DERMIS

Review Article 2025; 5(3):40

Metabolomic Profiling of Sebum in Acne Patients to Identify Precision Treatment Targets Beyond Isotretinoin

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Received : June 14, 2025
Published : June 30, 2025

ABSTRACT

Metabolomic profiling of sebum in acne patients offers a unique approach to identifying precision treatment targets beyond isotretinoin by characterizing lipidomic alterations, inflammatory mediators, and microbial metabolites that contribute to disease pathogenesis. Comprehensive analysis of sebum composition using mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy reveals distinct metabolic signatures associated with acne severity, including dysregulated free fatty acids, altered ceramide ratios, and increased pro-inflammatory lipid mediators such as leukotrienes and prostaglandins. Elevated levels of squalene peroxidation and linoleic acid deficiency contribute to follicular hyperkeratinization and microbial dysbiosis, exacerbating inflammatory cascades driven by *Cutibacterium acnes*. Metabolomic data also highlight systemic metabolic shifts, including insulin resistance-associated lipid perturbations and androgen-driven sebaceous hyperactivity, providing insight into individualized acne subtypes that may respond differentially to treatment. Identification of these metabolic biomarkers facilitates the development of targeted interventions such as lipid-modulating agents, antioxidant therapies, and microbiome-based treatments tailored to specific acne phenotypes. Challenges remain in standardizing metabolomic analysis across diverse populations and

DOI: https://doi.org/10.35702/Derm.10040

integrating findings into clinical practice, but advances in computational modeling and machine learning offer promising pathways for refining precision dermatology approaches. Expanding acne therapeutics through metabolomics-guided strategies may improve treatment efficacy, reduce reliance on systemic retinoids, and minimize adverse effects associated with conventional therapies.

Keywords: Metabolomic Profiling, Metabolomics, Lipidomics, Targeted Acne Treatments, Acne Pathogenesis, Nuclear Magnetic Resonance Spectroscopy, Dermatology

INTRODUCTION

Acne vulgaris is a common chronic inflammatory skin disorder of the pilosebaceous units of the skin [1]. The pathogenesis of acne vulgaris is influenced by multiple factors, including excessive sebum production, altered keratinization, bacterial involvement (*Cutibacterium acnes*), and Th17-driven inflammation [2]. Acne development is also linked to changes at the transcriptional level of insulin-like growth factor 1 (IGF-1) and androgen signaling, which ultimately suppresses the nuclear activity of p53, forkhead box O1 (FoxO1), and forkhead box O3 (FoxO3), leading to increased sebum production, inflammation, and clogged pores [2]. Individuals suffering from acne may experience several adverse effects, including discomfort, emotional distress, disfigurement, and permanent scarring, which ultimately diminish the patient's physiological and social well-being [1]. The primary goal of acne treatment is to control existing lesions, prevent scarring, reduce the duration of the condition, and minimize morbidity by addressing contributory pathogenic factors [1]. Current treatment options include a variety of topical therapies, including retinoids and benzoyl peroxide, oral antibiotics such as doxycycline, hormonal therapy such as oral contraceptives and spironolactone, systemic retinoids, and procedural therapies [3]. However, each treatment modality has variable efficacy and unique side effect profiles, most commonly noted dryness and skin irritation with topicals, GI upset with oral antibiotics, and mood changes with hormonal therapies [3]. Isotretinoin, a systemic retinoid and currently the most effective anti-acne drug, restores the expression of the major pathogenic mechanisms of acne by upregulating key transcription factors: p53, FoxO1, and FoxO3, ultimately reducing sebaceous gland activity and inflammation [2]. Despite being the most effective treatment option, isotretinoin has the most significant side effect profile, including teratogenicity, ovarian reserve reduction, depression risk, extremely dry skin, hypertriglyceridemia, and intracranial hypertension [2]. Therefore, while various treatment options exist, achieving optimal acne management requires balancing efficacy with potential side effects, often necessitating a personalized, combination-based approach.

Metabolomic profiling has the potential to serve as a novel approach to the personalized management of acne. Typically, via nuclear magnetic resonance (NMR), liquid chromatography-mass spectrometry (LC-MS), or gas chromatography-mass spectrometry (GC-MS), metabolic profiling analyzes low-molecular-weight metabolites to assess biological responses to genetic, physiological, pathological, and developmental factors [4]. Metabolomics has become a valuable tool in medical research, aiding early diagnosis, personalized treatment, and drug efficacy evaluation [5]. By examining biological samples, metabolomics allows the investigation of external influences (e.g., drug treatments) and the understanding of inherent metabolic variations within populations [4]. Its relevance to acne treatment lies in its ability to detect small yet significant metabolic changes without requiring whole-genome sequencing [5]. Analyzing metabolites in easily accessible body fluids like sweat and sebum, metabolomics can help identify acne-specific biomarkers, assess treatment responses, and optimize therapeutic strategies [5]. Techniques such as LC-MS, GC–MS, and NMR enable both broad-spectrum (non-targeted) and specific (targeted) analyses, enhancing our understanding of acne pathophysiology and improving treatment precision [5]. Zhu et al. have already begun to demonstrate the relevance of metabolomic profiling to acne management by utilizing metabolomics to evaluate Cryptotanshinone's mechanism of action and potential as an acne intervention [6]. With continued use, metabolomic profiling holds great promise for advancing personalized acne management by identifying metabolic disruptions in sebum composition, offering new insights into acne pathophysiology, and uncovering potential treatment targets beyond conventional therapies.

A focused literature search was conducted using PubMed and Google Scholar, prioritizing studies between 2000 and 2024 that utilized mass spectrometry technologies, nuclear magnetic resonance, and related methodologies to study acne pathogenesis. This review provides insight on the current landscape and application of metabolomic and lipidomic profiling for the treatment of acne, with the goal

of identifying potential treatments with greater precision beyond isotretinoin.

Lipidomic Alterations in Acne

The skin surface lipid (SSL) film maintains the skin barrier, a continuous hydrolipidic film made of sebaceous and epidermal lipids that serve as the interface between the skin and the outside environment [7]. The SSL is a unique composition of lipids due to contributions from sebum and keratinocytes and metabolic contributions of skin surface microbial flora [7]. The outermost layer of the epidermis, the stratum corneum, consists of corneocytes, keratinocytes that have undergone terminal differentiation, suspended in a lipid matrix that mainly consists of ceramides, non-esterified fatty acids (NEFAs), cholesterol, cholesterol esters, and cholesterol sulfate [8,9]. There is wide diversity in NEFAs found in the stratum corneum, with the most prevalent being linoleic acid, oleic acid, palmitic acid, and stearic acid [9]. The other major contributor to SSL, sebum, consists mainly of squalene, wax esters, and triglycerides [7].

Alterations in the SSL from sebaceous and cellular lipid contributions have been implicated in acne pathogenesis. Overall, patients with acne were found to have higher levels of cholesterol, wax esters, and squalene-related compounds and decreased levels of linoleic acid in their SSL [10]. While increased oleic acid and its peroxides increased comedogenesis in rabbit-ear models, significant sebum linoleic acid concentration decreases have been observed in acne patients [11,12]. Linoleic acid alterations are implicated in hyperkeratinization and comedone formation. Pappas et al. showed that linoleic acid is used in sebaceous glands in a beta-oxidation reaction, resulting in acetyl Co-A, a precursor for squalene and wax ester synthesis. This process is unique to sebocytes and involves their differentiation. Decreased linoleic acid disrupts the skin barrier, allowing higher permeability for inflammatory substances and increased comedogenesis [12-14]. The formation of comedones results from hyperproliferation of keratinocytes, a process driven by alterations in sebaceous lipid composition, androgens, local cytokine production, and bacteria [13]. The dysregulation of NEFAs in SSL results in the breakdown of the skin barrier and increased comedogenesis, making these free fatty acids potential targets in the treatment of acne.

In addition to alterations in sebaceous lipids and SSL composition, altered ceramide ratios also disrupt the skin barrier. Ceramides are the backbone of the stratum corneum extracellular matrix, making up 50% of its total lipid content [9,15]. The ceramides are a heterogeneous group of varied hydrophobic chain lengths, saturations, and hydroxylation patterns. While long-chain ceramides are strongly associated with maintaining skin barrier function, an increase in short-chain ceramides results in barrier impairment [15]. Two ceramides, sphinganine and phytosphingosine, are the most prevalent in SSL and are associated with decreased acne in adolescents. Zhou et al. found that these ceramides were increased in adolescent patients with more mild acne, suggesting a protective effect, but were significantly decreased in patients with severe acne [16]. This is likely secondary to the anti-inflammatory effects of these molecules. Phytosphingosine has antimicrobial properties against Propionibacterium acnes (P. Acnes), a bacterium linked to an inflammatory host response.

Furthermore, acne is associated with an overall proinflammatory state, with increases in cytokines, hypothesized to be induced by an immune reaction to P. Acnes. The upregulation of cytokines is associated with increased comedogenesis, with increased interleukin alpha and interleukin 1 in many comedones [9,17]. Additionally, proinflammatory lipid mediators such as leukotrienes and prostaglandins can increase the inflammation contributing to acne. Leukotriene B4 is a proinflammatory molecule derived from arachidonic acid that is increased by inflammatory mediators such as endotoxin, complement fragments, TNF-alpha, and interleukins. It is involved in the recruitment and activation of neutrophils, monocytes, and eosinophils and stimulates the production of proinflammatory cytokines resulting in augmented and prolonged inflammation [18]. Zouboulis found a 60% decrease in acne severity index at 3 weeks and a 70% reduction in inflammatory lesions at 3 months following treatment with a specific lipo-oxygenase inhibitor. A selective increase in prostaglandin E2 has also been associated with acne-involved sebaceous glands, with Alestas et al. finding a significant upregulation of COX-2 in these glands in a mouse model. These findings support the association between increased prostaglandin synthesis in sebaceous glands and increased acne. The findings of increased prostaglandin and leukotrienes in acne support their role in inflammation, contributing to acne vulgaris pathogenesis.

While it is widely recognized that patients with acne vulgaris

have increased sebum production, the alteration in NEFAs and ceramide composition of SSLs also contributes to the pathogenesis of acne through the disruption of the skin barrier, hyperkeratinization, and increased proinflammatory mediators. Isotretinoin targets sebaceous glands, reducing their activity, but targeting these lipid alterations or the proinflammatory mediators they induce represents another mechanism of action of treatment.

Lipidomic Analytic Techniques

Advancements in analytical technologies such as mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMR) have the potential to assist the direction of treatment for moderate to severe acne due to their ability to provide highly detailed lipidomic profiles. There are multiple MS techniques that can provide detailed lipidomics, such as matrix-assisted laser desorption and ionization mass spectrometry, electrospray ionization mass spectrometry, and ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry. These technologies provide a comprehensive analysis of cutaneous lipids involved in acne pathogenesis and can deliver further insight into their function and mechanism of action [19]. Sebum and lipids play a known role in acne pathogenesis; however, their composition is quite complex. Therefore, MS and NMR can provide comprehensive data for more precise analysis. Early pioneering thin-layer chromatography studies helped identify eight subclasses of ceramides in the stratum corneum. The implementation of MS increased sensitivity, allowing for the identification of 12 ceramide subclasses plus additional lipid classes [20]. Technological advancements will only continue to improve and expand the detailed analytics available for cutaneous lipids.

There is varying data on what is considered the ideal analytical technique for lipid profiles. Over the years, ceramide composition has been obtained using high performance thin layer chromatography (HPTLC) in conjunction with NMR. One study indicates that using 600 MHz NMR equipment is more advantageous than MS-based approaches and is helpful for preclinical and clinical monitoring of the efficacy of sebum-reducing agents in animals and humans [21]. One disadvantage of MS techniques included their labor-intensive nature and requirements for large sample amounts. However, as technology continues to advance, a solution for these disadvantages appears. A newer technique using layer chromatography plus MS was proven more efficient, requiring less analysis time and fewer quantities of material while providing a more detailed profile [22]. In addition, gas chromatography mass spectrometry (GC-MS) can provide structural information and detailed fingerprints of intact sebaceous lipids [23]. Furthering the idea that technological advancements allow for more sensitive and specific data that can help guide patient-specific treatment options.

One technique that can provide large-scale quantitative data is high-throughput shotgun mass spectrometry. High throughput is a prerequisite for any prospective clinical setting of skin lipidomics and derma-pharmacological and cosmetic applications, making its potential for evaluating acne severity very promising [20]. This technique has proven its capability as a tool for rigorous and systematic studies of the influence of drugs on the skin lipidome [20]. In addition, this method allows for observations of differences in lipid profiles between specific sites on the body, such as the forehead, compared to the chest and back. This can ultimately guide treatment options for acne based on the lipidomic profile that is specific to the location of the acne.

The manifestations of acne exist on a broad spectrum of severity, making it reasonable to assume that metabolomic profiles associated with acne also vary on a similar spectrum. As stated earlier, there are many ways patients can develop acne symptoms. Due to the complexity of the subclasses of lipids and their varying compositions, it is important to utilize these technological advancements as a more individualized approach with targeted diagnostic and treatment strategies. Camera et al. reported that the major differentiating lipid species when comparing healthy and acne sebum patients include diacylglycerols (DGs), fatty acyls, sterols, and prenols [23]. This study used high performance liquid chromatography-mass spectrometry (HPLC-MS) to analyze the lipid profile of both acne and healthy patients. They were the first to report the correlation between significantly high levels of DGs and acne severity, which could implicate the use of DGs as a potential biomarker of disease stage and therapeutic response to treatment [23]. Zhang et al. also utilized HPLC-MS to investigate the lipidomics of moderate-to-severe acne and identified 26 differential lipid metabolites when compared to healthy controls. Glycerophospholipids (GP), sphingolipids (SP), and glycerolipids (GL) were among the top components identified in moderate-to-severe acne patients [24]. These findings highlight the potential of detailed analytics in

advancing the understanding of acne pathophysiology and severity and ultimately improve targeted treatment approaches.

Microbial Dysbiosis and Inflammatory Cascades

Follicular hyperkeratinization remains an essential event in the development of acne vulgaris [25]. Keratinization is the normal biological process of hardening keratin proteins within epithelial cells throughout the body [26]. That said, the result of this process is the cornification, or drying and hardening of epithelial cells, resulting in the formation of a protective barrier [26]. Though essential for survival due to its role in protecting against pathogens and water loss, this process is a key element in developing acne lesions [27]. The pattern of hyperkeratinization involved in the development of acne vulgaris is otherwise known as retention hyperkeratosis, in which keratinocytes become cohesive and do not shed off of the skin's surface [27]. In individuals dealing with acne, an altered structure of the keratinocytes of the stratum corneum consisting of a more significant number of desmosomes and tonofilaments, both types of specialized junctions between skin cells, contributes to the development of a thicker and more cohesive stratum corneum, contributing to an abnormal shedding process of surface skin cells [27]. The lack of normal shedding of the skin in acne-prone individuals leads to the formation of microcomedones beneath the surface of the skin, ultimately leading to the development of acneic lesions [27]. The accumulation of these dead epithelial cells creates a favorable environment for the proliferation of bacteria such as *Cutibacterium acnes*, among many others, which have been implicated in the development of acne vulgaris.

The buildup of follicular debris occurs due to hyperkeratinization, leading to blockage of the pilosebaceous follicle and prevention of natural cleansing via sebum [28]. This results in excess sebum production as a compensatory mechanism, causing sebum accumulation and the development of microcomedones [28]. In addition to sebum's role in the development of comedones, it also plays a role in developing an environment conducive to the growth of a niche microbiome [29]. The skin's natural condition is acidic, desiccated, and lacking nutrients, with all of these factors contributing to the development of a rather hostile environment that is unwelcoming to pathogens [29]. That said, the role of sebum is immensely important, as it serves as a natural lubricant and protectant for the skin to help retain moisture. Alterations in sebum composition can contribute to the pathophysiology of acne vulgaris [30]. Sebum is mainly composed of triglycerides, diglycerides, free fatty acids, wax esters, squalene, and cholesterol [30]. Nearly all of the aforementioned components contribute to the comedogenic effects of sebum, with unsaturated fatty acids playing a major role in accelerating keratinocyte differentiation, leading to blockage of pores in the skin [30]. Thus, when sebum production becomes unregulated, acne vulgaris lesions ensue due to blocked pores due to keratinocyte accumulation.

Cutibacterium acnes, an anaerobic, gram-positive rod, has been found to have an established link to the development of acne vulgaris. Sebum contributes to the proliferation of these bacteria by providing a strong nutrient source and ideal follicular microenvironment [30]. According to Del Rosso et al., C. acnes is most abundant in areas with elevated sebum concentrations, thus providing evidence for the role of sebum in promoting the growth of this bacterium. C. acnes stimulates the production of proinflammatory cytokines within the pilosebaceous unit, further increasing sebum production [30]. In particular, IL-1 contributes to further hyperkeratinization, increasing the inflammatory potential of lipids present in the sebum [30]. Linoleic acid, the precursor fatty acid to squalene and wax esters, is found at a lower concentration within the sebum on skin affected by acne [30]. As a result, increased rates of follicular hyperkeratosis and impairment in the epidermal barrier function have been noted [30]. Together, these factors result in the increased permeability of comedones to inflammatory mediators, manifesting in inflamed skin [30]. Moreover, the lack of linoleic acid leads to a lack of arachidonic acid, causing decreased activation of the PPARγ pathway, which plays a role in the stimulation of anti-inflammatory processes [30]. It has also been found that elevated levels of squalene and squalene peroxidase give rise to comedones and inflammatory acne [30]. As a result of the physiological byproducts of *Cutibacterium acnes*, increases in inflammation and an impaired skin barrier are noted, causing a predisposition to acne vulgaris.

Another important factor in the development of acneic lesions can be attributed to the regional variations in sebum composition. Sebum levels have been discovered to be highest on the nose, forehead, and chin, otherwise known as the T-zone [30]. Sebum composition differences throughout these regions contribute to the development of clinically variable acne lesions [30]. Aside from the contribution of C.

acnes to the development of acne vulgaris, several other species, though found in much smaller ratios, have also been found within the pilosebaceous units of patients affected by acne vulgaris. In particular, Staphylococcus epidermidis, Propionibacterium humerusii, and Propionibacterium granulosum, each representing 1–2.3% of the total clones, have been isolated [31]. However, C. acnes was found to be the predominant bacterial subtype, thus serving as the target for many acne treatments [31]. The study of different probiotics, prebiotics, and symbiotics in treating skin lesions via fostering the growth of beneficial skin probiotics is under study [32]. In particular, Streptococcus thermophiles has been found to promote the production of ceramides in the skin when applied topically [32]. Harnessing the metabolic activity of this bacterial species has shown promise in those with acne-prone skin, as the production of ceramides aids in the maintenance of the skin's hydration and barrier function, which are often compromised due to other drying and irritating acne agents [32]. Improving the skin's barrier via harnessing the power of ceramides can mitigate the adverse effects of various acne treatments, allowing for better adherence to treatment and improved outcomes. More so, they can prevent the worsening of acne lesions due to secondary infection as a result of a compromised skin barrier.

Systemic Metabolic Shifts and Acne Subtypes

Acne vulgaris manifestation is typically considered an interplay between genetics and environment. The role of altered metabolic states in the development of acne presents an important area for further understanding and discovery. Many studies point to the typical Western diet as a possible risk factor for the development of the condition. Acne vulgaris is an extremely prevalent disease in developed nations, with 85% of adolescents experiencing the condition. This high degree of afflicted individuals is not found worldwide, as countries that follow more traditional dietary habits of their region do not see the high prevalence of the condition. A key difference is seen in areas with a high prevalence of acne: regular consumption of high glycemic index foods [33]. Glycemic index refers to the body's blood glucose levels after ingesting a carbohydrate relative to a reference food such as glucose. Consumption of a low glycemic index diet has been found to have health benefits in insulin control and lipid regulation [34]. This brings into question the possible relationship between metabolic dysregulation and the pathogenesis of Acne vulgaris.

Intake of hyperglycemic carbohydrates and dairy products increases growth factors like insulin and insulin-like growth factor 1 (IGF-1). These growth factors activate the mechanistic target of rapamycin complex 1 (mTORC1). This protein complex has implications for several pathologies, such as insulin resistance, type 2 diabetes, cancer, and obesity [33]. Increased mTORC1 signaling may also contribute to acne. In one small study by Monfrecola et al., a non-significant increase in mTOR gene expression was observed in acne patients vs healthy controls [35]. Although the study was limited by a small sample, a more recent study by Akdağ et al. observed the differences in mTORC1 levels in patients with acne and metabolic syndrome, patients with acne and no metabolic syndrome, and healthy controls. The study found significantly increased levels of mTOR gene expression in patients with acne and metabolic syndrome and increased levels in patients with acne and no metabolic syndrome [36]. This finding suggests that there may be an important underlying role of mTORC1 dysregulation in acne development, particularly in patients with metabolic syndrome.

One mechanism in which mTORC1 signaling may be implicated in acne pathogenesis is via androgen synthesis. It is well understood that increased androgens play a crucial role in sebum production and the development of acne [37]. At puberty, increased IGF-1 stimulates androgen synthesis, which results in the downstream activation of mTOC1. mTORC1 activates the transcription factor sterol response element binding factor 1 (SREBP1), leading to the expression of acetyl-CoA carboxylase. This enzyme acts as the rate-limiting enzyme in fatty acid synthesis. Additionally, SREBP1 desaturates free fatty acids, resulting in the production of oleic acid and free palmitic acid. Oleic acid encourages biofilm production by Propionibacterium acnes, which can result in disrupted follicular keratinization and barrier dysfunction. Palmitic acid can activate Toll-like receptor 2, resulting in inflammation due to activation of the NLRP3 inflammasome [33]. Additionally, mTOC1 plays a role in proinflammatory signaling within keratinocytes. In a study by Young et al., human keratinocytes were treated with TNFα, activating mTOR and NFκB signaling. This increased inflammatory cytokine such as TNFα, IL-6, and IL-8 [38]. Understanding the role of altered metabolic dysregulation and inflammation on the development of Acne vulgaris provides possible new avenues for treatment of the condition.

Isotretinoin has long been the mainstay treatment for severe Acne vulgaris due to its ability to suppress sebum production. Isotretinoin acts on the retinoic acid receptor, secondarily increasing FoxO expression. This set of transcription factors inhibits mTORC1 signaling by two mechanisms. FoxOs increase levels of Sestrin3, an AMP-activated protein kinase (AMPK) activator. This leads to the activation of tuberous sclerosis proteins (TSC1/TSC2), which have inhibitory effects on mTOC1. Secondly, FoxO leads to decreased IGF-1 concentrations [39]. However, as more understanding between metabolic syndrome and acne vulgaris pathogenesis develops, there is potential for more individualized treatments based on metabolic status.

One promising approach to treating acne in patients with metabolic syndrome is metformin. This drug activates AMPK, leading to mTORC1 inhibition. This treatment has classically been used in women with PCOS to improve insulin resistance and the side effects of increased androgens, such as acne [39]. Because of its efficacy in decreasing acne in female patients experiencing metabolic and hormonal dysregulation, a study by Fabbrocini et al. observed the impact of metformin on male acne patients with metabolic abnormalities. This study found a significant difference in acne reduction between patients treated with metformin versus those who did not receive metformin [40]. This finding suggests that in treating refractory Acne vulgaris, it may be important to consider metabolic status in both male and female patients.

Conservative methods may also help improve Acne vulgaris. Because of the suggested relationship between a high glycemic diet and acne, clinicians should help educate patients on dietary changes that may improve their metabolic state. This may include decreasing total energy intake, decreasing animal product consumption, and increasing fruit and vegetable intake [39]. Overall, in patients experiencing metabolic dysregulation and Acne vulgaris, treatment targeted at decreasing the activation of mTORC1 may help reduce or eliminate the condition.

Translating Metabolomic Findings into Targeted Therapies

Recent metabolomic studies have elucidated specific lipid alterations in acne patients, paving the way for targeted therapeutic interventions. A notable finding is the deficit of omega-3 fatty acids (ω-3 FAs) in individuals with acne, which has been linked to increased inflammation and dysregulation of lipid metabolism. A cross-sectional study demonstrated a lower mean ω-3 FA levels and higher mean IGF-1 levels in acne patients, as well as higher ω-3 FA levels in non-acne patients with regular legume intake and oral ω-3 FA supplementation, thus suggesting a protective role of ω-3 FAs against acne-related inflammation [41]. Subsequent research indicated that many acne patients have an ω-3 FA deficit, which can be ameliorated through a Mediterranean diet and oral supplementation with algae-derived ω-3 FAs, leading to significant improvements in acne severity [42]. Ceramides, an additional potential target for acne therapy, play a crucial role in maintaining skin barrier integrity and modulating inflammation. Ceramide-enriched topical formulations are emerging as a promising treatment approach, as lipidomic analyses have revealed that changes in lipid composition and increased lipid levels worsen with acne severity [43]. Ceramide deficiency can directly cause an increase in proinflammatory lipid mediators associated with acne progression. Furthermore, lipid-lowering drugs targeting genes such as PCSK9, LDLR, and LPL have been shown to reduce the risk of acne vulgaris, indicating the potential for expanding systemic therapeutic applications [44]. These findings collectively support the potential of lipid-modulating agents and dietary interventions in managing acne, offering alternatives to traditional systemic retinoid therapies, such as isotretinoin, which, while effective, are often associated with significant side effects.

Microbiome-based approaches offer non-antibiotic alternatives to acne treatment, avoiding the microbiome disruption caused by antibiotics. Probiotics and prebiotics provide a sustainable, long-term strategy with minimal side effects compared to conventional therapies. Probiotic therapies with Lactobacillus and Bifidobacterium strains have shown promise in modulating immune responses and reducing acne inflammation, with studies indicating significant reductions in inflammatory lesions and improved skin barrier function [45]. These strains have been found to reduce the production of proinflammatory cytokines, such as IL-6 and TNF-α, which are key contributors to acne-related inflammation, demonstrating their potential for acne treatment. Prebiotics, like fructooligosaccharides (FOS), alpha-glucan oligosaccharide, beta-glucan, and inulin, promote beneficial bacterial growth by providing essential nutrients while also suppressing acne-associated pathogens by enhancing the efficacy of probiotics [46]. By feeding beneficial bacteria, prebiotics strengthen the microbiome, encouraging the dominance of microbes that are less likely to trigger inflammatory responses, thus supporting skin health

and reducing acne outbreaks. Additionally, postbiotics, which include short-chain fatty acids (SCFAs), have been shown to directly combat acne-causing bacteria while preserving the overall diversity of the skin microbiome, which then minimizes the need for antibiotics and the risks associated with their overuse [47]. SCFAs ability to improve mitochondrial metabolism, promote keratinocyte differentiation, and inhibit inflammatory responses induced by C. acnes depicts its antimicrobial properties. Therefore, personalized acne treatments that are based on metabolomic and microbiome analyses may be able to improve acne patient outcomes.

One of the primary challenges in standardizing metabolomic analysis for acne is the variability in sebum composition across individuals and populations, making it difficult to develop universal metabolic markers. Factors such as age, gender, hormonal fluctuations, diet, and ethnicity can all influence sebum production and lipid composition, leading to significant heterogeneity in acne severity and response to treatments. For instance, studies have shown that androgen-driven sebum production varies between males and females, which contributes to differing acne phenotypes, particularly in puberty and adulthood [48]. These population-specific differences complicate the development of a universal set of biomarkers that could accurately predict acne severity or treatment efficacy across all groups. In addition, sebum composition can vary even within a single individual based on factors such as stress levels, diet, age, and environmental exposures like pollution [49]. This makes it difficult to establish consistent metabolic markers that can be generalized to all patients. Additionally, integrating metabolomic findings into clinical practice requires not only a better understanding of the pathophysiology but also the consideration of cost-effectiveness and accessibility. Despite these challenges, future advancements and standardization of reporting protocols offer potential solutions to refine and integrate metabolomic data into routine clinical practice for more personalized acne treatments [50,51].

CONCLUSION AND FUTURE DIRECTIONS

This review is meant to highlight the significant potential of metabolomic profiling in advancing our understanding of the pathogenesis of acne, with the goal of creating a more targeted approach to diagnosis and treatment. Acne development is correlated with sebum overproduction, lipid composition disruption, linoleic acid deficits, free fatty acid increases, and squalene peroxidation. Utilizing novel computational technologies such as nuclear magnetic resonance spectroscopy and mass spectrometry to analyze lipid metabolites opens avenues for large-scale exploration of the metabolome associated with acne. It is widely recognized that patients with acne vulgaris have increased sebum production. However, alterations in NEFAs and ceramide composition of SSLs are additional key mediators of skin barrier disruption leading to the hyperkeratinization and pro-inflammatory pathways seen within the development of acne vulgaris. Thin layer chromatography, MS, and HPLC-MS have identified ceramide subclasses and differential lipid metabolites compared to healthy controls, proving their potential as valuable tools for rigorous and systematic studies of the influence of drugs on the skin lipidome. While Isotretinoin reduces the activity of sebaceous glands, targeting sebum overproduction, lipid alterations, and pro-inflammatory mediators represent promising pharmacological targets that can diagnose and monitor acne vulgaris through lipidomic computational technologies.

As more understanding between metabolic syndromes and acne vulgaris pathogenesis develops, more individualized treatments based on metabolic status may be needed. Harnessing the metabolic activity of the bacterial species has shown promise in those with acne-prone skin, as the production of ceramides aids in maintaining the skin's hydration and barrier function. Additionally, the suggested relationship between a high glycemic diet, deficits of omega-3 fatty acids, and postbiotics is shown to directly combat acne-causing bacteria, open avenues for targeted diet interventions in which clinicians educate patients to improve their metabolic state and slow the progression or development of acne. These findings collectively support the potential of lipid-modulating agents and dietary interventions in managing acne, offering alternatives to traditional systemic retinoid therapies.

Population-specific, hormonal, and insulin sensitivity variations continue complicating the development of a universal set of biomarkers to accurately predict acne severity and treatment efficacy across diverse patient populations. Integrating metabolomic findings into clinical practice requires a more comprehensive understanding of the pathophysiology and consideration of cost-effectiveness and accessibility. Despite these challenges, metabolomic profiling is promising for advancing personalized acne management, offering new insights into acne pathophysiology, and uncovering potential

treatment targets beyond conventional therapies.

ACKNOWLEDGEMENTS

None.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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