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A Review of the Systemic Impacts of Isotretinoin in People with Acne

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Abstract

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous unit, which comprises the hair follicle, sebaceous gland, and arrector pili muscle. Acne can lead to significant physical and psychological morbidity, including scarring and reduced quality of life. For severe or treatment-resistant cases, systemic isotretinoin (13-cis-retinoic acid) is the gold standard treatment due to its ability to target multiple pathogenic factors, including sebum production, follicular hyperkeratinization, inflammation, and Cutibacterium acnes proliferation. A comprehensive literature search was conducted using databases such as PubMed, Google Scholar, ScienceDirect, and ResearchGate. The systemic effects of isotretinoin on hematological, inflammatory, and oxidative stress biomarkers highlight its broad impact on the body. While the drug's anti-inflammatory properties are beneficial for acne treatment, its effects on oxidative stress and hematological parameters may pose risks, particularly in susceptible individuals. The observed reduction in neutrophil and RBC counts, along with elevated platelet counts and Hb levels, suggests that isotretinoin influences multiple hematological pathways. Similarly, the reduction in IL-8 and elevation in CRP levels underscore its complex role in modulating inflammation. The increase in MDA and decrease in TAS levels indicate that isotretinoin may disrupt the balance between oxidative stress and antioxidant defenses, potentially contributing to its adverse effects. Systemic isotretinoin therapy is highly effective for severe acne but is associated with significant systemic effects on hematological, inflammatory, and oxidative stress biomarkers. Future research should focus on elucidating the mechanisms underlying these changes and identifying strategies to mitigate adverse effects while preserving the drug's therapeutic benefits.

Keywords: *Acne, Hematology, Isotretinoin, Inflammation, Oxidative Stress.*

Introduction

Acne vulgaris is indeed a common chronic inflammatory skin condition that affects the pilosebaceous units, which consist of hair follicles and their associated sebaceous glands. This condition is characterized by the formation of comedones (blackheads and whiteheads), papules, pustules, nodules, and sometimes cysts [1]. The pilosebaceous unit is a complex structure in the skin that consists of three main components; hair follicle, sebaceous gland and arrector pili muscle [2]. Acne vulgaris affects approximately 9.4% of the world's population with the highest prevalence in adolescents. More than 90% of males and 80% of females in all ethnic groups are affected by acne, but the prevalence in adolescents and adults varies among countries and ethnic groups [3]. Several factors that play a key role in acne vulgaris development include genetic factor, increased production of sebum, bacterial colonization, abnormal differentiation of follicles, and inflammation [4]. Acne vulgaris affects both males and females, and it can appear on one or more of the following body regions: face, chest, upper arms, and upper back. Acne lesions can be inflammatory or non-inflammatory [5]. Acne

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can cause a permanent scarring in addition to psychosocial problems and decreased emotional well-being. Withdrawal from the society, decreased self-perception, and depression may also occur in acne patients. Young people with acne have more feelings of uselessness and less body satisfaction compared with those without acne. Furthermore, patients acne may have poorer academic performance and higher unemployment rates [6]. Many treatment options for acne are available, ranging from topical agents such as antibacterials, benzoyl peroxide, or retinoids for mild cases, oral isotretinoin or oral antibacterial drugs for more moderate to severe cases. However, some severe acne lesions require both topical and systemic treatment. Hormonal treatments may be prescribed for women [7]. Light therapy and Chemical peeling are also used to treat acne vulgaris [8]. Light and laser anti-acne therapy provides many advantages, such as short duration of treatment, reduction of antibiotic use, reduction of bacterial resistance, and increased patient compliance [9]. However, oral isotretinoin is recommended for severe cases of acne vulgaris. It is a synthetic analogue of vitamin A, that has an important role in sebaceous gland apoptosis and shrinkage. It also has an antiandrogenic effects and it reduces insulin-like growth factor-binding protein-3, insulin-like growth factor-1, prolactin hormone, luteinizing hormone, adrenocorticotropic hormone and free triiodothyronine . Oral isotretinoin is a lipid-soluble drug, thus it is better to take it with a fatty meal, this can increase absorption by 60%. Unfortunately It is associated with adverse effects [10].

In acne vulgaris the oxidative stress is related to the increase in sebum production and the change in sebum components. These two processes may be due to Reactive Oxygen Species that are produced by neutrophils, inducing an irritation and destruction of the follicular wall and leading to the occurrence of inflammatory acne vulgaris.

When reactive oxygen species interacts with lipids the main product will be lipid hydroperoxide which is converted to malondialdehyde (MDA). Malondialdehyde may be considered the principal oxidative stress biomarker due to its specificity in lipid peroxidation [11]. systemic isotretinoin (commonly known by the brand name Accutane) is a highly effective treatment for severe or recalcitrant acne vulgaris, but it can have widespread effects on various hematological, inflammatory, and biochemical markers in the body. These effects are important to monitor, as they can influence both the efficacy and safety of the treatment [12]. Propionibacterium acnes (P. acnes) causes an activation of innate immunity by binding to TLRs 2 and 4, that are present on keratinocytes and monocytes resulting in release of IL-1, IL-6, IL-8, IL-12 and TNF-α [13]. C-reactive protein is a well-known inflammatory biomarker and its levels in acne patients were studied [14]. Use of oral isotretinoin for treatment of acne may lead to changes in patients lipid profile, therefore the level of HDL, LDL, VLDL, and TG are studied [15]. TAS (total antioxidant status) is one of the main markers used widely to evaluate the oxidative stress in many inflammatory diseases such as acne vulgaris [16].

The relationship between isotretinoin and oxidative stress is complex and not fully understood:

Pro-Oxidant Effects

Isotretinoin may increase oxidative stress by generating reactive oxygen species (ROS), leading to lipid peroxidation and DNA damage. Elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation, have been observed in some studies [15, 16].

Antioxidant Effects

Paradoxically, isotretinoin has also been shown to enhance antioxidant defenses by increasing the activity of enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). The net effect on oxidative stress may depend on individual factors such as dosage, treatment duration, and baseline antioxidant status [14, 15].

Factors Contributing to Pathogenesis of Acne Vulgaris

Various factors can play an important role part in development of acne vulgaris. These factors that will be discussed are as follow: genetic factor, increased sebum production, elevated androgen level, hyperkeratosis of the follicles, P. acne infection, and inflammatory response (see Figure 1).

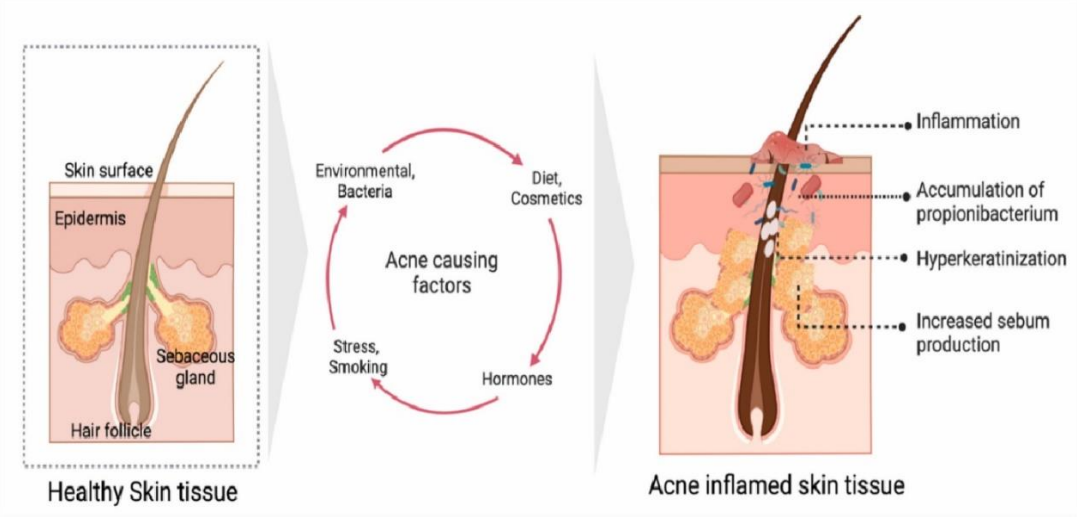

Figure 1. Normal Healthy Skin Tissue (0n the Left), Acne Inflamed Skin Tissue (0n the Right), Factors that Contribute to the Development of Acne (in the Middle) [4]

Propionibacterium Acnes Infection

Cutibacterium acnes (formerly known as Propionibacterium acnes) is a key player in the pathogenesis of acne vulgaris. This bacterium is an anaerobic, gram-positive bacterium that naturally resides in the pilosebaceous units of the skin, particularly in areas with high sebum production, such as the face, chest, and back [1], characteristics of Cutibacterium acnes (C. acnes):

Anaerobic Nature: C. acnes thrives in low-oxygen environments, such as the clogged hair follicles (comedones) characteristic of acne. The anaerobic conditions within the follicle promote its growth and proliferation.

Gram-Positive Bacterium: As a gram-positive bacterium, C. acnes has a thick peptidoglycan layer in its cell wall, which contributes to its ability to evade the immune system and persist in the skin.

Lipase Enzyme Secretion: C. acnes produces lipase enzymes, which break down the triglycerides present in sebum into free fatty acids (FFAs) and glycerol. This metabolic activity is a key factor in the inflammatory process of acne.

Genetic Factors

Genetic factors are a major determinant of acne vulgaris development, influencing sebum production, follicular keratinization, inflammation, and hormonal responses. These genetic predispositions interact with environmental and hormonal factors to shape the severity and presentation of acne. Understanding the genetic basis of acne not only provides insights into its pathogenesis but also opens the door to more effective, personalized treatments [17]. Genetic factors in acne vulgaris development.

1. **Heritability of Acne**:
    i. Studies have shown that acne vulgaris has a strong hereditary component. If one or both parents had acne, their children are more likely to develop acne, often with similar severity.
    ii. Twin studies have demonstrated that genetics account for approximately 50-90% of the variation in acne susceptibility.
2. **Genes Associated with Acne**:

Several genes have been implicated in acne development, including those involved in:

    i. Sebum Production: Genes regulating sebaceous gland activity and sebum composition (e.g., *FGF*, *EGFR*).
    ii. Follicular Keratinization: Genes affecting the shedding of skin cells in hair follicles (e.g., *IL-1α*, *TGF-β*).
    iii. Inflammatory Response: Genes controlling immune and inflammatory pathways (e.g., *TNF-α*, *IL-6*, *IL-8*).
    iv. Hormonal Regulation: Genes influencing androgen metabolism and sensitivity (e.g., *CYP17*, *AR*).

3. **Polygenic Nature**:
    i. Acne is a polygenic disorder, meaning it results from the combined effects of multiple genes, each contributing a small effect.
    ii. The interplay of these genes determines an individual's susceptibility to acne and its severity.

Increased Sebum Formation

A clear correlation is present between excessive sebum formation and the severity and frequency of acne vulgaris lesions [4]. At onset of puberty, the sebum production is increased due to testosterone [18].

Increased Androgen Level

Sebaceous gland has an ability to convert precursors of androgens such as dehydroepiandrosterone into more potent androgen hormones. Furthermore, androgen hormones have a significant role in sebum synthesis and sebaceous gland activity.

Sebaceous Glands and Androgen Metabolism [4, 18]

Conversion of Androgen Precursors: Sebaceous glands express enzymes that convert weaker androgen precursors into more potent androgens. For example: Dehydroepiandrosterone (DHEA)**,** a weak androgen produced by the adrenal glands, is converted
into testosterone and dihydrotestosterone (DHT) within the sebaceous glands. The enzyme 5α-reductase plays a key role in converting testosterone into DHT, which is a much more potent androgen.

Enzymes Involved in Androgen Metabolism

5α-Reductase: Converts testosterone to DHT.

17β-Hydroxysteroid Dehydrogenase (17β-HSD): Converts weaker androgens like androstenedione into testosterone.

3β-Hydroxysteroid Dehydrogenase (3β-HSD): Converts DHEA into androstenedione.

Local Androgen Production: The sebaceous glands can produce androgens locally, independent of systemic androgen levels. This means that even if blood levels of androgens are normal, local overactivity of these enzymes can lead to excessive androgen effects in the skin.

Follicular Hyperkeratosis

Hyperkeratinization of the hair follicle is a key pathological feature of acne vulgaris. It refers to the abnormal shedding and accumulation of keratinocytes (skin cells)

within the follicular canal, which contributes to the formation of microcomedones, the earliest acne lesions [19].

Normal Follicular Keratinization: In healthy skin, keratinocytes in the hair follicle undergo a process of differentiation and shedding, allowing sebum and dead cells to be expelled onto the skin surface. This process is tightly regulated to maintain an open follicular canal.

Abnormal Hyperkeratinization: In acne-prone skin, the process of keratinocyte shedding becomes dysregulated, leading to hyperkeratinization. This results in the retention of keratinocytes within the follicle, which mix with sebum and form a plug.

Inflammatory Response

C. acnes . is a key bacterium involved in the pathogenesis of acne vulgaris. One of its major roles is the activation of the innate immune system, primarily through interactions with toll-like receptors (TLRs), particularly TLR2 and TLR4. This activation triggers the production of numerous pro-inflammatory molecules, leading to the inflammation characteristic of acne lesions [1].

Innate Immune Activation by C. acnes

Recognition by Toll-Like Receptors (TLRs): TLRs are pattern recognition receptors (PRRs) expressed on immune cells (e.g., macrophages, dendritic cells, keratinocytes) that recognize pathogen-associated molecular patterns (PAMPs). C. acnes activates the innate immune system primarily through TLR2 and TLR4. TLR2: Recognizes bacterial lipoproteins and peptidoglycans present on the surface of C. acnes. TLR4: Recognizes lipopolysaccharides (LPS) and other bacterial components.

Downstream Signaling Pathways: Upon binding to TLR2 and TLR4, C. acnes triggers downstream signaling pathways, including; NF-κB Pathway (A key regulator of inflammation), and MAPK Pathway: Involved in cell proliferation and cytokine production. These pathways lead to the activation of transcription factors that promote the expression of pro-inflammatory genes [1, 2, 13].

Inflammatory and Immunomodulatory Effects: Isotretinoin exerts potent anti-inflammatory effects, which contribute to its efficacy in acne treatment. However, it may also modulate systemic immune responses:

Cytokine Levels: Isotretinoin reduces pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which are implicated in acne pathogenesis. This anti-inflammatory action may explain the improvement in acne severity and reduction in inflammatory lesions [2, 13].

Immune System Modulation: Isotretinoin has been shown to alter the expression of toll-like receptors (TLRs) and other immune mediators, potentially affecting the body's ability to respond to infections. Rare cases of isotretinoin-associated inflammatory bowel disease (IBD) have been reported, though a causal relationship remains controversial [1, 13].

Methods

Our search strategy well-structured for identifying studies on the effects of isotretinoin, particularly focusing on hematological, inflammatory, and oxidative stress markers. Below is a summary used to refine or optimize our search:

Key components of our search:

1. Databases: PubMed, Google Scholar, ScienceDirect, Wiley Online Library, and ResearchGate.
2. Timeframe: Studies published from 2020 to 2025.
3. Language: English-language studies only.
4. Access: Only open-access articles.
5. Keywords:

i. Primary terms: isotretinoin effect or isotretinoin.
ii. Combined with: hematological markers or inflammatory markers or oxidative stress markers.

Refinement methods used:

1. **Boolean Operators:**

• Used parentheses to group terms effectively.

For example:

• (isotretinoin effect OR isotretinoin) AND (hematological markers OR inflammatory markers OR oxidative stress markers)

• This ensures the search engine processes the terms logically.

2. **Truncation and Wildcards:**

- Use truncation () to capture variations of a word.

For example:

• `isotretinoin` to include terms like isotretinoin, isotretinoins, etc.

• `marker` to include markers, marking, etc.

3. **Filters:**

• Applied filters for the publication year (2020–2025) and open-access articles directly in the database search tools.

• Used filters for study type (e.g., clinical trials, observational studies) if relevant.

4. **Synonyms and Related Terms:**

• Considered adding synonyms or related terms to ensure comprehensive coverage.

For example:

• For isotretinoin: 13-cis-retinoic acid, Accutane.

• For markers: biomarkers, blood parameters, laboratory parameters.

5. **Database-Specific Adjustments:**

• Each database may have unique search syntax.

For example:

• PubMed: Use Medical Subject Headings (MeSH) terms like Isotretinoin/adverse effects or Oxidative Stress.

• Google Scholar: Use quotes for exact phrases and the `site:` operator to limit to specific domains (e.g., `site:.edu`).

6. **Exclusion Criteria:**

• Explicitly exclude irrelevant studies (e.g., animal studies, in vitro studies) they were not of interest.

Example Search Query:

Here's an example of a refined search query for PubMed:

(isotretinoin effect OR isotretinoin OR 13-cis-retinoic acid OR Accutane) AND (hematological markers OR inflammatory markers OR oxidative stress markers OR biomarkers OR blood parameters) AND (2020:2025[dp]) AND English[la] AND open access[filter]

Additional Tips:

• Manual Screening: After retrieving results, manually screen titles and abstracts to ensure relevance.

• Citation Tracking: Check references of included studies to identify additional relevant articles.

• Grey Literature: Consider searching for conference proceedings or preprints if relevant.

Impact of Isotretinoin on Hematologic Parameters

During sixth months of oral isotretinoin therapy for patients with acne vulgaris, Demirci E et al. found that there is a significant decrease in neutrophils count, a significant increase in platelets count, and non-significant changes in hemoglobin, and white blood cell count [20]. Another study done by Oğuz et al. concluded that there is a significant decrease in WBC count, RBC count, neutrophil count, and monocyte count. It also revealed a significant increase in platelet count and hemoglobin level [12]. In Iraq in 2022, Abdulwahab et al. revealed that isotretinoin effect on platelet, and white blood cells count was not significant [21].

Impact of Isotretinoin on Lipid Profile

The effects of systemic isotretinoin therapy on lipid profiles in acne patients have been widely studied, with varying results reported across different studies. A 2024 retrospective study by Alrasheed et al. revealed that treating acne patients with systemic isotretinoin led to an increase in high-density lipoprotein (HDL) levels and a decrease in total cholesterol and low-density lipoprotein (LDL) levels [22]. This suggests a potentially favorable lipid-modulating effect of isotretinoin in some patients. In contrast, Al Dhafiri et al. found that most acne patients treated with isotretinoin maintained normal cholesterol and triglyceride levels both before treatment and after 1 to 3 months and 4 to 6 months of therapy [23]. This indicates that isotretinoin may not significantly alter lipid profiles in certain patient populations.

However, other studies have reported less favorable outcomes. Al Yaqoubi et al. observed an elevation in LDL, HDL, cholesterol, and triglyceride levels in patients undergoing isotretinoin therapy [24], highlighting the potential for isotretinoin to induce dyslipidemia in some individuals. Similarly, a 2021 cross-sectional case-control study conducted by Mohamed et al. on 100 acne vulgaris patients demonstrated significant elevations in total cholesterol, triglycerides, and LDL levels following isotretinoin treatment [25]. These findings underscore the variability in lipid responses to isotretinoin therapy and suggest that its impact on lipid metabolism may differ among patients. Collectively, these studies indicate that systemic isotretinoin therapy can have diverse effects on lipid profiles, ranging from beneficial changes to significant elevations in cholesterol and triglyceride levels. This variability underscores the importance of monitoring lipid levels during isotretinoin treatment to identify and manage potential dyslipidemia, ensuring both the efficacy and safety of the therapy. Further research is needed to better understand the factors influencing these lipid changes and to develop strategies for mitigating adverse effects.

Impact of Isotretinoin on C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein synthesized by the liver and is widely recognized as a general biomarker for inflammatory and infectious diseases in clinical practice [26]. Studies investigating the relationship between CRP levels and systemic isotretinoin therapy in acne patients have yielded mixed results. Hareedy et al. reported that systemic isotretinoin therapy led to an increase in CRP levels, suggesting a potential pro-inflammatory effect of the treatment [27]. In contrast, Yavuz et al. found a statistically significant decrease in CRP levels among acne patients treated with systemic isotretinoin, indicating an anti-inflammatory effect of the therapy [28]. Additionally, Monib et al. concluded that serum CRP levels in acne patients were significantly higher compared to those in healthy controls, highlighting the presence of systemic inflammation in individuals with acne vulgaris [29]. Similarly, Nauli et al. demonstrated that CRP levels in patients with acne vulgaris were elevated compared to control subjects, further supporting the association between acne and systemic inflammation [30]. These findings suggest that CRP levels may be influenced by both the underlying inflammatory nature of acne vulgaris and the effects of systemic isotretinoin therapy. The discrepancies in study outcomes may be attributed to differences in study design, patient populations, treatment durations, or dosages. Further research is needed to clarify the relationship between isotretinoin therapy and CRP levels, as well as its implications for the management of acne and associated inflammatory responses.

Impact of Isotretinoin on Interleukin-8 level

P. acnes infection is a key factor in the development of acne vulgaris, as it triggers the production of interleukin-8 (IL-8) and various other proinflammatory molecules [31]. IL-8, a chemokine involved in neutrophil recruitment and inflammation, plays a significant role in the inflammatory processes associated with acne. In a 2023 cross-sectional study, Singh et al. concluded that IL-8 is critically involved in the pathogenesis of acne vulgaris, further emphasizing its importance in the disease's inflammatory mechanisms [32]. Supporting this, a randomized clinical trial conducted by Shubber et al. demonstrated that IL-8 levels were significantly elevated in acne patients before treatment compared to healthy controls. This finding highlights the association between IL-8 and the inflammatory nature of acne. The same study also reported a significant reduction in IL-8 levels after one month of systemic isotretinoin therapy, suggesting that isotretinoin effectively modulates inflammatory pathways in acne patients [33]. These findings collectively indicate that IL-8 is a key mediator in the inflammatory response to P. acnes infection and that systemic isotretinoin therapy can significantly reduce IL-8 levels, thereby alleviating inflammation. This underscores the dual role of isotretinoin not only in reducing sebum production and comedogenesis but also in mitigating the inflammatory component of acne vulgaris. Further research is needed to fully elucidate the mechanisms by which isotretinoin influences IL-8 and other inflammatory markers, as well as its broader implications for acne treatment.

Impact of Isotretinoin on Malondialdehyde Level

Puspita et al. demonstrated that malondialdehyde (MDA) levels, a marker of oxidative stress, increase in correlation with the severity of acne vulgaris [11]. This suggests that oxidative stress plays a role in the progression and severity of the condition. Further supporting this, Saleh et al. observed that after three months of systemic isotretinoin therapy, there was a significant elevation in MDA levels among patients with moderate acne and a highly significant elevation in those with severe acne [34]. This indicates that isotretinoin therapy may exacerbate oxidative stress, particularly in more severe cases. Similarly, a prospective cohort study conducted by Alaqrawi et al. found that two months of systemic isotretinoin therapy led to a significant increase in MDA levels in patients with acne vulgaris [35]. This further underscores the potential of isotretinoin to induce oxidative stress during treatment. In Iraq, a follow-up study by Abd-Alkareem et al. also reported that systemic isotretinoin therapy caused an elevation in MDA levels in individuals with acne [5]. Collectively, these studies highlight a consistent pattern of increased oxidative stress, as indicated by elevated MDA levels, in patients undergoing systemic isotretinoin therapy for acne vulgaris. This suggests that while isotretinoin is effective in treating acne, its impact on oxidative stress parameters should be carefully monitored, and strategies to mitigate oxidative damage may need to be considered during treatment.

Impact of Isotretinoin on Total Antioxidant Status

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. This imbalance plays a significant role in the pathophysiology of various diseases. Total antioxidant status (TAS) is a key indicator that reflects the cumulative effect of all antioxidant agents present in plasma, providing insight into the body's overall antioxidant capacity [36]. In a follow-up study conducted by Acer et al. on patients with mild to moderate acne vulgaris

who were not undergoing systemic isotretinoin treatment, it was found that the total antioxidant status was elevated compared to healthy controls [37]. This suggests that acne vulgaris itself may be associated with an adaptive increase in antioxidant activity to counteract oxidative stress. However, in patients treated with systemic isotretinoin, a decline in total antioxidant status has been reported [38]. This reduction in TAS may indicate that isotretinoin therapy could impair the body's antioxidant defenses, potentially contributing to increased oxidative stress.

Effects on Other Organ Systems

Musculoskeletal System: Isotretinoin has been associated with myalgia, arthralgia, and, rarely, premature epiphyseal closure in adolescents. Long-term use may contribute to bone mineral density loss, though evidence is inconclusive [39].

Ocular Effects: Dry eyes, conjunctivitis, and night vision disturbances are common side effects. These symptoms are typically reversible after discontinuation of treatment [39].

Psychiatric Effects: Isotretinoin has been controversially linked to mood changes, depression, and suicidal ideation. While some studies suggest a potential association, others have found no significant causal relationship.

Reproductive System: Isotretinoin is a known teratogen, and strict pregnancy prevention measures are mandatory for females of childbearing potential. Effects on male fertility remain unclear, with no consistent evidence of significant harm [39].

Conclusion

Systemic isotretinoin therapy, a widely used treatment for severe acne, has been shown to induce various hematological and biochemical changes in patients. Based on the review, it is evident that isotretinoin can significantly impact several blood parameters and inflammatory markers. Specifically, the therapy has been associated with a decrease in neutrophil count, red blood cell (RBC) count, monocyte count, interleukin-8 (IL-8) levels, and total antioxidant status (TAS). These reductions suggest that isotretinoin may exert suppressive effects on certain immune cells and inflammatory pathways, as well as on antioxidant defenses. On the other hand, systemic isotretinoin therapy has been linked to an increase in platelet count, hemoglobin (Hb) level, C-reactive protein (CRP) level, and malondialdehyde (MDA) level. The elevation in platelet count and Hb level may indicate a compensatory response or a direct effect of isotretinoin on hematopoiesis. The rise in CRP, a marker of systemic inflammation, and MDA, a marker of oxidative stress, suggests that isotretinoin may also trigger pro-inflammatory and oxidative processes in the body. However, the findings are not entirely consistent across all studies. Some research reports non-significant changes in platelet count, Hb level, and white blood cell (WBC) count following isotretinoin treatment. These discrepancies may be attributed to differences in study design, patient populations, dosages, or duration of therapy. Further research is needed to clarify the mechanisms underlying these changes and to determine their clinical significance.

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Conflict of Interest

The authors declare no conflict of interest.

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