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Acne vulgaris - review on pathogenesis and treatment

Bartłomiej Żmuda,

Norbert Barlicki Memorial Teaching Hospital No.1 of the Medical University of Lodz, ul. Dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland

https://orcid.org/0009-0005-6290-0455

zmudabartek98@gmail.com

Michał Żuberek,

Faculty of Medicine, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Jagiellonska 13, 85-067 Bydgoszcz, Poland

https://orcid.org/0009-0008-2358-6784

zuberekmichal99@gmail.com

Daniel Ślusarczyk,

Military Medical Academy Memorial Teaching Hospital – Central Veterans' Hospital, ul. Stefana Żeromskiego 113, 90-549 Łódź, Poland

https://orcid.org/0009-0000-3338-976X

dslusarczyk98@gmail.com

Piotr Pisera,

Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

https://orcid.org/0009-0002-7086-7307

ptrpsr5@gmail.com

Aleksandra Kiełkowicz,

Central Clinical Hospital of Medical University of Lodz, Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0003-7837-0925

aleksandra.kielkowicz@gmail.com

Zuzanna Popińska,

Faculty of Medicine, Comenius University Bratislava Špitálska 24, 813 72 Bratislava, Slovakia

https://orcid.org/0000-0002-8224-6770

Zuzpopinska@gmail.com

Filip Pactwa,

Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

https://orcid.org/0000-0002-9559-5072

filip.pactwa@onet.pl

Wiktoria Jakubowska,

Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland

https://orcid.org/0009-0008-9290-503X

wiktoria.jakubowska@stud.umed.lodz.pl

Corresponding author:

Bartłomiej Żmuda,

Norbert Barlicki Memorial Teaching Hospital No.1 of the Medical University of Lodz, ul. Doktora Stefana Kopcińskiego 22, 90-153 Łódź, Poland

+48 664 711 574, zmudabartek98@gmail.com

Abstract

Introduction:

Acne vulgaris is a common dermatological problem, resulting from a complex interaction of many factors. This article presents a comprehensive overview of the pathogenesis of this condition, examining key aspects such as inflammatory factors, sebum production, colonization by P. acnes, endocrine disruption and lifestyle influences. In addition, various treatments are discussed, including the effectiveness of isotretinoin-based therapy and the potential benefits of antibiotics and retinoids in specific patient groups.

Aim of study:

The aim of the study is to summarize the available knowledge about the Acne vulgaris. The epidemiology, etiology, and methods of treatment were summarized and described.

Materials and methods:

The literature available in PubMed database was reviewed using following keywords: “Acne vulgaris”, “Isotretinoin”, “Therapy of Acne”.

Conclusion:

Research into acne vulgaris has been extensive, yet variations in study methods and descriptions have prevented definitive conclusions. Tailored care for each patient is crucial due to these differences. The disease's development involves various factors including inflammatory mediators, excess sebum production, P. acnes colonization, hormonal imbalances, and lifestyle impacts. Isotretinoin remains the most effective treatment, albeit with potential side effects that need consideration. For specific patient groups, topical antibiotics and retinoids may offer beneficial effects.

Key words: Acne Vulgaris; Isotretinoin; Minocycline

Introduction

Epidemiology

Acne is one of the most common diseases observed in humans, with almost all people aged 15 to 17 years affected[1,2]. Although most prevalent in the teenage years, acne often continue into adulthood[3]. Large study performed on a total of 2155 Caucasian volunteers aged 18-70 revealed that 3% of men and 5% of women still present clinical acne, and aged 50-59 6% of men and 8% of women had physiological acne[4]. The typical age of onset of the disease is considered to be early puberty, it begins as an increase in the production of facial grease, mid facial comedones, with subsequent occurrence of inflammatory reaction[5]. Another study showed that the incidence of acne in children under the age of 12 is increasing, which is probably related to the earlier onset of puberty[6]. According to official data, two-thirds of dermatological interventions on the subject of acne are made by women[7].

Pathophysiology

Acne development is a multi-stage process, regulated by many factors. The most important of these processes are: release of inflammatory mediators into the pilosebaceous unit, formation of comedones due to impaired keratinization, increased sebum production, and colonization of follicles by Proprionibacterium acnes[8]. These processes leads to the transition of a normal pore to microcomedones, comedones, and further to inflammatory lesions. The intensity of the inflammatory response can be enhanced by bacterial antigens[5,9]. There is currently evidence of the influence of hereditary factors on the risk of developing acne[10]. Stress, modern lifestyle[11], smoking, diet[12], UV radiation and drugs[13] are described as triggering or aggravating factors.

Inflammatory background

Inflammatory mediators play major role in etiology of Acne vulgaris. There is proven link between increased activity of Interleukin-1 and keratinocyte hyperproliferation[14]. Inflammation promotes the production of metalloproteinases, beta-defensin 4, granulysin and Interleukin-8[15]. Levels of Interleukin-1β (IL-1β), Interleukin-10 (IL-10), Interleukin-8 (IL-8) and tumor necrosis factor (TNF), as cytokines regulated by nuclear factor-κB (NF-κB), are also elevated[16]. TNF are responsible for increased lipogenesis[17], and IL-8 attract inflammatory cells such as lymphocytes and polymorphonuclear leukocytes[18]. In patients with acne increased expression of COX2 and prostaglandins regulated by COX2 can be

observed[19]. Elevated prostaglandin E2 levels results in hyperplasia of sebaceous gland and excessive sebum production[20].

Sebum

Referring to the works of Sara Tuchayi et al. and Hywel C. Williams et al[21]. sebum, which emanates from the sebaceous gland, represents a composite amalgamation of diverse lipids, encompassing triglycerides, wax esters, squalene, free fatty acids, cholesterol, and related constituents. Its biosynthesis is subject to the regulatory influence of factors that govern cellular processes, lipogenesis, hormone metabolism, and the release of cytokines. Sebaceous lipogenesis, heretofore conceived as less intricate, reveals a heightened complexity involving MYCN-mediated hyperactivation of the epidermal growth factor receptor and the induction of perilipins, a substantial protein group that envelops lipid droplets. The surplus production of sebum is causatively associated with the onset of acne; however, the nexus between sebum production and the severity of acne manifests nuanced variations contingent upon age and gender. Particularly in men, acne demonstrates a more pronounced association with sebum production than is observed in women [21, 22] . Furthermore, in the study by Sara Tuchayi et al. acne is characterized by alterations in the free fatty acid composition of sebum. Individuals affected by acne demonstrate sebum with reduced essential free fatty acids, including linoleic acid. Pro-inflammatory lipid fractions, such as monounsaturated fatty acids (MUFAs) and lipoperoxides, play a contributory role in the development of acne lesions. The skin's ratio of lipid oxidants to antioxidants also exerts an influence on acne. More precisely, the sebum of individuals with acne contains lipoperoxides resulting from the peroxidation of squalene lipids, impacting keratinocyte proliferation and differentiation and contributing to follicular hyperkeratinization. Ethnic groups exhibit distinctive lipid profiles, with discernible variations in specific wax ester lipid fractions observed between individuals of White and African American descent [21].

Role of Proprionibacterium acnes

In both the works of Sara Tuchayi et al. and Hywel C. Williams et al.[21], emphasis is placed on the bacterium Propionibacterium acnes as a pathogenetic factor. The cutaneous microbiota plays a role in the pathogenesis of acne, as evidenced by metagenomic analysis. Although the levels of Propionibacterium acnes (P. acnes) are comparable in both acne patients and healthy individuals, distinct strains exhibit associations with acne. Particularly, P. acnes type III, identified as a proinflammatory strain, induces the upregulation of key mediators, including

proteinase-activated receptor 2 (PAR2), TNF, matrix metalloproteinase 13, and tissue inhibitor of matrix metalloproteinase 2. Certain strains may exacerbate acne lesions through infections. P. acnes and its associated antigens stimulate proinflammatory cytokines in sebocytes, thereby contributing to inflammation. The activation of TH17 and TH1 pathways leads to the secretion of IL-17A and IFNγ. NLRP3 inflammasome activation occurs, and the secretion of IL-1β is inhibited by suppressing NLRP3 expression.The recognition and activation of keratinocytes and sebocytes involve CD1, CD14, and Toll-like receptors (TLRs). TLR2 activation triggers the release of IL-1α, with documented differences in TLR2 expression between acne-involved and normal skin. Antimicrobial peptides in pilosebaceous glands are upregulated in acne lesions and in the presence of P. acnes. Moreover, monounsaturated fatty acids (MUFAs), such as palmitoleic acid and oleic acid, present in the sebaceous gland, exhibit antimicrobial activity. TLR2 ligands stimulate the mRNA expression of enzymes involved in MUFA synthesis in sebocytes. Furthermore, the lauric acid, palmitic acid, and oleic acid found in sebum enhance the expression and activity of antimicrobial peptides in sebocytes against P. acnes. This suggests a significant role for sebum free fatty acids in fortifying the skin's innate immune defense mechanism. [21]

Hormonal imbalance

Debates on acne origins center on hormonal abnormalities, whether from circulating levels or peripheral tissue processing, particularly during puberty. In a cross-sectional study of 835 females over 15 with acne, 54.6% displaying hyperandrogenism had elevated dehydroepiandrosterone (DHEA). Another study found higher androstenedione and testosterone levels in acne patients, and male acne patients had elevated 17α-hydroxyprogesterone, correlating with increased acne severity[23]. In contrast to studies by Wei B et al. and Makrantonaki E. et al[24,25], 17α-hydroxyprogesterone levels were similar in women with or without acne, requiring further research on potential modulation through adrenocorticotropin treatment. Elevated estradiol in women was observed to be protective.

Acne is linked to both systemic and local steroid overproduction, primarily androgens. Sebocytes produce hormones—testosterone, 5α-DHT, oestradiol, oestrone, corticosterone, and cortisol—regulated by locally produced corticotropin-releasing hormone, adrenocorticotropic hormone, or cytokines. It involves systemic and localized alterations in steroid production, with testosterone and 5α-DHT enhancing sebaceous gland activity and sebocyte function. Testosterone influences sebocyte proliferation but not lipid synthesis, indicating additional

factors, such as peroxisome proliferator-activated receptors (PPARs). Changes in 17β-hydroxysteroid dehydrogenases impact lipogenesis genes, with a negative correlation with PPARγ, a key adipocyte differentiation factor [21, 24, 25]. In the works of Sara Tuchayi et al. and Hywel C. Williams et al., the authors also emphasize the involvement of glucocorticoids in the regulation of sebum. Enzymes converting cortisone to active cortisol are prominently expressed in keratinocytes, fibroblasts, and sebaceous glands, with upregulation observed in acne lesions. Adults, both women and men, experiencing acne exhibit elevated serum levels of insulin-like growth factor 1 (IGF1). In women, these levels correlate with acne lesion count, facial sebum excretion rate in post-adolescent patients, and serum levels of 5α-DHT and DHEA sulfate. Furthermore, a high glycemic Western diet and elevated dairy protein intake correlate with activated IGF1 and mTOR signaling, crucial for PPARγ-stimulated lipid uptake and sebocyte differentiation. Notably, testosterone induces mTOR phosphorylation in human sebocytes only in the presence of IGF1, highlighting the pivotal role of local androgen production with circulating IGF1 in sebum synthesis and acne [21].

Smoking, diet and style of life

In the works of Sara Tuchayi et al. and Hywel C et. al[21], attention is drawn to diet, lifestyle, and cigarette smoking. Modern lifestyle factors, including diet, stress, urban noise, socioeconomic pressure, light stimuli, and variations in sleep patterns, pose potential risks for acne. Diet, particularly low-glycemic-load diets, may influence sebum production through endocrine effects. A typical Western diet exacerbates acne, while severe caloric restriction temporarily reduces sebum excretion. Changes in dietary fat or carbohydrate intake can also impact sebum production and composition. Native non-Westernized populations in Papua New Guinea and Paraguay show an apparent absence of acne, supporting dietary influences. Patients with severe acne exhibit higher lipid levels, suggesting possible dyslipidemia. A lower body mass index reduces the risk of acne lesions. The role of smoking in acne development is unclear, with conflicting study results [26,27,28]. Smoking may induce acne through increased oxidative stress. Certain drugs, such as anti-epileptic agents and anticancer drugs, may cause acneiform eruptions, and anabolic drugs can lead to severe forms of acne. Dioxin exposure is associated with chloracne, a severe comedonal acne.

Family history

In the previously mentioned studies, attention was drawn to the fact that genetics contribute to acne. Polymorphisms in IGF1, PPARG, IL6, and IL1A genes are implicated. Genome-wide studies identified acne susceptibility loci in Han Chinese populations (1q24.2 and 11p11.2) [29]. In the UK, specific loci were linked to the transforming growth factor-β cell signaling pathway [30]. In the US, a significant association was found with the MYCN-related polymorphism (rs4133274) [31] . Proteomic analysis of sebaceous follicular casts highlighted proteins involved in inflammation and tissue remodeling, offering insights into acne pathogenesis. Further evidence is required for a comprehensive understanding of acne's genetic background.

Treatment

Acne and the complications it leads to are considered a significant problem because of the visibility of these lesions, and the impact they have on the patient's psychological sphere. Early and aggressive treatment can maximalize probability of therapeutic success. Currently, the most effective therapy is considered to be the combination of a topical retinoid plus an antimicrobial agent, nevertheless the method of treatment should be adapted to the individual patient in each case.

Topical retinoids

Retinoids that can be used topically include tretinoin, adapalene, retinaldehyde, isotretinoin[21]. The main mechanism of action of topical retinoids is to reduce hyperkeratinization and limit adhesion by binding to the retinoic acid receptors and the retinoid X receptors[32]. For this reason, they facilitate the penetration of other topical agents, but also have an inhibitory effect on the process of comedogenesis. Due to these characteristics, topical retinoids are recommended for both comedogenic and inflammatory acne, not only as initial treatment but also as treatment to prevent recurrence [8]. In preventing acne recurrence, it is important to use appropriate topical treatment even if the lesions are not clinically visible[33]. It is worth noting that the use of topical retinoids is not recommended during pregnancy, due to proven harm in human or animal studies.

Topical antibiotics

Topical antibiotics seem to reduce inflammation by acting directly on P acnes, and this is the reason why they show less effectiveness against non-inflamed lesions. The most commonly

used topical antibiotics are clindamycin, erythromycin and tetracycline, for more severe acne it is worth considering combinations with another agent such as benzoyl peroxide or topical retinoids[34].

Other topical therapies

Salicylic acid is an exfoliant present in many over-the-counter preparations, which has comedolytic effects, but no studies have shown its superiority over other topical treatments. Azelaic acid is considered as a potential first-line monotherapy for female adult patients, owing to its antibacterial, comedolytic and anti-inflammatory properties[35]. The patient should be informed about the side effect of the drug which is post-inflammatory hypopigmentation.

Oral antibiotics

Oraly administered antibiotics control acne through their direct antimicrobial properties, as well as their anti-inflammatory activity. Most promising effects are achieved in extensive lesions in areas that are difficult to access for topical treatment, such as the back region. Currently in common practice are used doxycycline, tetracycline, erythromycin and minocycline[36]. The superiority of any of the above tetracyclines has not been scientifically proven, but there are reports showing good results with use of extended-release minocyclline[37]. Systemic antibiotic therapy should always be associated with topical treatment and be limited to a duration of 3 months. Evaluation of response to treatment should take place 4-6 weeks after initiation[38,39].

Oral isotretinoin

Isotretinoin significantly lowers sebum production, even up to 90%, and with almost 85% cure rate is one the most efficient way of treatment[40,41]. Reduced sebum production can result from involution of sebaceous glands or induced sebocyte apoptosis[42]. Isotretinoin can cause a number of side effects, among the most serious and requiring monitoring are depression and teratogenicity[43]. Isotretinoin finds its use mainly in the treatment of severe, nodular, recalcitrant acne and can be introduced in patients with scarring acne.

Light therapy

Light therapy seems to exert their influence through thermal damage to the sebaceous glands, inhibition of P. acnes and immunomodulatory effect[44]. Increasing the effectiveness of the therapy is the administration of photosensitizing agent, most often aminolevulinic acid or

methyl aminoevulinic acid with subsequent irradiation with blue or red light, laser, pulsed light sources or non-pulsed broad spectrum light. Therapy with low doses of photosensitizer and light results in a short-term impact, while high-dose phototheraphy is followed by a longer-lasting anti-inflammatory effect[45].

Conclusion

Acne vulgaris is a multifactorial disease on which many studies have been performed. Nevertheless, due to the difference in methodology and description, it is impossible to draw clear conclusions. Each affected patient should be approached on an individual basis and care should be provided according to their needs. The pathogenesis of the disease is influenced by factors such as inflammatory mediators, sebum overproduction, colonization by P. acnes, hormonal imbalances and lifestyle influences. Currently the most effective treatment is the one based on isotretinoin, however, is not free of side effects, which must be taken into account in the choice of treatment. Topical use of antibiotics and retinoids may be helpful for special groups of patients.

Supplementary materials

Not applicable.

Autor's contribution:

Conceptualization, Bartłomiej Żmuda and Michał Żuberek; methodology, Daniel Ślusarczyk and Piotr Pisera; software, Filip Pactwa and Michał Żuberek; check, Michał Żuberek and Aleksandra Kiełkowicz; formal analysis, Wiktoria Jakubowska and Daniel Ślusarczyk; investigation, Bartłomiej Żmuda and Aleksandra Kiełkowicz; resources, Zuzanna Popińska and Filip Pactwa; data curation, Piotr Pisera and Michał Żuberek; writing - rough preparation, Bartłomiej Żmuda and Aleksandra Kiełkowicz; writing - review and editing, Bartłomiej Żmuda and Michał Żuberek; visualization, Bartłomiej Żmuda, Wiktoria Jakubowska and Zuzanna Popińska; supervision, Bartłomiej Żmuda and Daniel Ślusarczyk; project administration, Bartłomiej Żmuda; All authors have read and agreed with the published version of the manuscript.

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The data presented in this study are available upon request from the correspondent author.

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