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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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THE ROLE OF ORAL SUPPLEMENTS IN MITIGATING COMMON ISOTRETINOIN SIDE EFFECTS: A COMPREHENSIVE REVIEW

Maria Gierasimiuk *(Corresponding Author, Email: gierasimiukmaria847@gmail.com)*
116th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Opole, Poland
ORCID ID: 0009-0009-1450-9258

Adam Januszkiewicz
107th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Wałcz, Poland
ORCID ID: 0009-0008-9488-2273

Wiktoria Januszkiewicz
107th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Wałcz, Poland
ORCID ID: 0009-0005-5730-4333

Wojciech Machulski
Military Institute of Medicine, Warsaw, Poland
ORCID ID: 0009-0007-6337-5909

Martyna Ciarkowska
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0001-4635-378X

Jan Makulski
1st Military Clinical Hospital with Outpatient Clinic, Lublin, Poland
ORCID ID: 0009-0006-7545-499X

Kamil Franczyk
10th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Bydgoszcz, Poland
ORCID ID: 0009-0001-6294-5101

Karolina Swierk
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0003-3784-9630

Damian Podkościelny
Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0007-4979-1674

Michal Gorski
116th Military Hospital with Outpatient Clinic, Independent Public Health Care Institution, Opole, Poland
ORCID ID: 0009-0006-8762-2823

ABSTRACT

Acne vulgaris, a chronic inflammatory dermatosis, affects approximately 9% of the global population. This condition arises from the multifactorial interplay of genetic predisposition, hormonal imbalances, excessive sebum production, hyperkeratinization of follicular infundibula, and proliferation of Cutibacterium acnes, culminating in inflammation and comedone formation. While various therapeutic modalities exist, including topical retinoids, antibiotics, and hormonal agents, oral isotretinoin remains one of the most efficacious treatments for acne vulgaris. Notwithstanding its superior effectiveness, the drug is associated with a spectrum of adverse effects that warrant mitigation strategies.

The primary aim of this narrative review is to evaluate the efficacy and rationale for employing oral supplements to alleviate the most prevalent isotretinoin-related side effects. By synthesizing extant research, this study appraises the benefits and limitations of select supplement interventions. The central clinical question addressed is: What is the role of oral supplements in mitigating common adverse effects among patients receiving isotretinoin therapy? Findings are expected to furnish clinicians and patients with evidence-based guidance on adjunctive supplement use to enhance treatment tolerability.

KEYWORDS

Isotretinoin, Oral Supplements, Side Effects, Acne Vulgaris, Vitamin E, Vitamin D, Omega-3 Fatty Acids, Folic Acid, Vitamin B12, Biotin

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1.Introduction

Acne vulgaris is an inflammatory skin disease that occurs in approximately 9% of the world population. This condition primarily impacts adolescents and young adults. Acne vulgaris can lead to lasting physical scars and considerably impact mental well-being, manifesting as diminished self-esteem, heightened anxiety, and an increased risk of depression and suicidal ideation. Consequently, individuals suffering from acne often experience a notable decline in their overall quality of life. The profound effects of severe acne, particularly concerning these psychological and social aspects, are comparable to those observed in chronic conditions like bronchial asthma, epilepsy, diabetes, back pain, and arthritis. (Sakaniya et al., 2025)

Isotretinoin stands as a widely recognized and effective treatment approach for severe forms of acne, supported by extensive research and integrated into the clinical recommendations of dermatological communities across various countries.(Tlish & Shavilova, 2024)

Isotretinoin is an oral retinoid, a derivative of vitamin A. Since the 1980s, it has established itself as a highly effective treatment for severe, recalcitrant acne vulgaris. Beyond its established efficacy in treating severe acne, isotretinoin has also demonstrated considerable effectiveness in managing other dermatologic conditions, including rosacea and pityriasis rubra pilaris (Chu et al., 2020). Contemporary clinical guidelines recommend a cumulative oral isotretinoin dose of 120–150 mg/kg body weight for the management of severe acne vulgaris. The conventional daily dosage is 0.5–1.0 mg/kg body weight. It is important to note that therapeutic benefits of oral isotretinoin are often accompanied by a broad spectrum of side effects (Kapała et al., 2022) (Sitohang, 2021). These can range from common mucocutaneous manifestations such as xerosis, retinoid dermatitis and cheilitis to more systemic issues affecting liver, ocular, neurological and musculoskeletal systems (Brelsford & Beute, 2008) (Drozd et al., 2020). Among the reported side effects, laboratory abnormalities have been observed, including elevated triglyceride levels (hypertriglyceridemia), an increased erythrocyte sedimentation rate, disturbance in liver function tests (elevated Alanine transaminase and Aspartate transaminase), and heightened creatinine phosphokinase levels. Clinical guidelines therefore advise monthly surveillance of laboratory markers, including low-density lipoprotein, high-density lipoprotein,

triglycerides, total cholesterol, liver function tests, and complete blood counts. While most adverse events are dose dependant and resolve post-treatment, their prevalence and impact on patient quality of life necessitate investigation into mitigating strategies, including adjunctive oral supplements.(Soutou et al., 2022). Lowering the dosage of isotretinoin can help mitigate its side effects (Ghani et al., 2025); however, this approach typically necessitates a more prolonged treatment period, which in turn increases the likelihood of patients discontinuing therapy prematurely. Therefore, exploring the role of oral supplements in managing these side effects becomes crucial for improving treatment adherence and overall patient outcomes (Rajput & Anjankar, 2024). This narrative review aims to comprehensively evaluate the efficacy of various oral supplements in alleviating the mucocutaneous and musculoskeletal adverse effects associated with isotretinoin therapy. Specifically, this review will examine the evidence for omega-3 fatty acids, vitamin E, folic acid, vitamin B12 and biotin, among others, to determine their capacity to improve patient tolerability and adherence to oral isotretinoin treatment. This comprehensive analysis will synthesize findings from clinical trials and observational studies to provide a robust overview of current evidence and identify potential gaps for future research. (Reyes-Hadsall et al., 2023)

2.Methodology

The methodological approach employed in this narrative review involved a comprehensive synthesis of evidence from peer-reviewed journals, clinical trials, and observational studies. A detailed literature review was conducted across databases such as PubMed and Google Scholar. This review primarily incorporates studies published between 2018 and 2025, supplemented by select earlier works that remain relevant. It integrates data from diverse research to evaluate the efficacy of specific oral supplements, including omega-3 fatty acids, vitamin E, folic acid, vitamin B12, and biotin, in mitigating mucocutaneous and musculoskeletal adverse effects associated with isotretinoin therapy, aiming to provide a robust overview of current evidence to improve patient tolerability and adherence to oral isotretinoin treatment.

3. Results

3.1. Mechanism of action of isotretinoin

Oral isotretinoin or 13-cis-retinoic acid is a synthetic retinoid and derivative of vitamin A. Chemically, isotretinoin is characterized as a polyunsaturated carboxylic acid, possessing the empirical formula $C_{20}H_{28}O_2$. The mechanism of action of isotretinoin is mediated through its role in cell cycle and differentiation, immune function, and apoptosis. Retinoid plays a role through nuclear interactions with retinoic acid receptors (RARs), which are ligand-dependent transcription factors. In other words, the regulation of gene transcription solely occurs through the interaction of retinoid composition with the receptors. These receptors can be activated from various retinoid forms, their metabolites, and isomers with differences in binding affinity. RARs bind to 9-cis-trans-retinoic acid and two major natural vitamin A derivatives, whereas retinoid x receptors (RXRs) only bind to 9-cis-trans-retinoic acid. Retinoid can induce or suppress the expression of various genes and play an essential role in the cellular process. The mechanism of action includes normalizing follicular hyperkeratinization, decreasing the production of cytokeratin 1, 10, 14, filaggrin, matrix metallopeptidases (MMPs), and toll-like receptor 2 (TLR-2), and increasing the production of cytokeratin 7, 13, 19, laminina B1, and IL-1.(Sitohang, 2021) This leads to a reduction in sebaceous gland size and sebum production, apoptosis of sebocytes, an increase in epidermal turnover, a decrease in *Cutibacterium acnes* colonization, alongside anti-inflammatory and immunomodulatory actions binding to nuclear retinoic acid receptors and retinoid X receptors to modulate gene expression (Soutou et al., 2022).

3.2. Adverse effects of isotretinoin

Isotretinoin has demonstrated superior efficacy compared to alternative acne treatments, such as antibiotics and topical agents, in enhancing patient outcomes and satisfaction by effectively reducing inflammation and resolving acne symptomatology. Nonetheless, isotretinoin therapy is associated with a spectrum of significant side effects (Kapała et al., 2022). Of paramount concern is its teratogenicity, necessitating rigorous monitoring protocols (Sitohang, 2021). Additional systemic adverse effects reported with oral retinoids and tetracyclines encompass elevated liver enzyme levels, renal dysfunction, and benign intracranial hypertension (Brelsford & Beute, 2008). Furthermore, common manifestations include dyslipidemia, severe cutaneous eruptions and xerosis, ocular sicca, conjunctivitis, cheilitis, musculoskeletal discomfort (e.g., back pain, myalgia, arthralgia), increased susceptibility to bruising, hemorrhage, and anemia.

Certain adverse events are dose-dependent, implying variability in their manifestation among patients These effects are typically reversible upon dosage adjustment or discontinuation of therapy (Soutou et al., 2022).

As mentioned earlier, the most serious side effect is teratogenicity. A potential mechanism for this effect involves the increased apoptosis of neural crest cells, mediated by the overexpression of the proapoptotic transcriptional factor p53. Consequently, it is imperative to perform a pregnancy test prior to initiating isotretinoin therapy and subsequently on a monthly basis, ensuring that the patient's menstrual period has occurred before commencing treatment. Furthermore, patients must consistently utilize two reliable methods of contraception throughout the treatment duration and for one month following its cessation.(Tylczyńska et al., 2024)

The most prevalent adverse effects associated with isotretinoin therapy primarily involve the dryness of the skin and mucous membranes (Soutou et al., 2022). This phenomenon is attributed to a reduction in sebum production, thinning of the stratum corneum, and modifications in the skin barrier function. Specifically, common mucocutaneous manifestations include cheilitis, cutaneous xerosis, erythema, pruritus, desquamation, nasal mucosal dryness, epistaxis, exacerbation or induction of atopic dermatitis, telogen effluvium, ocular sicca, and blepharitis. These symptoms are generally characterized as reversible, controllable, predictable, and dose-dependent (Soutou et al., 2022). Additional potential adverse effects encompass headaches, alopecia, arthralgia, myalgia, insomnia, and hyperostosis.

Laboratory abnormalities, occurring in approximately 2% of adverse events, frequently include elevated levels of triglycerides, total and LDL cholesterol, and transaminases, though these changes are typically mild (Tylczyńska et al., 2024).

3.3. Vitamin D

Vitamin D, also referred to as calciferol, is a fat-soluble secosteroid derived from sun exposure, dietary sources, and supplements. In its native form, it remains biologically inert and requires two sequential hydroxylations for activation: the first, occurring in the liver, yields 25-hydroxyvitamin D (calcidiol), while the second, primarily in the kidneys, produces the physiologically active metabolite 1,25-dihydroxyvitamin D (calcitriol).

Vitamin D facilitates calcium absorption in the intestines and sustains optimal serum concentrations of calcium and phosphate, thereby promoting normal bone mineralization and preventing hypocalcemic tetany. It is also essential for bone growth and remodeling processes involving osteoblasts and osteoclasts. Inadequate vitamin D levels can lead to bones that are thin, brittle, or deformed. In combination with calcium, vitamin D helps protect older adults from osteoporosis. This vitamin possesses anticomedogenic and antioxidant characteristics, and it plays a regulatory role in the immune system, as well as in the proliferation and differentiation of sebocytes and keratinocytes. Consequently, a deficiency in vitamin D may contribute to the development of acne. Given its immunomodulatory effects and influence on keratinocyte growth and maturation, vitamin D plays a crucial role in the pathogenesis of various inflammatory skin disorders, including acne vulgaris (Hussein et al., 2023). Thus, supplementing with vitamin D could potentially ameliorate the inflammatory aspects of acne and counteract some of the systemic effects of isotretinoin, considering its established immunomodulatory properties and influence on cellular differentiation (Hussein et al., 2023) (Al-Dhubaibi et al., 2021).

A 2018 study conducted by Gülbahar Saraç, Tuba Tülay Koca, Serpil Şener, and Gülden Hakverdi, affiliated with the Departments of Dermatology and Physical Medicine and Rehabilitation at İnönü University and Sütçü İmam University, respectively, and the Department of Biostatistics at Cumhuriyet University in Turkey, investigated vitamin D3 levels in 90 patients receiving oral isotretinoin therapy. The study cohort comprised 51 females and 39 males, aged between 16 and 50 years. Eight participants withdrew from the study due to treatment incompatibility. Prior to treatment, the mean 25-hydroxyvitamin D3 level was

18.28±9.92 ng/mL, which subsequently decreased to 13.28±7.78 ng/mL after six months of therapy. This decline brought levels below the laboratory's defined normal range of 20 to 30 ng/mL. This reduction in vitamin D3 levels implies a potential interaction between isotretinoin therapy and vitamin D metabolism, underscoring the need for further investigation into whether supplementation could mitigate this effect and its associated musculoskeletal side effects. Acknowledged limitations of the study included the low mean baseline vitamin D levels in the cohort and the wide age range of female participants, which included both premenopausal and postmenopausal women, potentially influencing the results. (Saraç et al., 2018)

Conversely, other research indicates that isotretinoin treatment may lead to an increase in serum vitamin D levels, particularly in patients with mild acne (Al-Dhubaibi et al., 2021).

A 2021 study conducted in Saudi Arabia examined 68 patients with acne vulgaris. At baseline, the mean vitamin D levels were 26± 9.4 ng/ml for the mild acne group, 31.4 ± 6.9 ng/ml for the moderate acne group, and 28.4 ± 6.7 ng/ml for the severe acne group. Three months after initiating isotretinoin treatment, an increase in mean serum vitamin D levels was observed across all acne severity groups, reaching 35.6±6.5, 32.14 ±7.1, and 32.9 ± 4.9 ng/ml for mild, moderate, and severe acne, respectively. Despite these increases, no significant differences in serum vitamin D levels were found among these groups, and these elevated levels remained consistent post-treatment with isotretinoin. One proposed explanation for this phenomenon is that *Cutibacterium acnes* may enhance the gene expression of immunological factors, thereby inhibiting vitamin D production (Al-Dhubaibi et al., 2021). This suggests that isotretinoin, by reducing *C. acnes*, might indirectly improve vitamin D status by removing this inhibitory influence (Al-Dhubaibi et al., 2021). Another hypothesis suggests that isotretinoin may reduce the expression of 24-hydroxylase, an enzyme responsible for vitamin D catabolism, or enhance intestinal absorption of vitamin D (Hussein et al., 2023).

A prospective study in which 100 participants were administered 0.75 mg/kg of isotretinoin daily for four months investigated serum 25-hydroxyvitamin D levels at baseline, during, and post-treatment. The findings revealed a statistically significant elevation in serum 25-hydroxyvitamin D concentrations, progressing from a baseline of 15.3 ± 3.2 ng/mL to 16.7 ±3.8 ng/mL during isotretinoin therapy, and further to 18.5 ± 4.1 ng/mL after treatment. This trajectory implies that isotretinoin treatment positively influences vitamin D levels (Hussein et al., 2023).

A study by S. Johansson et al. noted that the highest incidence of osteoporosis occurs in northern Europe for enigmatic reasons, where sunlight exposure is limited and vitamin A intake is elevated. The interplay between vitamins A and D has been explored in numerous in vitro and animal investigations. The researchers examined the acute impacts of vitamins A and D on calcium homeostasis in nine healthy human volunteers through a double-blind crossover trial. They evaluated the effects of 15 mg retinyl palmitate, 2 µg 1,25-dihydroxyvitamin D_3, a combination of 15 mg retinyl palmitate and 2 µg 1,25-dihydroxyvitamin D_3, and placebo. Participants ingested the preparations at 10:00 p.m., with blood samples collected five times the following day from 8:00 a.m. to 4:00 p.m. Serum concentrations of 1,25-dihydroxyvitamin D_3 and retinyl esters rose accordingly. As anticipated, 1,25-dihydroxyvitamin D_3 administration elevated serum calcium levels and suppressed serum parathyroid hormone. Conversely, retinyl palmitate alone induced a significant decline in serum calcium and attenuated the calcium-elevating response to 1,25-dihydroxyvitamin D_3 in combination. Serum parathyroid hormone remained unaltered by retinyl palmitate. No notable variations were observed in serum levels of the C-telopeptide type I collagen degradation product or urinary calcium-to-creatinine ratio. In summary, vitamin A intake equivalent to approximately one liver serving counteracts the prompt intestinal calcium absorption elicited by physiological vitamin D concentrations in humans(Johansson & Melhus, 2001). These observations highlight the complex interaction between retinoids and vitamin D metabolism, indicating that elevated vitamin A doses may counteract vitamin D's physiological actions, especially regarding calcium homeostasis (Miziołek et al., 2019).

A study by C.M. Rohde et al. demonstrated that vitamin A antagonizes vitamin D action in rats. Although interactions between vitamins A and D have been hypothesized for decades without definitive confirmation, vitamin A has been proposed to exacerbate rickets—a bone mineralization disorder—and hinder vitamin D's ability to cure it. To test this, weanling Holtzman rats received a diet with 1.2% calcium and 0.1% phosphorus, supplemented with 15.5 ng ergocalciferol every 3 days for 21 days, alongside escalating doses of retinyl acetate. Escalating retinyl acetate doses caused a progressive, significant decline in total bone ash content and widened the epiphyseal plate. Repeating the experiment with varying vitamin D levels confirmed antagonism across all dosages. In a subsequent trial, rats on a 0.47% calcium, 0.3% phosphorus diet received 15.5 ng vitamin D every 3 days for 33 days with increasing retinyl acetate; without retinyl acetate, serum calcium remained normal, but higher doses abolished vitamin D's capacity to raise it. These results confirm retinyl acetate's in vivo antagonism of vitamin D effects on intestinal calcium absorption and bone mineralization.(Rohde et al., 1999)

Given the variability in reported findings, further investigation involving a more extensive cohort is warranted to ascertain whether adjunctive vitamin D supplementation during isotretinoin therapy is necessary to ameliorate its associated adverse effects, or if prophylactic vitamin D administration proves sufficient.

3.4. Biotin

Biotin, a B-complex vitamin, constitutes an essential nutrient for human health, abundantly distributed across diverse natural food sources and conveniently obtainable via dietary supplements. As a water-soluble vitamin, it functions as a critical coenzyme for five carboxylase enzymes essential to pivotal metabolic processes, encompassing the synthesis and catabolism of fatty acids, gluconeogenesis, and amino acid catabolism—pathways indispensable for cellular energy homeostasis and structural maintenance. In addition to its carboxylation roles, biotin modulates histone biotinylation, gene transcription, and cellular signaling cascades, thereby regulating cell proliferation, differentiation, and broader physiological functions.

Vitamin B7 plays a crucial role in various metabolic pathways, including fatty acid synthesis, gluconeogenesis, and amino acid metabolism, all of which are essential for maintaining healthy skin, hair, and nails. Its deficiency can manifest as dermatitis, alopecia, and brittle nails, symptoms that can sometimes overlap with or be exacerbated by isotretinoin therapy (Hussein et al., 2023).

A study carried out by Hind M. Almohanna in Department of Dermatology and Dermatologic Surgery, Prince Sultan Military Medical City, Riyadh, Saudi Arabia in 2018 investigated serum biotin levels in 541 women experiencing hair shedding. Low biotin levels were identified in 38% of these subjects. Among those with biotin deficiency, 11% had an acquired cause, such as gastrointestinal disease, valproic acid, antibiotic use, or isotretinoin, which is recognized as a potential inducer of biotin deficiency (Almohanna et al., 2018). Concurrently, 35% presented with associated underlying seborrheic dermatitis. These findings suggest that hair loss has a multifactorial etiology (Almohanna et al., 2018). Hair loss, a documented adverse effect of isotretinoin therapy, presents significant physical and psychological challenges for patients (Gurram et al., 2025), often leading to decreased treatment adherence and, in some instances, premature termination of the therapeutic regimen (Reyes-Hadsall et al., 2023).

In a study conducted by Nagwa Ibrahim and Ibrahim Mahsoub in Departments of Dermatology, Andrology and STDs and Clinical Pathology, Faculty of Medicine, Mansoura University, Egypt in 2023, the frequency and severity of different side effects of oral isotretinoin were estimated. Specifically, the incidence of hair loss was one of the side effects examined. The cohort consisted of 80 patients with a mean age of 22.77 years. The mean dose of the treatment at the first month was 28.62 mg and was 25.38 mg at the third month. The severity of acne vulgaris in the cohort varied, with 48.8% moderate. Prior to the initiation of treatment, hair loss was observed in 4 patients. This incidence subsequently increased to 7 patients after one month, and further to 34 patients after three months of oral isotretinoin treatment (“Most Common Isotretinoin Therapy Side Effects on Egyptian Acne Females in Dakahlia Governorate,” 2024). The mechanism may involve isotretinoin's influence on the keratinization of the hair follicle's inner root sheath during the anagen phase or the activation of retinoid X receptors (Alting & Hunsel, 2018). Additionally, excessive vitamin A can cause hair loss by overwhelming the transport system (Almohanna et al., 2018).

A 1979 case report described a 28-year-old woman undergoing chronic renal dialysis who suddenly developed hair loss. She had been taking daily vitamin A supplements, resulting in serum levels markedly exceeding normal ranges. Gentle traction yielded four to five hairs, all in the telogen phase, and the hair loss resolved completely within one month after discontinuation of vitamin A supplementation (Almohanna et al., 2018).

Biotin has been explored for its potential to mitigate isotretinoin-induced hair loss, especially given that isotretinoin can be an acquired cause of biotin deficiency (Almohanna et al., 2018; Hussein et al., 2023). While some research suggests that biotin supplementation might help by increasing the anagen hair ratio and decreasing the telogen hair ratio, and potentially maintaining skin hydration (Aksaç et al., 2021), direct, high-quality evidence definitively establishing its efficacy in counteracting isotretinoin-associated mucocutaneous adverse reactions, including hair loss, remains limited (Hussein et al., 2023) (Yelich et al., 2024).

A study by Sema E. Aksac and colleagues at the Department of Dermatology, Mersin City Hospital, Mersin, Turkey, in 2020, sought to investigate the alterations in skin and hair observed in acne patients undergoing isotretinoin treatment, and how these changes were influenced by the addition of biotin to their therapeutic regimen (Aksaç et al., 2021). In this study, 60 patients were divided into two groups, each consisting of 30 individuals. Both groups received a daily dose of 0.5 mg/kg of isotretinoin, with the second group also receiving a 10 mg/day vitamin B7 supplement. Hair changes were assessed in both groups using a digital dermoscope. These evaluations were conducted at the beginning of the study and again at the end of the fourth month. The findings indicated a significant increase in the anagen hair ratio and a decrease in the telogen hair ratio within the biotin-supplemented group, contrasting with the control group (Aksaç et al., 2021). Telogen hair value in the group of patients receiving both isotretinoin and vitamin B7 was statistically

significantly lower after treatment. There was no significant difference in the control group for telogen hair values. The mean value of terminal hair density decreased in both groups, but there was no statistically significant difference. The anagen hair ratio increased in both groups at the end of the treatment, but only the results of patients in the group receiving both isotretinoin and vitamin B7 were found to be significantly higher. In the control group, the anagen hair ratio was not statistically significantly different. Although there was a decrease in the count of total hair in both groups, this difference was not statistically significant. This suggests that while biotin may positively influence the hair cycle dynamics by promoting anagen hair growth, it does not entirely counteract the overall hair thinning effect of isotretinoin.

However, excessive biotin supplementation is known to cause significant analytical interference with immunoassays, yielding falsely elevated or depressed results across a wide range of laboratory tests. The U.S. Food and Drug Administration has issued safety alerts emphasizing this risk, including a case in which biotin-induced interference produced a spuriously low troponin level, delaying myocardial infarction diagnosis and contributing to patient mortality (Almohanna et al., 2018).

This discrepancy underscores the critical need for more rigorously designed, large-scale randomized controlled trials to clarify the role of biotin in ameliorating isotretinoin-induced dermatological and hair-related side effects (Reyes-Hadsall et al., 2023) (Aksaç et al., 2021).

3.5.Vitamin E

Vitamin E encompasses a diverse group of fat-soluble compounds, unified by their characteristic and vital antioxidant properties within biological systems. In its natural form, vitamin E manifests as eight distinct chemical entities, each exhibiting differential biological activities and potencies. Among these various isomers, alpha-tocopherol stands out as the sole form officially recognized as indispensable for fulfilling human nutritional requirements. The regulation of serum vitamin E concentrations is predominantly governed by hepatic processes; specifically, after the absorption of the various vitamin E forms from the small intestine, the liver assumes a pivotal role in their uptake and subsequent processing. Crucially, the liver demonstrates a marked selectivity, preferentially re-secreting only alpha-tocopherol back into the systemic circulation, a process facilitated by the specialized hepatic alpha-tocopherol transfer protein. In contrast, the remaining non-alpha-tocopherol forms undergo metabolic transformation and eventual excretion by the liver. Consequently, the physiological consequence of this selective hepatic processing is that the systemic blood and cellular concentrations of the non-alpha-tocopherol forms are inherently lower compared to alpha-tocopherol, which, in turn, has led to their being considerably less extensively investigated within the scientific literature.

A contributing factor to isotretinoin-induced oxidative stress is its established capacity to deplete serum vitamin E levels. In a prospective study by Şikar Aktürk, 70 patients with acne vulgaris treated with isotretinoin (0.6–0.8 mg/kg/day) in a dermatology department were enrolled, targeting a cumulative dose of 120 mg/kg over 5–7 months. Serum vitamin E levels were assessed at baseline and again in the final month of treatment. Forty-six patients completed the study, revealing a statistically significant decline in mean serum vitamin E from 20.22 mg/dL pretreatment to 16.24 mg/dL posttreatment; levels decreased in all but three participants. These findings confirm that isotretinoin therapy substantially reduces vitamin E concentrations.(Aktürk et al., 2013)

Given vitamin E's critical role as an intracellular antioxidant reserve, its depletion by isotretinoin compromises the body's antioxidant defense system, thereby heightening vulnerability to oxidative stress. This elevated oxidative stress has been directly associated with the manifestation of hepatotoxicity, a form of liver inflammation induced by certain pharmacological agents. Consequently, the increased propensity for oxidative stress is implicated in the elevated risk of hepatotoxicity observed with isotretinoin therapy. This depletion of antioxidant reserves and subsequent increase in oxidative stress can lead to various adverse effects, further underscoring the potential utility of adjunctive therapies (Xu, 2024).

Several studies have therefore investigated the effects of vitamin E in reducing mucous dermal effects on acne vulgaris patients on isotretinoin. However, the results have been mixed.

A double-blind, randomized controlled trial by Strauss et al. evaluated the effects of a fixed dose of vitamin E (800 IU/day) on isotretinoin-associated side effects in patients with treatment-resistant acne vulgaris. In this study, 140 subjects were randomly assigned to receive isotretinoin (1 mg/kg/day) combined with either vitamin E or placebo for 20 weeks, with assessments of side effect incidence, severity, and duration. The results demonstrated that vitamin E supplementation did not significantly reduce the incidence, severity, or duration of these side effects.(Strauss et al., 2000)

A similar outcome was reported by Küs et al., who randomly assigned 82 patients to receive either isotretinoin alone or in combination with vitamin E for 16 weeks. Mucocutaneous side effects—including facial erythema, dryness, and cheilitis—as well as serum lipid and liver enzyme profiles were assessed. No differences were found in the incidence or severity of isotretinoin-related side effects between the groups. Thus, supplementation with 800 IU/day of vitamin E did not alleviate the side effects associated with 1 mg/kg/day isotretinoin in acne vulgaris treatment.(Kuş et al., 2004)

In a study by Goforoushan et al., vitamin E supplementation was compared to cod liver oil in patients receiving isotretinoin therapy. Cheilitis was slightly less prevalent in the vitamin E group after 6 weeks. Both groups exhibited fewer mucocutaneous complications relative to baseline after several weeks. Notably, participants received a lower isotretinoin dose (0.5 mg/kg/day), potentially explaining divergences from the prior studies using higher doses.(Goforousha et al., 2013)

In addition to oral administration, vitamin E has been evaluated for topical use in managing cheilitis. An open-label study involving 254 patients demonstrated that multiple daily applications of a topical vitamin E balm to the lips led to a significant improvement in symptom severity within 10 days in 32% of participants, the majority of whom had isotretinoin-associated cheilitis.(Cassano et al., 2003)

3.6. Omega-3 fatty acids

Omega-3 fatty acids are a class of long-chain polyunsaturated fatty acids that are essential for human health but cannot be synthesized by the body, thus requiring dietary intake. These are primarily sourced from fish oils and various plant-based foods. According to the 2012 National Health Interview Survey, omega-3 is considered a safe supplement with no significant adverse effects. Beyond its safety, omega-3 has beneficial effects on the liver and can improve lipid profiles by lowering serum triglyceride and total cholesterol levels while increasing high-density lipoprotein cholesterol.

Weise et al. investigated the effects of oral polyunsaturated fatty acids and non-digestible oligosaccharides on allergen-induced dermatitis in a murine model. In this pilot study, skin inflammation was induced through serial epicutaneous applications of ovalbumin in OVA-sensitized mice, while the animals concurrently received solid feed enriched with arachidonic acid/docosahexaenoic acid, galactooligosaccharides/polydextrose, or their combination. Skin lesions were evaluated via clinical scoring, alongside assessments of skin barrier function, immunohistochemical markers, and local cytokine profiles. The lipid mediators derived from omega-3 fatty acids possess anti-inflammatory properties, playing a crucial role in resolving inflammation. Some studies have indicated their efficacy in alleviating eczematous lesions and preventing allergic diseases.

Both AA/DHA and GOS/PDX supplementation significantly attenuated dermatitis severity. Clinical improvements correlated with decreased transepidermal water loss and reduced Ki-67 proliferation marker expression in the epidermis. Lesional CD8+ T cells and mast cells were diminished across treatment groups, with the most pronounced reductions observed in mice receiving the combined AA/DHA/GOS/PDX regimen. Additionally, GOS/PDX treatment upregulated interferon-γ and transforming growth factor-β expression in lesional skin.

In conclusion, dietary AA/DHA and GOS/PDX ameliorated allergen-induced dermatitis symptoms, suggesting potential utility in managing human atopic eczema.(Weise et al., 2013)

Furthermore, Kangari et al. reported that omega-3 supplementation alleviated symptoms of dry eye syndrome. In this randomized controlled trial, 64 patients aged 45–90 years with dry eye symptoms were assigned to two groups: 33 in the treatment group and 31 in the placebo group.

Participants in the treatment group received two capsules of omega-3 daily for 30 days, each containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid, whereas those in the placebo group received two capsules of medium-chain triglyceride oil daily for 1 month. Outcomes were evaluated 1 month post-intervention.

The primary outcome was the change from baseline in tear break-up time at day 30. Secondary outcomes comprised the change from baseline in Ocular Surface Disease Index score and Schirmer's score at day 30.

In the placebo group, before the intervention, the mean TBUT, OSDI, and Schirmer's scores were 4.5 ± 2.1 seconds, 36.4 ± 13.8, and 6.0 ± 2.6 mm, respectively, and 1 month later were 4.7 ± 2.6 seconds, 37.6 ± 13.5, and 6.2 ± 2.5 mm, respectively. In the treatment group, these values were 3.9 ± 1.7 seconds, 38.7 ± 16.5, and 5.8 ± 2.5 mm before the intervention and 5.67 ± 2.6 seconds, 29.3 ± 15.9, and 6.8 ± 2.8 mm after the intervention, respectively. Repeated-measures analysis of variance showed that improvements in TBUT, OSDI, and Schirmer's scores were significantly better in the treatment group than in the placebo group. The changes

in the treatment and placebo groups were 71% and 3.3% for TBUT, 26% and 4% for dry eye symptoms, and 22.3% and 5.1% for Schirmer's score, respectively.

This study demonstrated that oral omega-3 fatty acid supplementation was associated with reduced rates of tear evaporation, alleviation of dry eye symptoms, and enhanced tear production.(Kangari et al., 2013) These observations are corroborated by Nagawa, who documented a significant decrease in contact lens-associated dry eye complications with omega-3 supplementation, as well as by Creuzot et al., who likewise observed improvements in dry eye symptoms following omega-3 administration.

While the benefits of oral omega-3 are well-documented, its impact on the mucocutaneous side effects experienced by acne vulgaris patients undergoing isotretinoin therapy has not yet been properly investigated. Given that omega-3 is an affordable, readily available oral supplement with no reported adverse effects, demonstrating its effectiveness in managing isotretinoin-induced mucocutaneous side effects could lead to its prescription for patients, potentially enhancing their satisfaction and treatment adherence.

In a clinical study conducted by Mina Mirnezami and Hoda Rahimi in the Department of Dermatology, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran, and Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, the efficacy of oral omega-3 in decreasing the adverse effects of isotretinoin was assessed. This was a randomized double-blind clinical trial that took place from May 2014 to May 2015. The study involved a total of 118 patients with moderate or severe acne. They were randomly divided into two groups. The control group was treated with isotretinoin 0.5 mg/kg, and the case group was treated with the same dose of isotretinoin combined with oral omega-3. The treatment lasted for 16 weeks, and mucocutaneous side effects of isotretinoin were recorded and compared between the two groups in weeks 4, 8, 12, and 16. The side effects considered in that study were dryness of lips, nose, skin, and eyes.

For dry lips, both groups started at 0% incidence. By week 4, the isotretinoin group reported 78.7% incidence compared to 58% in the omega-3 group. This statistically significant reduction in the omega-3 group continued through weeks 8 and 12. However, by week 16, the difference was no longer statistically significant.

Regarding dry nose, both groups began at 0% incidence. A significant reduction was observed in the omega-3 group at all measured time points: week 4, week 8 ($P = 0.003$), week 12 ($P = 0.020$), and week 16 ($P = 0.001$).

For dry skin, initial incidence was 0% in both groups. The omega-3 group consistently showed significantly lower rates of xeroderma: week 4, week 8 ($P = 0.021$), week 12 ($P = 0.002$), and week 16 ($P = 0.013$).

For dry eyes, both groups started at 0%. A significant difference was noted only at week 4, with 13% incidence in the isotretinoin group compared to 4% in the omega-3 group. By week 8, the difference was not significant (9.3% vs. 6%, $P = 0.533$), and by weeks 12 and 16, the incidence was negligible or 0% in both groups, with no significant differences.

In summary, oral omega-3 supplementation significantly reduced the incidence of dry lips, dry nose, and dry skin in patients undergoing isotretinoin therapy, particularly in the earlier stages of treatment and sustained for dry nose and dry skin throughout the 16 weeks. The effect on dry eyes was significant only at week 4.(Mirnezami & Rahimi, 2018)

A randomized controlled trial also demonstrated that omega-3 supplementation significantly mitigated cheilitis, lip dryness, and xerosis when compared to a placebo group.(Zainab et al., 2021) This study involved 48 patients with nodular acne, who were randomly allocated into two cohorts. One group received isotretinoin therapy for six months concurrently with a dietary supplement containing gamma linolenic acid, vitamin E, vitamin C, beta-carotene, coenzyme Q10, and *Vitis vinifera*. The control group received only isotretinoin for the same duration. Researchers assessed various parameters for all participants, including acne severity, sebum production, skin hydration, and erythema. Additionally, treatment adherence was evaluated by inquiring about the frequency of therapy follow-up.(Zainab et al., 2021)

The administration of the dietary supplement resulted in a reduction of adverse effects among patients, characterized by diminished erythema and xerosis, and enhanced skin hydration; additionally, improved treatment adherence was observed.(Zainab et al., 2021)

The ongoing research by Peiyang Du and colleagues is investigating the impact of isotretinoin, when combined with omega-3 fatty acids, on lipid metabolism in patients with acne vulgaris. This study aims to elucidate whether omega-3 can ameliorate the dyslipidemia frequently associated with isotretinoin therapy, thereby potentially mitigating cardiovascular risks.

These findings suggest that omega-3 fatty acids could effectively mitigate some of the most common mucocutaneous adverse effects associated with isotretinoin, potentially enhancing patient compliance and

overall treatment outcomes. Despite these encouraging preliminary findings, further comprehensive research is warranted to solidify the role of omega-3 fatty acids in managing isotretinoin-induced mucocutaneous side effects. Future studies should involve substantially larger cohorts of patients to enhance the statistical power and generalizability of the results. Moreover, a critical area for investigation is the precise determination of the optimal dosage of omega-3 fatty acid supplementation. Establishing a specific, evidence-based dosing regimen would enable clinicians to more effectively integrate omega-3 into treatment protocols, potentially leading to improved patient outcomes and adherence.

3.7. Vitamin B12 and Folic acid

Vitamin B12 is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement and a prescription medication. Because vitamin B12 contains the mineral cobalt, compounds with vitamin B12 activity are collectively called cobalamins. Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B12.

Vitamin B12 is needed for the proper development, myelination, and functioning of the central nervous system, as well as for healthy red blood cell formation and DNA synthesis. It serves as a cofactor for two crucial enzymes: methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase facilitates the conversion of homocysteine into methionine, an essential amino acid. Methionine is vital for the synthesis of S-adenosylmethionine, a ubiquitous methyl donor involved in methylating nearly 100 different substrates, including DNA, RNA, proteins, and lipids. L-methylmalonyl-CoA mutase, on the other hand, mediates the conversion of L-methylmalonyl-CoA to succinyl-CoA, a step in the metabolism of propionate, a short-chain fatty acid.

Dietary vitamin B12 is typically protein-bound and must be liberated before absorption. This process commences in the mouth, where food mixes with saliva. The released vitamin B12 subsequently binds to haptocorrin, a cobalamin-binding protein found in saliva. Further release of vitamin B12 from its food matrix occurs in the stomach due to the action of hydrochloric acid and gastric protease, after which it again binds to haptocorrin. In the duodenum, digestive enzymes dissociate vitamin B12 from haptocorrin, allowing the freed vitamin B12 to complex with intrinsic factor, a transport and delivery protein secreted by gastric parietal cells. This resulting complex is then absorbed in the distal ileum via receptor-mediated endocytosis. When vitamin B12 is incorporated into fortified foods or dietary supplements, it is already in its free form, thus bypassing the initial separation step. Following absorption, vitamin B12 acts as an essential cofactor in various metabolic pathways, including nucleotide synthesis, regulation of branched-chain amino acids, and long-chain fatty acid metabolism, all of which are critical for cellular development and optimal neurological function.(Carmel, 2008; “Subject Index Vol. 108, 2002,” 2002)

Folic acid, also known as vitamin B9, stands as another indispensable water-soluble B vitamin, playing a pivotal role in maintaining myriad physiological processes. Its critical functions encompass the foundational processes of DNA synthesis and repair, ensuring genomic integrity and proper cellular replication. Furthermore, it is essential for robust cell division, a process fundamental to growth, tissue repair, and overall cellular renewal. A key contribution of folic acid is its involvement in the formation of healthy red blood cells, thus preventing certain types of anemia. Crucially, folic acid works in close synergy with vitamin B12 in the metabolic pathway known as the methionine cycle. Within this cycle, it facilitates the methylation of homocysteine to methionine, a reaction that is not only vital for detoxifying homocysteine but also for generating S-adenosylmethionine (Elangovan & Baruteau, 2022; Qudsia & Riaz, 2021). SAMe is a universal methyl donor engaged in nearly a hundred diverse methylation reactions, influencing critical biological processes such as gene expression, neurotransmitter synthesis, and lipid metabolism. Therefore, the adequate intake of folic acid is paramount for cellular development, neurological function, and overall metabolic health, particularly due to its collaborative role with vitamin B12 in these intricate biochemical pathways.

In the study conducted by Hilal Gokalp and Isil Bulur in 2013 and 2014 in Turkey the concentrations of Vitamin B12 and Folic Acid were mesured in acne pacient before and after oral isotretinoin treatment.

The study enrolled a total of 120 patients diagnosed with moderate to severe acne vulgaris who underwent a 6-month course of oral isotretinoin therapy, alongside 100 healthy individuals serving as the control group. Demographic analysis revealed no statistically significant disparities in age or gender between the patient and control cohorts. No statistically significant difference was detected between the patient and healthy control groups in the terms of age or gender of the patients ($P>0,05$). Pre-treatment vitamin B12 values in the patient group were statistically significantly higher ($P<0,05$), but no statistically significant difference was observed for folic acid levels ($P=0,566$). Pre- and post-treatment vitamin B12 and folic acid levels were

compared. A statistically significant decrease was detected in post treatment vitamin B12 and folic acid levels. (Gökalp et al., 2014)

This observed decrease suggests a potential metabolic impact of isotretinoin therapy on these vital B vitamins, which are crucial for cellular function and homocysteine metabolism (Ibrahim et al., 2023) (Elgharably et al., 2022).

In the study conducted by Doaa H.A. Mohamed and others in the Dermatology, Venereology and Andrology Department, Aswan University Hospital between December 2020 and December 2021, serum homocysteine levels in Acne patients before and after oral isotretinoin treatment were measured.This investigation involved 60 participants, comprising 30 patients diagnosed with acne vulgaris and 30 age-matched healthy volunteers serving as a control group. Patients were administered 20 mg of isotretinoin daily for a duration of three months. Serum homocysteine levels were assessed both pre- and post-treatment in both the patient and control groups. No statistically significant difference in serum Hcy levels was observed between the patient and control groups prior to isotretinoin initiation. Conversely, a statistically significant elevation in serum Hcy levels was noted among acne patients after three months of isotretinoin therapy. These findings indicate that serum Hcy levels increased following three months of isotretinoin treatment, potentially attributable to drug-induced hepatic dysfunction.(Hamdy et al., 2025) This elevation in homocysteine levels holds considerable importance, as heightened homocysteine is recognized as an independent risk factor for numerous cardiovascular conditions and may also play a role in the neurological and psychiatric adverse effects sometimes associated with isotretinoin therapy (Kamal & Polat, 2015; Kim et al., 2019).

There was also case report documented by Emmanuelle Vigarios and others in Toulouse and Nantes, France in 2019 detailing a case of isotretinoin-induced severe aphthous stomatitis (secondary to vitamin B12 deficiency). This particular case, involving a 17-year-old woman, highlighted the potential for isotretinoin to exacerbate or induce significant mucocutaneous adverse effects beyond the commonly observed xerosis. This 17-year-old female, undergoing oral isotretinoin treatment for acne (a 7-month course following an earlier 11-month course), presented with severe recurrent oral ulcers, physical deterioration, and fatigue over four months. Clinical examination revealed aphthous stomatitis-like ulcers and Hunter glossitis. Infectious etiologies were excluded by culture and PCR. Biological assessment showed macrocytic anemia, transaminitis, elevated lactate dehydrogenase, thrombocytopenia, and critically low levels of vitamin B12 and B9. Immunologic markers were normal, and endoscopic evaluation found no gastric or duodenal atrophy. Vitamin B12 malabsorption was ruled out by Schilling test and barium small bowel meal. Discontinuation of isotretinoin, coupled with oral vitamin B12 and B9 supplementation, led to complete resolution of the oral ulcers within two weeks. Hemoglobin and vitamin B12 levels normalized one month post-intervention. At the 8-month follow-up, there was no recurrence of oral lesions, macrocytic anemia, or vitamin deficiency, even after vitamin B12 supplementation ceased after two months. Oral mucosal alterations, such as glossitis and aphthous-like lesions, are recognized as primary indicators of vitamin B12 deficiency and may constitute its earliest clinical manifestation, as observed in this patient. It is posited that prolonged or high-dose isotretinoin therapy may contribute to decreased folic acid and vitamin B12 levels. The progressive development of glossitis and oral ulcers during a second cycle of isotretinoin, alongside the absence of evidence for pernicious anemia or inflammatory bowel disease and the lack of recurrence post-treatment cessation, strongly suggests a direct relationship between isotretinoin therapy and the observed vitamin B12/folate deficiency in this case. Cumulative isotretinoin doses might influence the incidence of mucosal lesions, given that short courses may not be associated with such deficiencies. This report is believed to be the first clinical characterization of severe oral lesions linked to vitamin B12 deficiency induced by systemic isotretinoin therapy. Clinicians should therefore recognize the potential for isotretinoin therapy to induce vitamin B12 and folic acid deficiencies, leading to secondary oral mucosal changes. Given these findings, routine monitoring of vitamin B12 and folic acid levels, particularly in patients on prolonged isotretinoin regimens or those presenting with oral mucosal symptoms, appears warranted to mitigate potential adverse effects and ensure patient safety. (Vigarios et al., 2019)

A randomized controlled trial by Ghiasi et al. investigated the potential benefits of concomitant folic acid and vitamin B12 supplementation alongside isotretinoin therapy in preventing hyperhomocysteinemia among patients with acne vulgaris. Sixty-six patients were randomized into two groups: Group A received isotretinoin combined with folic acid and vitamin B12, while Group B received isotretinoin monotherapy. Treatment duration was two months, during which serum homocysteine, folic acid, and vitamin B12 levels were measured before and after intervention.

In Group A, homocysteine levels decreased significantly post-treatment (remaining within the normal range), with concomitant significant elevations in folic acid and vitamin B12 levels. Conversely, Group B showed no significant changes in homocysteine or vitamin B12 levels, but a significant decline in folic acid levels.

The study concluded that folic acid and vitamin B12 supplementation during isotretinoin therapy may prevent folate deficiency, normalize homocysteine levels, and thereby mitigate risks of associated cardiovascular and neuropsychiatric disorders.(Ghiasi et al., 2019)

Additionally, a case series involving six patients with acne vulgaris who developed musculoskeletal pain during isotretinoin therapy demonstrated partial symptom alleviation after 2 weeks and complete resolution after 6 weeks of biweekly folic acid and vitamin B12 injections. No adverse events were reported. The author proposed that folic acid and vitamin B12 supplementation merits consideration as an adjunctive intervention to attenuate isotretinoin-associated musculoskeletal adverse effects. Nonetheless, the study is constrained by the omission of isotretinoin dosage details, its limited sample size, and the absence of placebo control or double-blinding.(Feily, 2019)

4.Discussion

4.1. Impact of oral supplements on isotretinoin-induced side effects.

The aim of this systematic review was to assess the efficacy of various oral supplements in alleviating common isotretinoin-induced side effects, drawing upon extant literature. In particular, this review assesses the efficacy of these supplements in alleviating mucocutaneous and musculoskeletal adverse effects, which are commonly identified as factors affecting patient adherence and overall treatment satisfaction.

4.2. The role of Vitamin D supplementation.

Regarding vitamin D supplementation in the context of isotretinoin therapy, the existing body of literature presents notably conflicting evidence concerning alterations in serum vitamin D levels. Certain studies have documented a reduction in these levels post-treatment, potentially attributable to mechanisms such as enhanced hepatic metabolism or interference with intestinal absorption induced by isotretinoin. In contrast, other investigations have observed elevations, which may stem from compensatory physiological responses or variations in baseline patient characteristics, such as sunlight exposure, dietary habits, or genetic factors influencing vitamin D metabolism. These inconsistencies highlight the challenges in establishing a definitive causal relationship and underscore the heterogeneity in study designs, sample sizes, and measurement methodologies employed across the research.

A pivotal study has illuminated the potential mechanistic interplay between retinoids and vitamin D, demonstrating that elevated doses of vitamin A can antagonize or counteract the physiological actions of vitamin D, including its roles in calcium homeostasis, immune modulation, and bone health. However, a critical limitation of this finding is its applicability: the research primarily addresses supplemental vitamin A rather than the pharmacologically distinct synthetic retinoid isotretinoin, which exhibits unique pharmacokinetics, tissue distribution, and receptor-binding affinities.

Further preclinical evidence from animal models reinforces this antagonism. For instance, one study reported that vitamin A effectively inhibits vitamin D-mediated actions in rats, employing retinyl palmitate as the retinoid source. Yet, this model diverges significantly from clinical scenarios involving oral isotretinoin in humans. Retinyl palmitate represents a preformed ester of vitamin A with different bioavailability compared to isotretinoin, a 13-cis-retinoic acid derivative designed for acne treatment. Compounding these differences, the bone mass of rats is considerably smaller than that of humans, necessitating proportionally higher daily doses on a body weight basis to achieve comparable therapeutic effects—often exceeding human-equivalent exposures by several-fold. Such extrapolations from rodent models to human physiology must therefore be approached with caution, as interspecies variations in retinoid metabolism, receptor expression, and vitamin D receptor interactions may profoundly influence outcomes.

These divergences and limitations collectively emphasize the imperative for more robust, high-quality research, including large-scale randomized controlled trials in human cohorts specifically evaluating isotretinoin-treated acne patients. Prospective longitudinal studies incorporating standardized vitamin D assays (e.g., 25-hydroxyvitamin D levels), alongside assessments of parathyroid hormone, calcium, and bone turnover markers, would provide greater clarity on potential interactions and clinical relevance.

In light of these uncertainties, a prudent clinical approach entails recommending prophylactic vitamin D supplementation, particularly for patients at risk of deficiency (e.g., those with limited sun exposure, darker skin phototypes, or concurrent malabsorptive conditions). Dosage regimens should align with established

guidelines, such as 800–2000 IU daily, titrated based on individual needs. Moreover, clinicians are encouraged to implement routine monitoring of serum vitamin D levels in all patients undergoing isotretinoin therapy. Integrating such monitoring into standard protocols could enhance patient safety, optimize therapeutic outcomes, and mitigate broader health risks associated with vitamin D insufficiency, including impacts on immune function and cardiovascular health.

4.2. The role of Biotin suplementation.

Regarding biotin supplementation, the extant literature frequently emphasizes its established role in promoting and maintaining the health of skin, hair, and nails—tissues that are particularly vulnerable to the xerotic (dryness-related) and fragility-inducing effects commonly observed during isotretinoin therapy. Although biotin is widely promoted in both popular media and clinical anecdotes for ameliorating these dermatological concerns, rigorous empirical evidence directly substantiating its effectiveness in counteracting isotretinoin-specific mucocutaneous adverse effects remains scarce and predominantly relies on case reports or uncontrolled observations rather than high-quality clinical trials.

It is well-established that oral isotretinoin treatment can precipitate hair thinning, a distressing side effect that impacts patient quality of life. One small-scale study has suggested that biotin supplementation at a dose of 10 mg per day may favorably shift hair cycle dynamics by reducing the proportion of hairs in the telogen (resting) phase and elevating those in the anagen (growth) phase. Nevertheless, this intervention did not fully offset the net hair thinning attributable to isotretinoin, underscoring its partial and limited utility. Overall, the body of research on this topic is exceedingly sparse, with only a handful of investigations available.

Compounding these evidential limitations, several practical concerns militate against routine biotin supplementation. Notably, isotretinoin-associated hair loss is typically transient and resolves spontaneously upon cessation of therapy in the majority of cases. More critically, excessive biotin intake has been implicated in significant analytical interferences with laboratory assays, potentially yielding falsely elevated or depressed results across a range of tests. The U.S. Food and Drug Administration has issued warnings highlighting this risk, including a documented case where biotin interference produced a falsely low troponin level, resulting in a missed diagnosis of myocardial infarction and a patient's death. Consequently, clinicians must exercise serious consideration regarding the necessity of biotin supplementation, weighing its unproven benefits against these potential diagnostic hazards and prioritizing evidence-based alternatives where possible.

4.3. The role of Vitamin E supplementation.

Regarding vitamin E supplementation, preclinical and observational data indicate that oral isotretinoin therapy is associated with a measurable decline in serum vitamin E concentrations. This depletion may stem from isotretinoin's propensity to induce oxidative stress and lipid peroxidation, processes in which vitamin E, as a lipid-soluble antioxidant, is preferentially consumed to protect cellular membranes. Anecdotal clinical reports, coupled with findings from smaller-scale investigations, have posited that concurrent oral administration of vitamin E alongside isotretinoin could attenuate certain therapy-related adverse effects, potentially by bolstering antioxidant defenses and mitigating inflammatory cascades implicated in dermatological toxicities.

However, the evidentiary foundation for this approach remains tenuous. Rigorous evaluations, particularly those derived from large-scale randomized controlled trials, have consistently failed to substantiate a clinically meaningful reduction in the incidence or severity of mucocutaneous side effects, such as cheilitis, xerosis, or xerostomia. These high-quality studies underscore the limitations of extrapolating from preliminary observations, highlighting the need for caution in endorsing routine systemic supplementation. Intriguingly, the topical application of vitamin E-containing ointments has helped in localized management of cheilitis, possibly owing to its direct emollient and barrier-restorative properties on affected mucosal surfaces, without the systemic exposure concerns attendant to oral dosing.

In view of these mixed findings, clinicians should adopt a measured stance, reserving oral vitamin E supplementation for select cases predicated on documented deficiency or heightened oxidative risk, while prioritizing topical formulations where symptomatic relief is sought. Future research, encompassing adequately powered prospective trials with standardized antioxidant biomarkers and patient-reported outcomes, is essential to delineate optimal strategies and resolve persisting uncertainties.

4.4. the role of Omega-3 fatty acids supplementation.

Regarding omega-3 polyunsaturated fatty acids, a substantial body of research affirms their therapeutic efficacy in the management of atopic dermatitis, augmentation of cutaneous hydration, and mitigation of xerophthalmia. These benefits are attributable, at least in part, to the anti-inflammatory properties of omega-3 fatty acids, which modulate pro-inflammatory eicosanoid production, enhance epidermal barrier function, and stabilize tear film integrity through incorporation into cellular membranes.

Notwithstanding these established advantages in dermatological and ophthalmological contexts, the evidence base pertaining specifically to the amelioration of adverse effects engendered by oral isotretinoin therapy remains comparatively sparse. Nonetheless, certain studies have reported beneficial effects of omega-3 supplementation in attenuating mucocutaneous toxicities, such as xerosis and cheilitis. Complementarily, ongoing preclinical and clinical inquiries are scrutinizing whether omega-3 fatty acids can counteract the dyslipidemia, frequently attendant to isotretinoin administration, potentially via upregulation of lipid metabolism regulators such as peroxisome proliferator-activated receptors.

In light of these developments, clinicians may judiciously consider omega-3 supplementation as a supportive measure in isotretinoin-treated patients, particularly those exhibiting pronounced mucocutaneous or metabolic perturbations. Nonetheless, as with antecedent supplements, rigorous prospective randomized controlled trials are imperative to corroborate efficacy, delineate optimal dosing (typically 1–3 g/day of combined EPA/DHA), and ascertain long-term safety profiles before integration into routine practice.

4.5. The role of Vitamin B12 and folic acid supplementation.

Regarding vitamin B12 and folic acid supplementation, preliminary investigations have documented a decline in serum levels of these vitamins during oral isotretinoin therapy. Concurrently, elevated homocysteine concentrations have been observed, attributable in part to this nutritional depletion. Such reductions in vitamin B12 and folic acid may predispose patients to adverse sequelae, including anemia and oral lesions, thereby warranting clinical vigilance.

In one study, supplementation with vitamin B12 and folic acid engendered a significant diminution in homocysteine levels, ostensibly mitigating the cardiovascular hazards linked to hyperhomocysteinemia, which is a metabolic perturbation associated with isotretinoin administration. Additionally, a small-scale investigation reported the successful amelioration of isotretinoin-induced musculoskeletal pain through this supplementation regimen. However, the evidentiary weight of this latter finding is circumscribed by methodological limitations, including a paucity of participants, absence of reported isotretinoin dosages, and lack of a placebo-controlled design.

Given these nascent insights, clinicians are advised to consider routine monitoring of vitamin B12 and folic acid levels in patients undergoing oral isotretinoin therapy. Although supplementation appears physiologically rational and potentially beneficial, the paucity of robust data underscores the imperative for larger, well-controlled prospective trials to validate efficacy, establish optimal dosing protocols, and delineate safety parameters prior to broader clinical endorsement.

5.Conclusions

In conclusion, while ancillary supplementation with antioxidants such as vitamin E, anti-inflammatory agents like omega-3 fatty acids, and essential micronutrients including vitamin B12 and folic acid holds theoretical promise for mitigating the mucocutaneous, metabolic, and musculoskeletal adverse effects of oral isotretinoin therapy, the current evidence base, which is predominantly derived from preliminary, small-scale studies, remains insufficient to warrant routine clinical endorsement. Topical vitamin E emerges as a pragmatic option for localized symptom relief, whereas systemic approaches necessitate individualized assessment predicated on documented deficiencies or risk profiles, coupled with vigilant biochemical monitoring. Ultimately, the integration of these adjunctive strategies into standard practice hinges on forthcoming large-scale, randomized controlled trials that rigorously evaluate efficacy, optimal dosing, long-term safety, and mechanistic underpinnings. Until such data accrue, clinicians are best served by prioritizing established dermatological supportive care measures, thereby optimizing patient outcomes while minimizing unsubstantiated interventions.

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