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The Role of Diet in Hyperpigmentation: A Systematic Review Examining the Impact of Nutrition on Skin Pigmentation

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ABSTRACT

Introduction: Hyperpigmentation is a common skin condition characterized by excess melanin production, resulting in dark patches or spots on the skin. While genetic, sun exposure, and hormonal factors contribute to hyperpigmentation, emerging evidence has demonstrated a potential link between diet and skin pigmentation. This systematic review aimed to investigate the impact of specific nutrients, dietary patterns, and interventions on skin pigmentation disorders.

Methods: A comprehensive literature search was conducted in PubMed, Embase, Scopus and Cochrane using relevant keywords and MeSH terms. Inclusion criteria included manuscripts published within the last ten years, in the English language. Studies encompassed research on the association between diet, nutrition, and hyperpigmentation. Two independent reviewers assessed study eligibility based on predetermined criteria. Data extraction covered characteristics, participant demographics, dietary factors, hyperpigmentation outcomes, and relevant findings.

Results: This systematic review synthesized and analyzed the impacts of diet on hyperpigmentation and assessed the effectiveness of dietary interventions in managing skin pigmentation disorders based on existing literature. Primary outcomes included changes in hyperpigmentation severity, melanin production, and skin color improvement. Secondary outcomes may explore the role of specific nutrients (e.g., antioxidants, vitamins, minerals), dietary patterns (e.g., Mediterranean diet, low glycemic index diet), and potential underlying mechanisms.

Conclusion: This review provides valuable insights into the relationship between diet and hyperpigmentation. Our findings identify dietary strategies or interventions for managing hyperpigmentation and improving skin pigmentation disorders.

INTRODUCTION

Hyperpigmentation is the abnormal accumulation of pigmentation resulting in localized or widespread darling of affected areas. Common causes of hyperpigmentation include, but are not limited to, postinflammatory hyperpigmentation, melasma, solar lentigines, ephelides, and cafe-au-lait macules. [1] Pigmentation of the skin is multivariate and can be influenced by the amount of melanin, degree of vascularity, presence of carotene, and thickness of stratum corneum. [1]

Currently, there are a myriad of treatments for hyperpigmentation respective to its etiology and progression. Topical treatments are widely used for targeted hyperpigmentation treatment, with hydroquinone as the gold standard treatment. [2]. Hydroquinone specifically acts to reduce epidermal hyperpigmentation by inhibiting the production of melanin through the inhibition of tyrosinase, ultimately preventing the conversion of L-DOPA to melanin. [41]. Oral drugs are considered a second-line treatment for hyperpigmentation, and Tranexamic is the most common. Tranexamic works by reducing tyrosinase enzyme activity by inhibiting UV-induced plasmin activity, causing a reduction in arachidonic acid, prostaglandins, and downstream tyrosinase. [2] Recently, laser therapy with intense pulsed light (IPL) has shown improvements in the treatment of hyperpigmentation, however, the safety and efficacy of this therapy are still debatable. [2]

A balanced human diet of both macronutrients and micronutrients is essential for the optimal development and efficiency of metabolic processes, including adequate vitamin levels [3]. The most common causes of vitamin deficiencies globally are due to poor quality or quantity of food, increased dietary requirements, greater metabolic losses, or decreased gastrointestinal absorption. [3] These can be greatly affected by psychological, social, environmental, and financial factors. General symptoms of malnutrition include weight loss, muscle wasting, and failure to thrive. [3] However, specific vitamin and mineral deficiencies can present with unique manifestations such as megaloblastic anemia, microcytic anemia, edema, immunosuppression, diarrhea, and ocular manifestations. [3]. These vitamin and mineral deficiencies have also been suggested to play a role in the development of epidermal hyperpigmentation, though these relationships have not been well outlined. These vitamins and minerals include but are not limited to, vitamins C, B3, B12, D and Iron. In this review, we aim to identify the key vitamin and mineral deficiencies that lead to dermatologic manifestations, explore their roles in the development of hyperpigmentation, and define their treatments.

METHODS

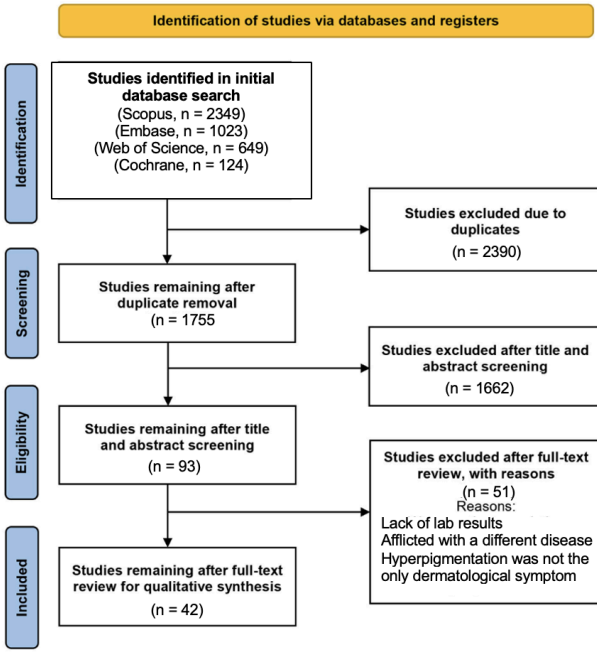

Figure 1: Process flow diagram of literature screening using PRISMA guidelines

Search Strategy

An electronic literature search was conducted using four databases: Scopus, Embase, Cochrane Library, and Web of Science. This search was based on studies analyzing the results of patients with a variety of vitamin deficiencies, such as Vitamin A, Vitamin B3, Vitamin B12, Iron, Vitamin C, Vitamin D, and Cronkhite Canada syndrome, which causes malabsorption of multiple essential vitamins and leads to hyperpigmentation.

Eligibility criteria

The following included: (1) randomized controlled trials, non-randomized controlled trials, cohort studies, case series, and case reports (2) diet-causing hyperpigmentation studies; (3) the investigation provided reliable data that could be examined, including the total number of participants and insightful outcomes of each metric.

The following criteria were excluded: (1) research that did not provide adequate information about experimental or control group results; (2) in vitro and animal studies; (3) research reported in foreign languages; (4) meta-analyses, systematic reviews, and other reviews (excluding primary sources); (5) studies lacking full-text or only presenting abstracts;

Data Extraction

A search of all four databases was conducted from inception until August 12, 2023, to find published studies. A total of 1755 identified articles were independently reviewed for eligibility using Rayyan systematic review software by two authors (F.A. and R.C.). The inclusion of 93 articles was determined based on a full-text review of their title and abstracts. A full-text review of the studies resulted in 42 remaining studies. Conflicts were resolved through discussion or consultation with an unbiased third investigator (R.A). The study design, participant count, deficiency and hyperpigmentation parameters, and study findings were extracted. An overview of each vitamin deficiency was provided. Because of the wide variety of tests evaluated and their non-standardized presentation, statistical analysis was not feasible.

DISCUSSION

Understanding the role of nutritional deficiencies in diffuse hyperpigmentation across common areas, such as the face, skin folds, dorsal, and palmar surfaces, is essential in formulating effective treatment methodologies. Diet can act as a preventive and additional form of treatment to help resolve and maintain dermatologic treatment of hyperpigmentation. This systematic review

identified 42 articles that investigated the role of diet in hyperpigmentation. Amongst these articles, nutritional deficiencies in Vitamin C, iron, and B12, B3, and D were investigated for their role in hyperpigmentation.

Vitamin C

Vitamin C, or ascorbic acid, is an essential antioxidant to protect the skin from harmful reactive oxygen species. Poor nutritional intake and limited access to fresh foods have been correlated to an increased risk of deficiency with this vitamin [4] with studies showing a higher prevalence in lower and middle-income parts of the world than in higher-income areas [7]. Vitamin C deficiencies have been linked to hyperpigmentation disorders and a prominent example is Porphyria Cutanea Tarda (PCT) [5]. Studies have shown a relationship between vitamin C deficiency and PCT, with the disorder being characterized by lesions developing on the skin due to the lack of protection from UV-induced stress from the sun [5]. Vitamin C can inhibit the oxidation of CYP1LA2, therefore decreasing the conversion of uroporphyrinogen into uroporphyrin via oxidation by the cytochrome [6]. One main treatment for PCT is oral supplementation of ascorbic acid, which has been shown to reduce oxidative damage caused by prolonged sun exposure without proper protection [6]. Topical vitamin C has been suggested as another potential treatment for PCT, whose effects have yet to be observed and require further studies to determine its effectiveness [6]. Addressing Vitamin C deficiency through adequate oral supplementation is crucial as a preventative intervention. Though topical Vitamin C has been explored in the literature, its effectiveness is still in question and warrants further investigation.

Iron

Iron deficiency anemia is associated with the development of melasma, a skin condition characterized by hyperpigmented facial patches. The development of melasma is attributed to skin melanin degradation due to iron deficiency. Iron deficiency anemia (IDA) affects around 30% of the global population, making it the most prevalent nutritional deficiency [12]. Anemia is characterized by a hemoglobin level below 120 g/L in women and 130 g/L in men [12]. A ferritin level below 100 ug/L and elevated inflammatory markers (e.g. C-reactive protein) serve as a diagnostic criterion for iron deficiency anemia [11]. Physiologically increased iron demands in children, adolescents, young, and pregnant women contribute to absolute iron deficiency. Factors like decreased iron consumption, poor absorption, or chronic blood loss exacerbate this even more [14]. These factors set the stage for understanding conditions like melasma, characterized by irregularly outlined hyperpigmented facial patches that predominantly affect young to middle-aged women. Research suggests a link between melasma and iron deficiency, particularly in nonpregnant women who exhibit reduced serum iron levels [8]. Lower mean ferritin levels are also observed in individuals with melasma compared to controls, further establishing the association with iron deficiency [9]. Low iron ions may enhance hyperpigmentation in melasma by impeding melanin degradation [13]. Conversely, widespread hyperpigmentation can also result from an intravenous iron infusion. A case report showed that a patient, who experienced an urticarial rash during the transfusion, later developed brown discoloration indicative of iron deposition [10]. This observed increase in melanin associated with iron infusion contradicts the known mechanism of iron ions accelerating melanin degradation [13]. This suggests unexplored mechanisms in the interplay of iron levels and melanin dynamics, warranting further scientific investigation. Therefore, it is important to remember that abrupt iron infusion can also lead to hyperpigmentation,

presenting as a brown discoloration. Hydroquinone monotherapy and triple combination cream are traditional therapies for melasma, however, recent studies have shown improvements with the use of chemical peels, laser therapies, and oral tranexamic acid as well [15].

Vitamin B12

Vitamin B12, or cobalamin, is a water-soluble substance obtained in the diet from animal foods or added by fortification and supplementation (16). The vitamin B12- intrinsic factor complex is absorbed in the distal ileum, where it can then be freed and used in various pathways of cellular metabolism. Due to its regulatory influence on metabolic processes and homeostasis within the human body, its imbalance is implicated in hematological, gastrointestinal, and neurological disorders. The literature search highlighted nine articles linked to Vitamin B12 deficiency and its impacts on hyperpigmentation (17, 24, 25, 26). These studies explored the impact of early intramuscular or oral supplementation as a means to reverse hyperpigmentation induced by a Vitamin B12 deficiency. Most often, this form of hyperpigmentation presents on the knuckles, over the dorsum of the hands and feet, and in the skin folds as well (22). Mucocutaneous manifestations are less common, though still very important in diagnosing and understanding vitamin B12-associated disorders and its role within the human body. Vitamin B12 is a co-factor in many vital mechanisms in the body. It is involved in DNA synthesis, the methylation cycle, fatty acid and amino acid metabolism, cell division, myelin synthesis, blood cell formation, antioxidant defense, and wound healing (16,18). Vitamin B12 is even implicated in acne pathogenesis between the host and skin microbiota (19). Of interest to this review is its influence on melanin production, contributing to pigmentation disorders.

Vitamin B12 can be stored in excess within the liver, thus making its incidence of deficiency less likely. However, if B12 cannot be absorbed, it can result in hepatic depletion and subsequent deficiency (20). Plasma concentration below 200 pg/ml (148 pmol/L) is deficient (21). Skin hyperpigmentation, vitiligo, glossitis, angular stomatitis, and hair changes have all been noted as symptoms of vitamin B12 deficiency, though the symptoms are not suggestive of deficiency alone (17, 23). Skin hyperpigmentation from vitamin B12 deficiency is typically observed more often in darker skin and presents in a localized distribution over the dorsum of the hands, feet, and knuckles as well as in skin folds (22).

The exact cause of hyperpigmentation from vitamin B12 deficiency remains to be determined. However, the most accepted theory stands that increased tyrosinase levels are associated with hypomelanosis (21,23). Low glutathione concentration leads to decreased DNA synthesis and cell division. The level of glutathione decreases with vitamin B12 deficiency. Since glutathione is a tyrosinase inhibitor, as the concentration of this enzyme increases it stimulates melanocytes to produce melanin resulting in hyperpigmentation (6,8).

Kannan et al reported two cases of vitamin B12 deficiency in which skin lesions were the only clinical signs of disease. It concluded that a deficiency of vitamin B12 should be considered in the differential diagnosis of individuals who present with skin and mucosal lesions, especially lesions that do not respond to conventional treatments (17). Prompt vitamin B12 supplementation can reverse consequent hyperpigmentation in these instances (17,24,25,26).

An et al explored the effect of methylcobalamin (MeCbl), an active form of vitamin B12, on melanocytes under oxidative stress by hydrogen

peroxide (27). Oxidative stress is a crucial determinant in vitiligo development, and MeCbl has been shown to oppose oxidative stress and reduce apoptosis in various disease models. Treatment with MeCbl was found to increase melanocyte viability and melanin content while reducing the accumulation of reactive oxygen species and subsequent apoptosis. While the exact pathway is still unknown, this study suggests the protective effects were attributed to the upregulation of the Nrf2/HO-1 pathway, and it indicates MeCbl as a potential treatment option for vitiligo (27).

Vitamin B3

Vitamin B3 (nicotinic acid, niacin) is used in the synthesis of the NAD+ family of coenzymes, which aids in cellular energy, metabolism, and cellular defense systems [28]. It plays a vital role in oxidation-reduction reactions, specifically as a vital component in coenzyme 1 and coenzyme 2. Pellagra is a nutritional disorder caused by Vitamin B3 deficiency, which results in systemic disease with clinical symptoms present on the skin, in the gastrointestinal tract, and nervous system [29]. Most commonly presenting with the triad of dermatitis, dementia, and diarrhea [30]. Primary vitamin b3 deficiency is caused by a severe lack of niacin in the diet, however drugs, alcoholism, gastrointestinal diseases, and malignancies are the leading cause for secondary vitamin b3 deficiency [30].

In a melano-keratinocyte co-culture, with a reconstituted skin tissue model, Vitamin B3 consistently showed a decrease in melanin content or pigmentation [30]. Vitamin B3 slowed melanosome transfer from melanocyte to keratinocytes suggesting that Vitamin B3 plays a strong role in hypopigmentation of the skin and thus a deficiency in Vitamin B3 can cause the opposite; hyperpigmentation. Clinical studies have shown that Vitamin B3 has strong skin-lightening effects, a randomized, split-face, double-blind study with eighteen Japanese women showed a visual reduction in hyperpigmentation with the use of Vitamin B3.

Vitamin D

Vitamin D often termed the “sunshine vitamin”, is a fat-soluble vitamin with well-known roles in calcium and phosphorus homeostasis, essential for bone and immune health. Vitamin D’s role in dermatological processes isn’t as well defined, though many pathologies are linked to vitamin D deficiency.

Vitamin D is produced in the human skin in response to UVB omitted from sunlight. 7-dehydrocholestrerol (7-DHC), located in the epidermal keratinocytes, undergoes photoconversion in response to UVB into pre-vitamin D3 (cholecalciferol). [32] Before UVB can induce this photoconversion, melanin cells absorb the UVB (290-320 nm) and filter it first, acting to protect the skin barrier from the harmful effects of the radiation. [34] Melanin’s absorption of the UVB competes with excessive ultraviolet rays. This protective role leaves those with higher amounts of skin pigmentation at a greater risk of developing vitamin D deficiency. Previtamin D3 then undergoes a thermal conversion process in the skin before being transported to the liver as the active form of vitamin D in the body.

Unlike melanin's role in vitamin D synthesis, vitamin D’s role in melanogenesis is not well understood. There have been studies suggesting vitamin D protects against melanocyte apoptosis, drawing a potential link between vitiligo’s loss of melanocytes and concurrent vitamin D deficiency and potential hyperpigmentation linked to vitamin D. [36]. Other studies suggest that vitamin D is involved in melanogenesis through increasing tyrosinase activity, thus aiding in the repigmentation process. However, further studies

are needed to clearly define the involvement of vitamin D in the melanogenesis process. [37].

Vitamin D deficiency has been linked to different skin pathologies, including psoriasis, atopic dermatitis, and vitiligo as previously mentioned. Vitamin D insufficiency has been seen in a broad range of psoriatic patients, with an inverse relationship between its levels and the severity of the disease. [33] This is due to its role in suppressing inflammation in psoriasis through

inhibiting plasmacytoid dendritic cells' ability to induce T-cell proliferation and IFN-γ secretion. [38]. The vitamin deficiency's role in atopic dermatitis isn't as well defined, though previous studies have found a higher incidence of the disease in populations that live in higher latitudes, and there were greater chances of those with vitamin D deficiency developing atopic dermatitis. [33].

CONCLUSION

A review of the current literature was conducted to provide valuable insights into the relationship between dietary factors and hyperpigmentation. The findings elucidate potential dietary strategies or interventions that can be considered in the prevention and treatment for the management of hyperpigmentation and the amelioration of skin pigmentation disorders. Among the nutritional elements included in this paper, it is evident that deficiencies in Vitamin B3 and B12 most strongly correlate with the onset of skin hyperpigmentation, whereas vitamin D and iron displayed an unclear role, with hypothesized indirect implications.

A Vitamin B3 deficiency manifests as pellagra, a hyperpigmentation disorder that presents on the face, neck, dorsum of hands, and extensor surface of the forearms [29]. The current understanding of the pathophysiology of pellagra is a disruption in the melanosome-keratinocyte transfer due to a lack of inhibitory responses [30]. Similarly, vitamin B12 deficiency is associated with the onset of hyperpigmentation or vitiligo on the feet, hands, knuckles, and skin folds [17,21,22]. Though the underlying pathophysiology of vitamin B12's role in pigmentation is not clearly understood, it is postulated that diminished levels contribute to increased tyrosinase and decreased glutathione, resulting in downstream melanin synthesis alteration and thus hyperpigmentation [21, 23].

Iron deficiency can present with melasma among other things, and hyperpigmentation which presents as scattered patches, primarily on the face, with irregularly outlined borders [8]. The direct link between iron deficiency and melasma is not well defined, though it is hypothesized that low levels of iron can enhance melanoma due to the impedance of melanin degradation. [15].

Lastly, vitamin D deficiency can present with multiple systemic presentations, including osteomalacia and bone and joint pain. It is hypothesized that a potential indirect link can be seen through vitamin D's role in protection against melanocyte apoptosis, though further studies are needed to better characterize this role. [36].

The clinical implications of our findings include the importance of taking a patient's nutrition, particularly their vitamin levels, into consideration when treating dermatologic pathologies, emphasizing the importance of a holistic approach in treatment regimens and demonstrating the need for further preventive measures in the realm of adequate diet to prevent the progression of dermatologic disorders. Our findings highlight a gap in investigation efforts on direct links between nutrition and dermatologic pathologies, and future interventions as well as public health efforts should draw people's attention to the importance of having a balanced diet and adequate nutrition on cutaneous manifestations. We suggest continued

awareness through regular nutritional deficiency screenings and management of deficiencies when treating hyperpigmentation.

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