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REVIEW ARTICLE **OPEN ACCESS**

Acne aetiopathogenesis: A review of concepts

Mohinder Pal Singh Sawhney, Urender Singh, Archana Chaudhary, Busi Karunanand
Department of Dermatology and STD, Department of Biochemistry and Department of Environmental Sciences, Faculty of Medicine and Health Sciences, SGT University, Gurugram, Haryana-122505, India.
Address for correspondence: Dr MPS Sawhney, Department of Dermatology and STD, Faculty of Medicine and Health Sciences, SGT University, Gurugram, Haryana-122505, India
Email: drsawhney@live.com

ABSTRACT
Besides hyperproduction of sebum, the ratio of oxidant and antioxidant of lipids on the skin's surface, control of the synthesis of androgens locally, antimicrobial peptides synthesis and the formation of lipids having antimicrobial properties, all contribute to the pathogenesis of acne. In 20th century, it was believed that sebum secretion, follicular hyperkeratinization, and microbes were the causative agents for acne. By the mid of the 20th century, none of the proposed explanations could fully describe the processes but a 'chain of factors' are responsible for the lesions, namely follicular hyperkeratinization, bacterial growth, increased sebum prodution and inflammation. Acne is basically an exaggerated response to normal serum levels of hormones. However, association of acne in syndromes with hyperandrogenism, like PCOS, HAIR-AN and SAHA syndromes further highlight the role of androgens. Presence of insulin resistance with high circulating serum insulin as is seen in PCOS and HAIR-AN syndrome highlight the role of insulin growth factor 1 (IGF1) on the keratinisation. Propionibacterium acnes as a causative bacterium responsible for inflammatory lesions has been further augmented by its demonstration in bone biopsies in SAPHO syndrome. Role of inflammation is highlighted, as is also seen in PAPA syndrome. Two of the recent case controlled studies have highlighted the role of high glycemic diet with the same premise of high circulating serum insulin. PAPA syndrome with autosomal dominant inheritance with mutation of gene on chromosome 15 responsible for CD2 binding protein 1 (CD2BP1) and FGFR2 mutations in Apert syndrome and neavus comedonicus lend further support to the hypothesis that genetics may be playing an important role in androgen receptor transactivation and IGF-1-signalling which is crucial in acne pathogenesis.
Keywords*: Acne vulgaris, Pathogenesis, Androgens, Sebum.*

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INTRODUCTION

The term "acne" was likely first used in the sixth century by Aetius Amidenus, a physician in Constantinople, who called the lesions that appeared on the face during the "acme" of life, or puberty. [1] The term "acme," was used informally and the similarity of the letters "m" and "n" up until the 12th century lends to the notion that the name "acne" originated from a misspelling of "akme" in Aetius' treatise. [2-4] Grant's [5] recollection of a different interpretation contends that the name "acne" refers to the lack of pruritus. According to this theory, the word "acne" comes from the Greek language. Acne vulgaris is a relatively common skin condition that affects 20–90% of all teenagers. It usually resolves spontaneously in late adolescence or the early twenties but in some individuals, it can last up to 40 years of age. [6,7] Due to the hormonal changes brought on by puberty, teenagers are the group who experience acne the most frequently. According to recent statistics, 85% of persons between the ages of 12 and 25 will get acne at some point. [8] Since the earliest clinical description of acne, there have been numerous papers on the topic, with the key phrase "acne vulgaris" appearing in about 10,000 of them in PubMed. Only a very small number of them addressed the disease's history while concentrating on semantic problems (see above) or citing the key authors and their works. [9] Parish and Witkowski [10] and currently, Plewig and Kligman [11] provided detailed histories of the development of acne, emphasizing crucial points in chronological order. As far as we are aware, there hasn't been any historical research done on the origins and evolution of the four elements that make up the pathogenic framework for acne. Therefore, the purpose of this work is to investigate these elements, highlight the regions of overlap, and demonstrate the therapeutic repercussions of the pathogenic trends. The master acneologists ideas, discussions and conflicts, will be highlighted by this study, and it will also provide a comprehensive overview of the development of acne pathogenesis.

SEBORRHEA AND ACNE

After observing individuals with acne who also had seborrhea, Cunliffe and Shuster [12] came to the conclusion that acne is caused by an interaction between an elevated rate of sebum production and seborrhea and correlated with the severity of the condition. While Kligman and Katz [13] argued that not all cases of acne could be attributed to sebum.

Sebum comedogenicity

According to Lorincz et al. [14], free fatty acids stimulate follicular hyperkeratosis and that there may be a connection between some skin lipid fractions and the development of comedones. According to Nicolaides and Wells [15] the production of free fatty acid from sebaceous glands is due to lipase. In fact, it was shown that P. acnes contributed significantly by causing the lipids to break down. [16] According to Strauss and Kligman [17], the short-chain fatty acids were the inciting agent of inflammation, which when administered alone, caused significant harm. Kligman [18] emphasised that it is important to separate irritancy from comedogenicity of free fatty acids, suggesting that the fatty acids involved in comedo production are likely dissimilar from those that may contribute in provoking the later events of inflammation. A few researchers disagreed with these justifications for the use of free fatty acids. Savin [19] noted how interesting it would be to assign the role of free fatty acids in pathogenesis of acne development as P. acnes and aerobic cocci contain lipase enzyme that can release fatty acids by breakdown of triglycerides in sebum. Comedogenic chemicals are found in sebum, according to Kligman. [20] Free fatty acids are particularly significant. Proteases, lecithinases, lipases, hyaluronate lyases, and neuraminidase, are produced by P. acnes and attack the follicular epithelium, causing comedonal contents to discharge. [21]

Diet and Acne

According to Downing and colleagues [22–24], a lack of linoleate would prevent its integration into epithelial acylceramides, leading to hyperkeratotic follicular epithelium that is more permeable to sebum fatty acids. According to Melnik et al. [25], overproduction of sebum dilutes the follicular epithelium's lipids, lowers cholesterol levels, and lowers ceramide and linoleoyl ceramide levels. A novel and speculative pathogenic sequence was proposed by Holland et al. [26] that also raised the significance of linoleic acid deprivation. Despite the large number of research, the majority of which were of subpar quality, Davidovici and Wolf [27] underlined that there is a shortage of trustworthy data regarding the impact of dietary factors on acne. However, Bowe et al [28] noted that the significance of omega-3 fatty acids, antioxidants, zinc, and vitamin A is unknown and that there is "fairly significant proof" that a highly glycemic diet may aggravate acne. According to two recent research, eating a high-glycemic diet is closely related to acne inflammation and severity. [29, 30] It is hypothesised that a high glycemic diet causes high blood levels of insulin, which drive sebocyte proliferation and sebum production. It is also hypothesised that high glycemic diets lower SHBG concentrations and raise androgen levels, which aggravate acne.

HORMONES AND SEBUM

Hamilton [31] claimed that testosterone treatment could cause acne in castrated men who had never had it. However, the hormone of the sebaceous glands rely mostly on androgenic steroids which was observed by Strauss et al [32]. Rony and Zakon [33] also confirmed that testosterone treatment in prepubescent boys caused their sebaceous glands to expand. Also, Thiboutot et al. [34] showed increased plasma androgen levels in women with acne than in women without acne. Even in the absence of systemic androgen problems, the observation that acne patients' skin contains more 5-reductase—the enzyme that converts testosterone to dihydrotestosterone, a more potent androgen—suggested a disordered local endocrine event. [35] Therefore, more research was done on the probable function of androgens in follicular keratinocytes. Pochi and Strauss [36] found that estrogens cannot counteract the activity of androgens in the sebaceous gland and proposed that the inhibitory action of large dosages of oestrogen may be caused by a decrease in the production of androgens in the body. According to Williams et al. [37], each sebaceous gland acts as a separate endocrine organ that is regulated by corticotropin-releasing hormone that demonstrates the relationship between stressful conditions and acne flare-ups. Sebum matrix metalloproteinases may play a significant role in inflammation, cell growth, and dermal matrix breakdown.

HYPERANDROGENISM AND ACNE

"Hyperandrogenism" is the term used to characterize the hirsutism, acne, and alopecia that represent the most prevalent clinical symptoms in women with hyperandrogenemia. The various additional pathologic diseases in many other tissues and organ systems are also driven by the hyperandrogenic state. Ovulatory abnormalities and polycystic ovary syndrome are the two problems linked to hyperandrogenism in women of reproductive age that are most frequently identified (PCOS). [38] Adolescent girls frequently have acne. Nearly 50% of teenage subjects experience it. However, if acne persists into the late adolescent or early

adult years, a physician or endocrinologist should be informed about the potential for hyperandrogenism. This possibility is more likely if the acne is linked to hirsutism or monthly irregularities, is resistant to standard dermatologic treatment methods, or both. Given these facts, acne should be viewed as an indication of hyperandrogenism that calls for the proper diagnostic testing. [39, 40] Variations in the clinical presentation of hyperandrogenism are correlated with variations in the genetic susceptibility of the pilosebaceous unit to androgen stimulation. [41] Females with acne alone may have plasma testosterone levels that are as high as those who have hirsutism, whether or whether they also have acne. The levels of plasma free testosterone and the severity of acne are also unrelated. [42] The study of other androgen-related illnesses should be done if acne persists for long, indicating pilosebaceous unit's reaction to hyperandrogenism. The prevalence of ovulatory failure in young women with acne is prevalent. [43] In one study, polycystic ovaries were linked to 45% of cases among women who had appointments primarily for acne. [44]

SAHA Syndrome (seborrhea, acne, hirsutism and/or androgenetic alopecia)

The predominant cutaneous signs of peripheral hyperandrogenism in young females are included in the SAHA syndrome. SAHA syndrome, first used in 1982 by Orfanos CE [45], refers to seborrhea, acne, hirsutism as well as androgenetic alopecia. Although only about 20% of patients exhibit all four SAHA syndrome symptoms, [46] understanding them is crucial for identifying androgen metabolism-related hormonal problems. The four subtypes of SAHA syndrome are idiopathic, ovarian, adrenal, and hyperprolactinemic. Acne can become worse due to hyperprolactinemia, as seen in the SAHA syndrome's hyperprolactinemic form. [47] The release of adrenal androgens is induced by prolactin. Cutaneous hyperandrogenism is caused by an increase in the production of active androgen metabolites in the pilosebaceous unit. [48, 49] However, the typical phenotype does not necessarily correspond with increased levels of androgens. [50] Additional symptoms of systemic virilization include a deeper voice, more muscle mass, clitoris hypertrophy, a loss of smooth skin contours or obesity, irregular menstruation cycles, and infertility. The SAHA syndrome shares several clinical traits with cases of polycystic ovaries (PCO) and other illnesses of a similar nature. [51, 52]Careful diagnostic and clinical assessment is required in SAHA syndrome cases to determine the aetiology of peripheral hyperandrogenism and rule out androgen-producing tumours. [53]

PCOS (Polycystic ovary syndrome) and Acne

One of the most prevalent endocrine illnesses affecting women of reproductive age is polycystic ovarian syndrome (PCOS). [54, 55] It can also be the most common etiological factor for infertility in people of the same age. [54, 56] Stein and Leventhal published the characteristic features of the PCOS in 1935. [57] They did a study on seven women who had amenorrhea, hyperandrogenism, and obesity along with bilaterally enlarged polycystic ovaries. About 3% to 5% of females have polycystic ovarian syndrome, which may be the main reason for infertility in females. Clinically, PCOS manifests as a plethora of signs and symptoms, the most prevalent of which are irregular menstruation, increased androgen level, infertility, and obesity. Although the underlying aetiology has not been fully explained, there is increasing consensus that insulin resistance and gonadotropin dynamic dysfunction are important characteristics. [58] Thick hair development in regions of body that are androgen dependant, truncal obesity, and acne are indicating excessive androgen. [54, 59]. The pathogenesis of PCOS is not fully understood. The complex nature of the condition is reinforced by its heterogeneity. In PCOS females high LH levels and normal-to-low FSH secretion contribute to increased ovarian and adrenal androgen production, resulting in acne, and hirsutism. [60] In our clinical work, we have seen that the majority of PCOS women also exhibit symptoms of pelvic inflammatory illness. Therefore, we propose that inflammation surrounding the ovaries causes ovarian enlargement or the development of many cysts, which then results in higher discharges of hormones and their effects.

HAIR-AN syndrome

Hyperandrogenism (HA) and Insulin Resistance (IR) associated with acanthosis nigricans (HAIR-AN syndrome) is a rare subset of polycystic ovary syndrome. [61] It played a key role in elucidating the pathogenesis of later. IR is of two types, presence of insulin receptor blocking antibodies and congenitally absent or decreased insulin receptors. In both types there are high levels of androgens. These high levels of androgens produce various manifestations including acne lesions. They also have high levels of serum insulin with normal or diabetic range of blood glucose. These are the patients who benefit from oral hypoglycemic agents like metformin in the treatment of PCOS and coexisting acne.

Comedogenesis

According to Bateman [62], comedones are made of sebaceous materials moulded in sebaceous glands ducts and responsible for the dilatation of the ducts." According to Plumbe, [63], the simplest definition of acne is "merely a blockage of the sebaceous follicle," which results in the follicle's loss. Hebra states that it is necessary to distinguish between normal comedones and those that cause inflammation around them as they are responsible for inflammatory lesions due to sebum retention.[64]

Follicular hyperkeratosis (Unna's Concepts)

By Cornil, Leloir, and Vidal, follicular hyperkeratosis and infection were discovered. In Unna's study, follicular hyperkeratosis became the pathological hallmark of comedogenesis. In addition to the histopathological findings, Unna [53] noted an oat-shaped "bottle bacillus" in the comedones and noted that mostly every comedo in acne "contains a large group of microorganisms. The dermatologist and microbiologist Sabouraud [66] supports the combined function of seborrhea and bacteria. According to Sabouraud's physiopathological theory, seborrhea, which manifests as two clinical features in hairless areas: expansion of the pilosebaceous openings and increased sebum production, is where the acne process begins. While dermatologist, pathologists and microbiologists emphasised the roles of sebum, follicular hyperkeratinization and bacteria in the development of acne, other dermatologists proposed a variety of pathogenic sequences, which focused on the relationship between hair growth and comedo formation. According to O'Brien's [67] theory, primary or secondary infection causes the primary lesion of acne, by causing obstruction at the follicular "keratin ring." The more sebum produced, the less keratin (hair) created in the pilosebaceous follicle, according to Cohen [68]. Cohen [66] denied giving precedence to hypotheses that interlinked hair and acne and stressed upon the function of hyperkeratosis and microorganisms in pathogenesis of acne. The correlation between hair and comedones was first proposed by Grant [69] and further substantiated by the evaluation of an index that changed in tandem with acne severity. Van Scott and McCardle [70] also made a point to note that, in terms of facial acne lesions, the hair's stage of growth has no influence in clearing off sebaceous channels. The sebaceous gland plays an important role in formation of comedone as suggested by Strauss and Kligman in 1958 [71]. Kligman distinguished between two types of comedones: primary and secondary. In primary comedones first microcomdones develop which then develop into closed comedones and further into open comedones and secondary comedones developed after rupture and reepithelialisation of primary comedones. Plewig and Kligman [72] included the precomedones, sebaceous filaments that are the basis for the development of the comedones, in addition to the closed and open comedones. This description is comparable to Sabouraud's from a century earlier. Cunliffe et al. [73] studied role of comedones in acne process. Plewig [74] noted regular shedding of cells of stratum corneum through pilosebaceous duct in the closed comedones and labeled it as starting stage of acne. Knutson [75] stated that difference of comedones from normal follicles is that comedones have intracellular lipid inclusions in keratinised and granular cells. According to his theory, three potential pathways might cause improper keratinization: synthesis of an abnormal fatty acid, deficiency of enzyme responsible for lipid breakdown, or synthesis of an defective keratin that cannot usually bond with lipid. According to Knutson's theory, aberrant keratinization might either be a secondary cellular reaction to comedogenic chemicals in sensitive follicles or it could be the fundamental event occurring at the same time as puberty. He acknowledged that the causes of the abnormal follicular keratinization in comedones were yet unknown. Cunliffe and Shuster [76] published a study on the role of increased sebum in pathogenesis of acne and came to a conclusion that acne is caused by two factors—one is follicular duct obstruction and a second is interaction of excessive sebum production and decreased sebum flow due to increased viscosity. Plewig [74] argued that follicular hyperkeratosis was the primary cause of acne, but he also acknowledged that in some forms of acne like steroid acne, inflammatory lesions came first and horny cell formation came afterwards. Consideration of the function of androgens in follicular keratosis resulted from the appearance of acne that occurs concurrently with an increase in dehydroepiandrosterone. [77,78] The pilosebaceous unit is currently thought to contribute to the generation of cutaneous androgens in addition to being impacted by androgens. This new function might be responsible for the antiandrogen therapy's effectiveness. [79]

Role of Propionibacteria in Acne

The microbacillus is "responsible for the comedo, not for the seborrhea," according to Withfield. [80] He proposed that the microbacillus would be dealt as foreign body entrapping it into cells of stratum corneum leading to comedo formation. Additionally, no researcher has been able to verify Koch's postulates, which lay out the procedures that need to be taken to establish that a particular bacterium is the root cause of a certain infectious disease: the organism has to be persistently present in the affected tissue; it needs to be cultivated in a pure culture; and the pure culture needs to incite the disease when injected into an animal. The effectiveness of medicines, particularly tetracyclines, on acne lesions reemphasized the significance of

microorganisms. [81] Tetracycline-treated acne patients showed a significant decrease in C. acnes, which was linked with a decrease in free fatty acids. [82-84] In the end, Kligman et al. [85] proposed that preventing triglyceride hydrolysis in sebum by either inactivating lipases or suppressing the bacteria would reduce comedogenicity. The mentioned syndrome emphasizes the part that infection plays in the aetiology of acne even further.

SAPHO Syndrome

Synovitis (S), Acne (A)-usually involving face and back, Pustulosis (P) of palms and soles, Hyperostosis (H) and Osteitis (O) described as a syndrome was first described by Chamot et al in 1987. [86] Acral pustulosis and bone and joint involvement is similar to pustular psoriasis and hence has to be treated accordingly. Some of the cases respond to treatment with broad spectrum antibiotics, the rationale being that *Propionibacterium acnes* , a bacteria known for its role in acne has been isolated from bone biopsies. [87-88]

Genetics and Acne

Following two syndromes highlight the role of genetics in pathogenesis of acne:-

PAPA Syndrome

PAPA syndrome, an autosomal dominant disease and is stands for pyogenic arthritis, pyoderma gangrenosum and acne**.** [89] The gene on chromosome 15 responsible for this was recently discovered. [90] Two mutations of a protein known as CD2 binding protein 1 has been found. [91] Acne is usually of a severe nodulocystic variety and responds to treatment with doxycycline or isotretinoin.

Apert Syndrome

A variant of acrocephalosyndactyly known as "Apert syndrome" which consists of abnormalities of the skull, face and extremities. Forkhead box class O (FoxOs)-mediated transcriptional regulation with androgen receptor transactivation and insulin or insulin-like growth factor-1 (IGF-1)-signaling are critical in acne pathogenesis is strongly backed by FGFR2 mutations in Apert syndrome and acne nevus of Munro.[92]

CONCLUSION

Sebum production in both sexes increases with the onset of puberty as a result of androgen-mediated activation of the sebaceous gland. Increased sebum production, increased keratinization of the pilosebaceous duct, proliferating microbial flora like Propionibacterium acnes, and inflammation are all part of the pathophysiology of acne. Resident of the skin flora, Propionibacterium acnes resides in the pilosebaceous units and thrives on lipid-rich sebum. It is significant to emphasize that acne is not brought on by high amounts of hormones, but rather by an aberrant response to these hormones and this does not require further investigation. However, in cases of post-adolescent acne and those with other features of hyperandrogenism especially in females need to be investigated for PCOS, SAHA syndrome, HAIR-AN syndrome or other causes of the same. Association of acne with other rarer syndromes like SAPHO and PAPA syndromes has to be kept in mind. The patient should be advised to consume low glycaemic diet for better outcome in acne.

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