway epithelium is a major source of cytokines, chemokines, and other inflammatory mediators that affect both the adaptive and innate immune responses.⁹ Epithelial cells recognize molecules of microbial origin by the use of different pattern-recognition receptors, including Toll-like receptors, nucleotide-binding oligomerization domain like receptors, and retinoic acid-inducible gene 1–like receptors. These receptors are known to play important roles in pathogen recognition, cell activation, and regulation of immune responses^{9,10} and thus may have a role in the exacerbation of inflammatory diseases such as allergic rhinitis and CRS.¹¹ These molecular mechanisms may be modifiable through dietary modifications, as demonstrated in other inflammatory disorders.

THE GUT MICROBIOME IS CENTRAL TO REGULATION OF INFLAMMATION

Microorganisms that populate the human body are most densely found in the nasal, oral, skin, gastrointestinal, and urogenital environments. The gut microbiota has been extensively studied and is known to have a beneficial role in maintaining normal homeostasis and in modulating the host's immune system, and has been previously studied in the context of inflammatory diseases.¹²

Excess inflammation, which represents dysregulation in immune signaling, is a feature of several inflammatory and autoimmune dis-

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eases.¹³ Symbiotic microorganisms in the intestine can reduce unnecessary inflammation through several mechanisms. Immune tolerance is induced by these microbes by coordinating or regulating the immune system.^{13–15} Moreover, the gut microbiota is able to modulate cell survival, replication, and apoptosis.¹⁶ Indeed, several researchers reported that the microorganisms in the gut play a major role in regulating the immune cells, such as Th1, Th2, Th17, regulatory T cells, dendritic cells, and Toll-like receptors, that are relevant to asthma, allergic diseases, CRS, and autoimmune diseases.¹³

Several factors play a role in influencing inflammation in the gut microbiome (Fig. 1). Composition of the gut microbiome can alter host physiology, inflammation, and disease pathogenesis.¹⁷ The majority of bacteria in the colon are strict anaerobes and thus derive energy from fermentation. The amount, type, and balance of the main dietary macronutrients (carbohydrates, proteins, and fats) have a great impact on the large intestinal microbiota.¹⁸ The two main fermentative substrates of dietary origin are proteins and nondigestible carbohydrates, which are more energetically favorable for bacteria (Institute of Medicine (US) Food Forum, 2013).¹⁹ Microbial metabolism of dietary carbohydrates results mainly in the formation of gases and short-chain fatty acids (SCFA), the major bacterial fermentation product. SCFA influence microbial composition and directly affect host health. Examples of SCFA include acetate, propionate, and butyrate.^{18,20} Butyrate is the preferred energy source for colonocytes and has been shown to improve mucosal inflammation at the intestinal level.²⁰

Disease-associated changes in the microbiome increase the permeability of the intestine and allow intestinal bacteria and lipopolysaccharide to go through the various tissue barriers, which eventually lead to chronic systemic low-grade inflammation.²¹ As a result, the microbiota influences barrier integrity, promotes gut-associated lymphoid tissue maturation, tissue regeneration of the villi, and gut mobility, and reduces the permeability of epithelial cells lining the gut.^{12,22} Dysbiosis has been linked to the recent increased expression of functional and inflammatory disorders, such as irritable bowel syndrome and inflammatory bowel disease.²²

Several animal studies also showed the importance of a normal gut flora and support that the composition of the gut microbiome affects the mucosal immune system. One such study used a collagen-induced arthritis mice model and showed that partial depletion of natural gut flora with orally administered antibiotic enrofloxacin, which aggravates disease severity when compared with control mice.²³ Another animal study demonstrated that transfer of gut microbiota from diabetes-protected MyD88-deficient nonobese diabetic mice reduced insulinitis and significantly delayed the onset of diabetes.²⁴

Clinical studies provide further support for these animal studies. Culture-independent analysis of patients with Crohn's disease and ulcerative colitis revealed a distinct loss of symbiosis within the colonic mucosa compared with healthy individuals.²⁵ A population-based cross-sectional survey in Taiwan showed that a diet rich in protein and fat of animal origin, both associated with dysbiosis, is associated with a higher prevalence of asthma in teenagers.²⁶ Although pathogenesis of CRS has been widely investigated, the relationship of the gut microbiome and CRS is still not well known.

PREBIOTICS AND PROBIOTICS

The Russian immunologist, Metschnikow, first studied probiotics in the early 1900s.⁴ Recognition of the importance of the human microbiome concept in health and disease has motivated a strong revival of interest in both probiotics and prebiotics.⁴ Probiotics and prebiotics are increasingly being considered for the prevention and treatment of a variety of diseases. Human and animal studies have provided evidence that specific strains of probiotics are able to stimulate and regulate several aspects of natural and acquired immune responses.²⁷

Prebiotics are nondigestible fermentable carbohydrates and fibers (e.g., inulin-type fructans and galactooligosaccharides). Prebiotics are

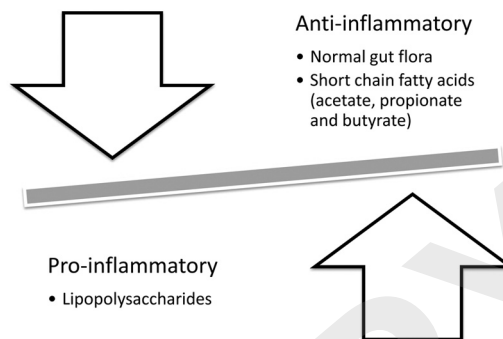


Figure 1. The gut microbiome: Factors that influence inflammation.

selectively fermented ingredients that facilitate specific changes that affect both the composition and/or activity of the gastrointestinal microflora.²⁸ However, the World Health Organization defines probiotics as “live microorganisms, which, when administered in adequate amounts, confer a health benefit to the host.”²⁹ Probiotics contain at least 10–100 million bacteria per gram or milliliter of food. Only a few types of bacteria meet the characteristics to be the ideal probiotic, and these include *Bifidobacteria*, *Lactobacillus casei*, and *Lactobacillus acidophilus*.³⁰

Probiotics may modulate the immune and inflammatory response by the recognition of specific microbial molecules or patterns by Toll-like and nucleotide-binding oligomerization domain-like receptors.^{4,31} They are also involved in the lipoteichoic acid pathway, which can stimulate T cells to release anti-inflammatory cytokines, e.g., interleukin (IL) 10.³² Moreover, several *in vitro* studies showed that *Lactobacillus* strains possess antioxidant properties.³³ These strains are able to inactivate reactive oxygen species *via* enzymic mechanisms, such as the coupled nicotinamide adenine dinucleotide oxidase-peroxidase system and catalase,³⁴ and stimulate interferon- α production, which influences a Th-1 phenotype and suppresses a Th-2 response.^{4,35} The well-studied responses in the gut though may not be concordant to respiratory responses.

Probiotic consumption has been shown to be beneficial in chronic respiratory diseases^{4,36,37} and thus may be beneficial in the prevention and treatment of chronic rhinitis and CRS.⁴ In animal models of allergen sensitization and murine models of asthma and allergic rhinitis, orally administered probiotics can decrease allergen-specific immunoglobulin E production by altering systemic cytokine production.³⁸ Furthermore, these probiotics have been shown to decrease airway hyperresponsiveness and inflammation by inducing regulatory mechanisms.³⁸ A randomized placebo-controlled trial demonstrated that *Lactobacillus paracasei* subspecies *paracasei* LP-33 improved the quality of life of subjects with persistent allergic rhinitis who were concurrently being treated with an oral H1 antihistamine.³⁹

Upper respiratory tract infections often precede rhinosinusitis, and a Cochrane review in 2011 supported the use of probiotics that showed that probiotics were better than placebo in reducing the number of participants who experienced an episode of acute upper respiratory tract infections and reduced antibiotic use.⁴⁰ A meta-analysis provided evidence that the effect of probiotics, specifically *Lactobacillus* and *Bifidobacterium* strains, reduces the duration of respiratory illness episode in otherwise healthy children and adults.⁴¹ The probiotic strain *L. casei* DN-114 001 in the elderly was associated with a decreased duration of upper respiratory tract infection, e.g., rhinopharyngitis.⁴² However, Mukerji *et al.*⁴³ showed no significant improvement on sinonasal quality-of-life scores in patients who orally took *L. rhamnosus*.

Topical treatment with probiotics for CRS has also recently been evaluated and has shown some promising results. Patients with CRS have been shown to have reduced bacterial diversity that results in a

Table 1. Summary of diet options to potentially modify inflammation in RCRS

Proposed Mechanism of Action	Diet Examples	Foods to Include
<i>Via</i> modification of gut microbiome	High in nondigestible carbohydrates and limited in proteins and fats Prebiotics and/or probiotics	Fruits and vegetables Prebiotics: Fermentable carbohydrates and fibers (inulin-type fructans and galactooligosaccharides) Probiotics: <i>Bifidobacteria</i> , <i>L. casei</i> and <i>L. acidophilus</i>
<i>Not via</i> modification of gut microbiome	Low salicylate diet MD PUFA diet	Meats, dairy, certain fruits and vegetables Cereals, fruits, vegetables, legumes, tree nuts, seeds, and olives Omega-3 fatty acids: plants and fish Omega-6: soy, corn, safflower, and sunflower oils

depletion of lactic acid-producing bacteria, which, in turn, can cause an increase in the amount of *Corynebacterium tuberculoasteracium*, which is pathogenic and contributes to the development of sinusitis. Abreu *et al.*⁸ showed that the topical application of *Lactobacillus sakei* in mice may have a protective effect against colonization by *C. tuberculoasteracium*. Cleland *et al.*⁴⁴ further showed, by using a mice model of sinusitis, that *Staphylococcus epidermis* may have a protective effect against *Staphylococcus aureus*, possibly by altering bacterial interactions. Although the evidence is limited in relation to CRS, the results are promising in potentially preventing acute on chronic episodes.⁴⁵

The treatment option of modulating the microbiome through the administration of pre- or probiotics remains controversial because not all studies demonstrated a consistent positive impact on humans.^{45,46} However, the possibility exists that prebiotics or probiotics may offer a realistic prophylactic or therapeutic option for inflammatory diseases linked to microbiome dysbiosis, *e.g.*, CRS.⁴

SPECIAL DIETS

Although inflammation is an essential immune response, chronic inflammation results in diseases, *e.g.*, CRS. Reducing inflammation through dietary modifications may yield a significant health benefit to patients with CRS. A few specific diets and their relationship to CRS were reviewed (Table 1).

Influence of Diet on the Microbiome

The relationship between the microbiome and host diet is a subject of great interest. Dietary macronutrients (fats and sugars) can induce inflammation through activation of an innate immune receptor, Toll-like receptor 4.²¹ Several studies confirmed that a chronic intake of diets low in fruits and vegetables and high in fats and sugars may alter microbial composition and mucosal structure and function. A diet that is rich in insulinogenic foods and proteotoxins is likely detrimental to the gut microbiota and may contribute to obesity and other chronic diseases.¹⁶ However, polysaccharides contribute to the proliferation of “good bacteria” and improve microbial diversity in the human gut.⁴⁷ Gut health can be maintained through the consumption of a diet high in nondigestible carbohydrates and limited amounts of proteins or fats.^{15,48}

Nonmicrobiome Dietary Strategies

Low-Salicylate Diet. Aspirin-exacerbated respiratory disease (AERD) is described as the quadrad of asthma, eosinophilic rhinosinusitis, and nasal polyposis, and the onset of respiratory reactions after the ingestion of aspirin.⁴⁹ Patients with AERD are generally more treatment-resistant to standard therapies.⁵⁰ Aspirin intolerance in the setting of AERD is not an immunoglobulin E-mediated reaction but rather due to abnormal metabolism of arachidonic acid, which causes an imbalance in the production of leukotrienes and prostaglandins.^{51,52} Some foods contain high levels of nonacetylated salicylates and have been shown to inhibit cyclooxygenase gene expression

selectively,⁵³ which contributes to nasal polyps in patients with AERD.^{53,54} Therefore, patients with AERD are more likely to react to dietary salicylates.

A Scottish systematic review by Wood *et al.*⁵⁵ in 2011 demonstrated that the intake of dietary salicylates for men and women was 4.42 mg and 3.16 mg per day, respectively.^{55,56} Links between dietary salicylates and asthma have been determined based on studies of aspirin in patients with asthma.⁵⁷ Sommer *et al.*⁵¹ demonstrated through a randomized cross-over trial that patients with AERD who followed a low-salicylate diet for 6 weeks had improvements in both subjective and objective sinonasal outcome scores compared with a regular diet for 6 weeks.

Mediterranean Diet. The traditional Mediterranean Diet (MD) is generations old and originated in the Mediterranean basin. The diet was originally based on Mediterranean agricultural and rural models.⁵⁸ The MD includes a diet rich in plant foods (cereals, fruits, vegetables, legumes, tree nuts, seeds, and olives), with olive oil as the principal source of added fat, along with high-to-moderate intakes of fish and seafood; moderate consumption of eggs, poultry, and dairy products (cheese and yogurt); low consumption of red meat; and a moderate intake of alcohol (mainly wine during meals).⁵⁹

Numerous epidemiologic and clinical studies revealed that the anti-inflammatory properties of the MD help reduce the risk of developing type 2 diabetes, cardiovascular diseases, metabolic syndrome, certain neurodegenerative diseases, and cancer.^{59,60} A randomized trial that compared an MD versus a low-fat diet showed that patients in the MD group had a significant reduction in CD40 expression on monocyte surfaces, C-reactive protein, and IL-6 compared with the patients on the low-fat diet.⁶¹ The supplementation of virgin olive oil and nuts to the MD diet contributes to the anti-inflammatory effects by reducing serum C-reactive protein and IL-6 as well as chemokines and endothelial and monocyte adhesion molecules.⁶² Moreover, an interventional study in a Crohn’s disease population demonstrated that adherence to an MD for 6 weeks reduced markers of inflammation and normalized the microbiota.⁶³ Interestingly, an MD has been shown to be protective for patients with asthma.⁶⁴ Until now, the relationship between MD and CRS has not been studied; however, given the multitude of anti-inflammatory benefits of an MD, following the diet would be an interesting adjunctive approach in the treatment of CRS.

Polyunsaturated Fatty Acid. Polyunsaturated fatty acids (PUFA), such as omega-3 and omega-6 fatty acids, are essential fatty acids because they are not found endogenously. PUFAs play an important role in human health and disease.

Long-chain omega-6 fatty acids include linoleic, γ -linolenic, and arachidonic acids. The typical Western diet contains at least 20-fold more omega-6 than omega-3 fatty acids. This predominance of omega-6 fatty acids is due to the abundance of linoleic acid, which is present in high concentrations in soy, corn, safflower, and sunflower oils.⁶⁵ Omega-3 fatty acids include the long-chain α -linolenic acid (ALA), eicosapentaenoic acid, and docosahexaenoic acid (DHA).⁶⁶

There are two main dietary sources for omega-3 fatty acids: plants and fish. Plant oils from walnuts, flaxseed, and canola contain the omega-3 fatty acid ALA, and the most-concentrated food source of eicosapentaenoic acid and DHA is fatty fish, such as albacore tuna, salmon, mackerel, sardines, and herring.⁶⁷

After consumption, PUFAs are incorporated into cell membranes, where they modulate membrane protein function, cellular signaling, and gene expression.⁶⁸ However, dietary omega-3 fatty acids compete with omega-6 fatty acids for incorporation into cell membranes. When omega-6 fatty acids predominate in cell membranes, proinflammatory mediators, such as thromboxanes, prostaglandins, and leukotrienes, are produced *via* the cyclooxygenase and 5-lipoxygenase pathways. On the contrary, the presence of omega-3 fatty acids promotes secretion of anti-inflammatory prostaglandins and less potent leukotrienes, which results in a shift to a milieu of less inflammatory mediators.²⁷

Many epidemiologic and clinical studies support the anti-inflammatory activity of omega-3 fatty acids. Several studies showed that omega-3 fish oil fat emulsion-based parenteral nutrition alleviates inflammatory reactions, improves lung gas exchange, liver function, antioxidant status, and fatty acid composition of plasma phospholipids, and reduces the rate of inflammatory complications.^{69,70} In addition to their anti-inflammatory activity, very-long-chain omega-3 fatty acids have well-described effects on various risk factors for cardiovascular disease.⁷¹

However, the role of dietary PUFA in allergic inflammation and asthma is controversial, with mixed reports. A systematic review and meta-analysis indicates that supplementation with omega-3 and omega-6 oils do not offer benefits for the primary prevention of sensitization or allergic disease.⁷² PUFAs were demonstrated to reduce serum eosinophils and leukotrienes in patients with asthma.⁷³ Moreover, a recent Japanese cohort study linked maternal intake of ALA and DHA during pregnancy to a reduced risk of wheezing in 2-year-old children as well as an increased risk of eczema and allergic rhinitis with the intake of ALA.⁷⁴ PUFA has not been considered as part of the treatment of CRS to date.

CONCLUSION

A new treatment paradigm based on other chronic diseases can be considered through the complementary aspects of nonpharmacologic dietary modifications and known existing pharmacologic options for RCRS. Histopathologic assessment of sinonasal mucosa in patients with RCRS may help to provide more information on the specific therapies that would benefit an individual patient, *e.g.*, dietary modifications.⁷⁵ Evidence exists that anti-inflammatory diets may offer an additional means of reducing inflammation in other chronic diseases and may thus find a role in the management of patients with RCRS. Additional clinical trials will help to further validate dietary modifications as an interesting adjunct to existing management strategies for RCRS.

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