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Concise Communication

The Role of Nutrition, Supplements, and the Gut Microbiome in Vitiligo

Marlee Hewitt, MD, Karan Pandher, MD, Indraneel Prabhu, MD, Aunna Pourang, MD, Nada Elbuluk, MD, MSc, Richard H. Huggins, MD

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Affecting up to two percent of individuals worldwide, vitiligo is an acquired chronic depigmenting skin disease associated with a host of other autoimmune disorders. The pathogenesis is complicated and multifactorial with evidence showing that environment, genetics, oxidative stress, and one's immune system play a role. More recently, theories involving the role of nutrition and the gastrointestinal microbiome in the pathogenesis of vitiligo have been posited. Increased oxidative stress and inflammation are the underlying mechanisms at the forefront of such theories. Potential improvement of vitiligo by the consumption of antioxidant supplements or certain foods has been explored in the literature. Additionally, gut microbiome alterations have been associated with the development of vitiligo. This article provides an overview of the available research on the role of nutrition and the gastrointestinal microbiome in vitiligo.

INTRODUCTION

Vitiligo is a chronic autoimmune disorder, characterized by cutaneous depigmentation.[1] Currently, it is estimated to affect between 0.2% and 1.8% of the global population.[1] Individuals living with vitiligo can experience a poor quality of life, psychosocial issues, and comorbidities such as autoimmune thyroid disease, alopecia areata, and diabetes mellitus.[2] While the exact etiology of vitiligo is not well understood, it is thought to be multifactorial with a large interplay between the immune system, genetics, oxidative stress, and the environment.[3] The adaptive immune system plays a role in the pathogenesis of vitiligo by inducing CD8 T-cells to destroy melanocytes after responding to cytokines released in the skin.[3] The innate immune system is also involved in vitiligo development, as there is dysregulation in innate activation as a response to melanocyte stress, which results in an increased production and distribution of pro-inflammatory cytokines by natural killer cells.[3] Additionally, genetics are thought to play a role as genome-wide association studies have confirmed that there are several common genetic variants in the innate and adaptive immune system of vitiligo patients.[3] Evidence also suggests that an imbalance of reactive oxygen species (ROS) causes a cycle of melanocyte destruction due to an inability to manage cellular stress in vitiligo patients.[3] The interplay between these mechanisms culminates in the destruction of melanocytes and the subsequent depigmentation of skin.

It has previously been determined that the microbiome is intricately connected to immune homeostasis, gene expression, and oxidative stress suggesting that it may have a role in one or more of the postulated theories for the pathogenesis of vitiligo. Additionally, gut microbiome dysbiosis is associated with diseases such as lupus and psoriasis, which supports the possibility of a role for it in other autoimmune diseases such as vitiligo. Therefore, understanding the possible contributions of nutrition and the gastrointestinal microbiome to vitiligo is important to further elucidate disease pathogenesis and potentially expand its treatment repertoire. This paper aims to discuss the available research on the potential involvement of nutrition and the gut microbiome in vitiligo.

THE ROLE OF SUPPLEMENTS IN VITILIGO

Markers of oxidative stress are found in the blood and epidermis of individuals with vitiligo, and this oxidative stress is postulated to alter melanocyte structure and activate autoimmune-mediated melanocyte destruction.[4-7] As such, the role of antioxidants and antioxidant-containing foods may be of increasing importance in a vitiligo patient's overall treatment plan. Thus, antioxidant supplementation is sometimes recommended in clinical practice as part of the treatment of vitiligo, more specifically for support in disease stabilization and as adjuvant therapy complementing phototherapy.[8,9] There have been several studies that have investigated the use of different antioxidant supplementation in the treatment of vitiligo. Supplements that have been found to be beneficial for those with vitiligo include vitamin E, alpha-lipoic acid, *Gingko biloba*, PLE, and *Cucumis melo*.[10] These supplements work as antioxidants to inhibit the destruction of melanocytes caused by oxidative stress. Additionally, we hypothesize that it is possible that these supplements may help to reduce negative changes to the gut microbiome in vitiligo patients because of their ability to reduce oxidative stress, a process which has been previously linked with gut dysbiosis.

Table 1. Dietary Compounds that May Play a Role in Vitiligo

Effect on Vitiligo	Foods/Compounds	Comments
Potentially protective	Small red bean	• These are the top ten foods with the highest total antioxidant capacity[10]
	Wild blueberry	
	Red kidney bean	
	Pinto bean	
	Cultivated blueberry	
	Cranberry	
	Cooked artichoke	
	Blackberry	
	Prune	
	Raspberry	
	Quercetin	• Cytoprotective against H_2O_2-induced cell death[11] • Found in green tea, apples, onions, and berries
Potentially harmful	Gluten	• Possible relationship between vitiligo and celiac disease[14] • Case reports have shown repigmentation with gluten free diet[14,15]

THE ROLE OF NUTRITION IN VITILIGO

In addition to antioxidant supplements, there are also antioxidant-containing foods that may potentially be protective against vitiligo (Table 1). The foods with the greatest antioxidant capacity include small red beans, red kidney beans, wild blueberries, cultivated blueberries, cranberries, blackberries, raspberries, prunes, and artichokes among many others.[10] Although these foods have not been specifically tested in individuals with vitiligo, increased consumption of these foods rich in antioxidants may confer the benefit of reducing oxidative stress in these individuals which may help overall with their vitiligo. Additionally, certain dietary compounds found in foods have been studied and shown to be potentially protective in vitiligo. For example, quercetin, found in green tea, apples, onions, and berries, is cytoprotective against H_2O_2-induced cell death, one of the processes involved in vitiligo pathogenesis.[11,12] Diet has also been studied for other immune-mediated dermatologic diseases such as psoriasis. A study evaluating psoriasis and the Mediterranean diet highlighted the validity and importance of adhering to healthy diets to maintain a healthy body composition and improve skin disease; psoriatic area and severity index and adherence to a Mediterranean diet was negatively correlated ($r = -0.576$, $p<0.001$).[13] Thus, it is reasonable to consider that there may be a similar benefit in vitiligo, and further studies should investigate the utility of the Mediterranean diet in individuals with vitiligo.

Although there are foods and supplements that appear to be beneficial for vitiligo patients, there are also foods which may contribute to vitiligo exacerbation through an increase in inflammation and oxidative stress.[16] For example, gluten may be detrimental to vitiligo patients. Improvements in vitiligo after consuming a gluten-free diet have been reported in some case reports, in individuals both with and without celiac disease.[14,15] In one cross-sectional case control study, IgA antibodies to endomysium and transglutaminase were detectable in 3.1% of vitiligo patients, as opposed to none in the control group.[17] While these individuals did not have a prior diagnosis of celiac disease, the authors suggested that a common autoimmune mechanism may underlie both disorders. Nevertheless, more evidence is required to confirm the benefits of a gluten free diet in vitiligo patients.

THE ROLE OF THE GUT MICROBIOME IN VITILIGO

In addition to nutrients and diet, the gastrointestinal microbiome itself may also play a role in vitiligo. The gut microbiome has been proven to play an integral role in overall health through several mechanisms including autoimmune and anti-inflammatory roles. Specifically, gut microbiome dysbiosis has been shown to play a role in other skin conditions such as psoriasis. Given this, it is possible that a similar mechanism may exist with changes to the gut microbiome of patients with vitiligo.

To date, there are a handful of studies that have sought to investigate the link between the gut microbiome and vitiligo. One such study conducted by Dellacecca et al found that the gut microbiome of a murine model with vitiligo played a key role in its development of vitiligo.[18] Treating mice with oral ampicillin resulted in acceleration of vitiligo development not attributable to intestinal oxidative stress. Conversely, the experimental mice treated with oral neomycin had a decreased development of vitiligo. Neomycin-treated mice did not exhibit upregulation of CD8+ T cells as seen in the ampicillin-treated group, although they did exhibit more regulatory T-cells compared to untreated mice. In addition to decreased gut microbial diversity observed in both groups, gut microbial richness also differed among treated groups. A predominance of *Pseudomonas* species was seen in the ampicillin group, and *Bacteroides* species in the neomycin group, the latter of

Table 2. Bacteria of the Gut Microbiome that May Play a Role in Vitiligo

Effect on Vitiligo	Bacteria
Potentially protective	• *Bacteroides*[18-21]
Potentially harmful	• *Pseudomonas*[19-21] • *Psychrobacter*[19-21] • *Butyricicoccus*[19-21] • *Escheria Shigella*[19,21] • *Ruminococcus 2*[19] • *Gemmobacter*[19] • *Subdoligranulum*[19,21]

which are known to have an anti-inflammatory effect through the upregulation of regulatory T-cells.[6,18] These findings raise the possibility that microbial dysbiosis may be a pathogenic factor of vitiligo, and as such warrant further studies in humans with vitiligo.

To investigate the link between the gut microbiome and vitiligo further, Ni et al conducted a case control study comparing the gut microbiome between thirty vitiligo patients and thirty matched healthy controls. Using 16S rRNA sequencing, they found that the gut microbiome of individuals with vitiligo was subject to dysbiosis, having distinct gut microbial β-diversity compared to their healthy counterparts.[19] Additionally, they determined that the vitiligo patients had a lower rate of *Bacteroidetes* (54.4 vs. 63.1%, $p<0.05$), a higher rate of *Firmicutes* (35.0 vs 27.2%, $p<0.05$), and a lower *Bacteroidetes: Firmicutes* (1.6:1) compared to healthy controls (2.3:1). Similarly, a case control study done by Bzioueche et al compared the gut microbiome of ten individuals with vitiligo to ten healthy controls. The results showed that vitiligo patients had a decreased relative abundance of *Bacteroides* with an increased *Firmicutes* to *Bacteroidetes* ratio in individuals with vitiligo compared to healthy controls ($p<0.01$).[20] Additionally, the gut microbiome of the vitiligo patients in this study was shown to have lower gut microbial α-diversity compared to the microbiome of the controls. Lastly, Wu et al investigated the gut microbiome of thirty-two young-adults with vitiligo and twenty-seven healthy controls using 16s rRNA sequencing. Like the previous two studies, they also determined that the composition of the microbiome between groups was significantly different, with an increased *Firmicutes* to *Bacteroidetes* ratio in the vitiligo group (*t*-test, $p<0.05$).[21] All three studies identified potential bacteria of the gut microbiota that may play a role in the progression of vitiligo (Table 2).

Given that *Bacteroides* was found to have a protective role against skin depigmentation in the mouse model, and that all three studies investigating the gut microbiome of individuals with vitiligo found a significant decrease in *Bacteroides*, there appears to be a reproducible commonality between these studies that links a decrease in *Bacteroides* to the possible progression of vitiligo. Given that it has been previously seen that *Bacteroides* is involved in the regulation of the immune system, this indicates a connection between changes in the gut microbiome and the dysregulation of the immune system thought to play a role in the pathogenesis of vitiligo. Additionally, the three case control studies demonstrated an increase in certain bacteria, with all three finding an increase in *Pseudomonas*, *Psychrobacter*, and *Butyricicoccus*. This may indicate that an increase in these bacteria could impact the progression of depigmentation in vitiligo. However, it is unclear as to what these bacteria may be producing that is contributing to the pathogenesis of vitiligo. As a result, further studies are necessary to understand the function of these bacteria within the gut microbiome of individuals with vitiligo to further characterize the possible role of the gut microbiome in the pathogenesis of disease.

Additionally, the studies that assessed the gut microbiome in individuals with vitiligo to date have used 16S rRNA-based analysis. However, this may need to be expanded to analyze whole-genome sequencing in further studies so that the functional roles of the involved bacteria of the gut microbiome can be properly assessed and understood. Lastly, in addition to the bacteria studied in the gut microbiome, further studies should also consider assessing the role of fungi and yeast of the gut may play in disease pathogenesis.

Considering the possible role of diet and nutrition in the progression of vitiligo and the gut microbiome in vitiligo, it is also reasonable to consider how these factors might interact. Diet has been found to affect the gastrointestinal microbiome, with changes in key nutrients such as proteins, fats, carbohydrates, probiotics, and polyphenols affecting the composition of the microbiome.[22] However, the impact of diet and nutrition on the gut microbiome of vitiligo patients has not been studied specifically. Nevertheless, it is possible with further exploration that gut microbiome modulation through diet modification may be employed as part of the treatment plan of vitiligo.

CONCLUSION

Vitiligo is a chronic autoimmune disorder with a multifactorial pathogenesis leading to destruction of melanocytes and subsequent depigmentation of the skin. In addition to one's environment, genetics, and the immune system playing a role in the pathogenesis of vitiligo, the evidence reported in this review suggests that nutrition and the gut microbiome may also play important roles. Diet and sup-

plementation should be explored as potentially important adjunctive parts of treating vitiligo as these can help to reduce oxidative stress and may also help to reduce changes in the gut microbiome. Further studies, such as randomized controlled dietary interventions, are needed to further explore these concepts. Further studies are also necessary to characterize the function that the gut microbiome plays in disease pathogenesis.

DISCLOSURES

Dr. Hewitt, Dr. Pandher, and Dr. Prabhu have no disclosures to report. Dr. Pourang has previously served as an investigator for Pfizer, Incyte, Biofrontera, L'Oréal, Arcutis, and the Immune Tolerance Network. Dr. Elbuluk has served as a consultant, advisory board member, and/or speaker for Avita, Incyte, VisualDx, La Roche Posay, Beiersdorf, Unilever, Allergan, Eli Lilly, Galderma, Pfizer, Takeda, Abbvie, Janssen, Sanofi, L'Oréal, McGraw Hill, Dior, Medscape. She has grant funding from Pfizer, has received royalties from McGraw-Hill and has stock options in VisualDx. Dr. Huggins has served as an investigator for Pfizer, Incyte, Arcutis, and the Immune Tolerance Network, has been an advisory board member for Incyte and is a Board Member of the Global Vitiligo Foundation.

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