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ACNE ETIOPATHOGENESIS: A REVIEW OF CONCEPT

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Abstract
Along with the hyper production of sebum, some of the other functions like oxidant/antioxidant ratio of the lipids on the skin's surface, synthesis of local androgen, antimicrobial peptides production and synthesis of sapienic acid which is lipid with antimicrobial play a crucial role in acne pathogenesis. Until the middle of the 20th century, inflammation was considered to be the result of seborrhea, follicular keratosis, and microbes acting individually as the cause. However, by the mid-twentieth century, none of the aforementioned factors could fully explain the processes. but a 'chain of some other factors' such as bacterial inversion, keratinization follicular opening, sebum alteration and inflammation were responsible for the formation of the lesions. One of the reason for acne is an abnormal reaction to normal levels instead of excess hormone levels. 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 for the hypothesis that genetics may play a role in androgen receptor transactivation and IGF-1 signalling, both of which are important in acne pathogenesis.

Key words: Acne vulgaris, Pathogenesis, Androgens, Sebum.

Introduction
Aetius Amidenus, a physician in Constantinople, apparently used the term "acne" for the first time in the sixth century when he called the lesions that appeared on the face during the "acme" of life, or puberty, "ionthos" (v), or "acnae."[1] The name "acme," when used colloquially, actually had no official spelling, and the resemblance of the letters "m" and "n" up until the 12th century lends credence to the idea that a mistake of "akme" (acne) in Aetius' book led to the development of "v" (acne). [2-4]. Grant[5] recalled another theory that asserts the name "acne" refers to the lack of pruritus. According to this theory, the word "acne" comes from the Greek letter "acne" as a prefix to a "v" that stands for "scratching." The third and least likely theory proposes that the word "acne" stands for

"anything that comes off the surface."

Acne vulgaris is a fairly common skin condition that affects between 20 and 90 percent of all teenagers.. It usually resolves spontaneously in late adolescence or the beginning of the 20s, [6] but in some persons, it can last up to 40 years of age. Due to the hormonal changes brought on by puberty, teenagers are the group who experience acne the most frequently. [7] A recent study found that between the ages of 12 and 25, approximately 85% of people will have acne. [8]

Acne has been the subject of numerous papers since its initial clinical description.; in fact, using the key phrase "acne vulgaris" in PubMed yielded over 10,000 results. Only a very small number of them addressed the disease's history while concentrating on semantic issues (see above) or citing the significant authors and their works. [9] The history of acne was illustrated by Parish and Witkowski[10], as well as Plewig and Kligman[11] more recently, who summarised significant events in sequential sequence. As far as we know, historical investigations into the origins and development of the four components that comprise the pathogenic framework of acne have not been done. In order to study these elements, identify regions of overlap, and demonstrate how the pathogenic trends have therapeutic implications, our effort will do just that. The master acneologists' ideas, as well as their passionate and occasionally contentious discussions and conflicts, will be highlighted by this method, and it will also provide a comprehensive overview of the development of acne pathogenesis.

Relation between Seborrhea and Acne

According to Cunliffe and Shuster [12], acne is caused by an interplay between an elevated rate of sebum production and seborrhea in individuals who have acne, and they relate the rate of sebum secretion to the severity of the illness. Kligman and Katz, [13] however, argued that not all occurrences of acne could be attributed to sebum - "while sebum may start the process, not everyone will burn".

Sebum comedogenicity

According to Lorincz et al. [14], free fatty acids encourage follicular hyperkeratosis and that there may be a connection between some skin lipid fractions and the development of comedones. The free fatty acid fraction discovered on the skin surface, according to Nicolaides and Wells [15], was likely produced by a lipase that is housed in the sebaceous ducts. In fact, it was shown that P. acnes contributed significantly by causing the lipids to break down. [16] According to Strauss and Kligman [17], Short-chain fatty acids were the main inflammatory agents, and when supplied alone, they had serious negative effects. Kligman [18] highlighted that the difference between free fatty acid irritancy and comedogenicity must be made, as those that contribute to the development of comedones are likely different from those that may also be involved in causing later inflammatory events. Some researchers thought it was foolish to use free fatty acids, in contrast to these justifications for their use. Given that P. acnes and aerobic cocci contain lipases that can release fatty acids from the triglycerides in sebum, Savin [19] noted how seductive it was to suggest that free fatty acids had a part in the emergence of acne. Sebum is said to include comedogenic chemicals, according to Kligman [20]. Free fatty acids rank first among them in importance. Proteases, lecithinases, lipases, hyaluronate lyases, and neuraminidase, collectively known as "quite a cocktail of active material," are produced by P. acnes and attack the follicular epithelium, causing comedonal contents to extrude. [21]

Diet and Acne

The absence of linoleate would prevent it from being incorporated into epithelial acylceramides, increasing the follicular epithelium's hyperkeratotic state and fatty acid permeability, according to Downing and his team's research [22–24]. According to Melnik et al. [25], increased sebum synthesis (triglycerides, free fatty acids, squalenes, and wax esters) dilutes the follicular epithelium's epidermal 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 dearth of trustworthy data regarding the impact of dietary factors on acne.

However, Bowe *et al* [28] highlighted that there is "pretty strong evidence" that a high-glycemic diet may exacerbate acne, but that the roles of omega-3 fatty acids, antioxidants, zinc, and vitamin A are unknown. Two current research investigations have suggested a close relationship between intake of high glycaemic diet and inflammation and severity of acne. [29, 30] It is postulated that high glycaemic diet leads to high blood levels of insulin (which stimulates sebocyte proliferation and sebum production), decrease SHBG concentrations and increase androgen levels in blood leading to worsening of acne.

Hormones and Sebum

Hamilton [31] reported that testosterone therapy could cause acne in castrated people without acne.. However, Strauss *et al*. [32] confirmed the sebaceous glands' hormonal dependency on androgenic steroids in particular. Rony and Zakon [33] also confirmed that testosterone treatment in prepubescent boys caused their sebaceous glands to expand. However, Thiboutot *et al*. [34] indicated that acne-prone women had greater plasma testosterone levels than acne-free women. The finding that acne sufferers' skin contains more 5-reductase—the enzyme that transforms testosterone into dihydrotestosterone, a more potent androgen—suggested an abnormal local endocrine event even in the absence of systemic androgen issues. [35] Therefore, more research was done on the probable function of androgens in follicular keratinocytes. Pochi and Strauss [36] showed that estrogens do not interfere with the activity of androgens at the sebaceous gland and hypothesised that a decrease in the production of androgens on an endogenous level may be the origin of the suppressive effect of high doses of oestrogen .According to Williams *et al*. [37], each sebaceous gland acts as a separate endocrine organ that is regulated by corticotropin-releasing hormone, which may act as a mediator in the relationship between stress 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 word used to characterise the hirsutism, acne, and alopecia that are the three most prevalent clinical symptoms in women with hyperandrogenemia. The numerous additional pathologic diseases in a variety of tissues and organ systems are similarly 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. Almost half of teenage subjects experience it.

However, if acne continues into the late teens or early 20s, a paediatrician or endocrinologist should be notified about the potential for hyperandrogenism. Its possibility is more expected if the acne is related to hirsutism or monthly irregularities, is resistant to standard dermatologic treatment methods, or both. Given these facts, acne should be viewed as a sign of hyperandrogenism that calls for the proper diagnostic testing. [39, 40]. Changes in the pilosebaceous unit's genetic vulnerability to androgen stimulation are connected with variations in the clinical manifestation of hyperandrogenism. [41] Women 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 prompted by chronic acne, as it does with other indications of the pilosebaceous unit's reaction to hyperandrogenism. Noteworthy is the prevalence of ovulatory failure in women and teenage girls with acne. [43] Polycystic ovaries were present in 45% of cases in a study of women who primarily saw doctors for acne. [44]

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

The predominant cutaneous signs of peripheral hyperandrogenism in young females are encapsulated in the SAHA syndrome. This phrase, first used in 1982 by Orfanos CE [45], refers to seborrhea, acne, hirsutism on the face, trunk, and extremities, as well as androgenetic alopecia of the scalp. Even while only about 20% of individuals 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. As seen in the SAHA syndrome's hyperprolactinemic version, hyperprolactinemia can make acne worse. [47] Adrenal androgens are secreted in response to prolactin (DHEAS).

Skinny hyperandrogenism manifests as an excess production of active androgen metabolites in the pilosebaceous unit [48, 49]; however, elevated blood androgen levels are not invariably linked to the clinical phenotype. [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]

A thorough diagnostic and clinical evaluation is necessary in instances of SAHA syndrome to rule out androgen-producing tumours and identify the cause of peripheral hyperandrogenism. [53]

Acne and PCOS (Polycystic ovary syndrome)

Polycystic ovarian syndrome is one of the endocrine conditions that affects women of reproductive age most frequently (PCOS). [54, 55] It can also be the most frequent reason for infertility in people of the same age. [54, 56] Stein and Leventhal published the initial description of the PCOS paradigm in 1935. [57] They presented details on seven women who had obesity, hyperandrogenism, amenorrhea, and polycystic ovaries that were bilaterally enlarged. About 3 to 5 percent of females have polycystic ovarian syndrome, which may be the major cause of infertility in women who are sexually active. Clinically, There are several ways that PCOS can present itself, but the most common ones include

irregular menstruation, hyperandrogenism, infertility, and obesity. Though the underlying aetiology is not well understood, there is growing agreement that gonadotropin dynamic dysfunction and insulin resistance are significant features. [58] Course hair development in androgen-dependent body regions (sideburns, chin, upper lip, peri-areola, chest, lower abdominal midline, and thigh), truncal obesity, and acne are indications of excessive androgen. [54, 59]

The pathogenesis of PCOS is still not fully understood. The complex nature of the condition is reinforced by its heterogeneity. Increased levels of circulating LH are one of PCOS's endocrine, reproductive, and metabolic effects. Additionally, normal to low FSH secretion causes increased ovarian and adrenal androgen production, which in turn causes acne and hirsutism. [60]

In our clinical work, we have seen that the majority of PCOS-afflicted 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

Comedones are thought to be composed of "concreted mucus or sebaceous materials moulded in the ducts of sebaceous glands and responsible for the distension of the ducts," according to Bateman [62]. According to Plumbe, [63], the simplest definition of acne is "merely a blockage of the sebaceous follicle," which results in the follicle's demise. Hebra states that it is necessary to distinguish between regular comedones and those that cause inflammation around them [64]. Only the latter result in acne's inflammatory lesions, which are a reflection of the site of sebum retention.

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. Along with the histopathological findings, Unna [53] observed an oat-shaped "bottle bacillus" in the head and mantle of the comedones. She also stated that nearly every acne comedone "contains a swarm of microorganisms" that have been kept "in a protected and temperate chamber, often in pure culture," so up until this point, we should have had no suspicion of their existence.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 symptoms in glabrous areas: expansion of the pilosebaceous ostiums and overproduction of sebum, is where the acne

process begins rather than the epidermis. While dermatohistopathologists and microbiologists emphasised the roles of sebum, follicular keratosis, and bacteria in the development of acne, other dermatologists proposed a variety of pathogenic sequences, some of which focused on the relationship between hair growth and comedo formation. According to O'Brien's [67] theory, primary or secondary infection is what causes the early lesion of acne, which is "disruptive in nature" and situated in the follicular "keratin ring." The more sebum produced, the less keratin (hair) created in the pilosebaceous follicle, according to Cohen [68]. Cohen [66] declined to give precedence to hypotheses that related hair and acne above those that stressed the function of hyperkeratosis and microorganisms. The correlation between hair and comedones was first proposed by Grant [69] and further substantiated by the measurement of an index that changed in tandem with the clinical harshness of acne. Additionally, Van Scott and McCardle [70] underlined that in terms of acne lesions on the face, the stage of hair growth shouldn't physically affect maintaining the sebaceous channel's clearance of sebum and cells.

The sebaceous gland was given a crucial part in the comedo creation method Strauss and Kligman [71] proposed in 1958. Kligman made a distinction between two types of comedones: primary ones, which start out as microcomedones that are only visible at the histopathological level and later develop into closed comedones and open comedones, and secondary ones, which are created when the primary ones rupture and reencapsulate. Plewig and Kligman [72] included the precomedones, sebaceous filaments that are the genesis 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] just finished cataloguing comedones, whether they were visible or not, to further support their function in the acne process. Plewig [74] observed continual sloughing of tagged cells in closed comedones, followed by "a glacier-like flow" of horny cells through the pore and referred to them as "sealed time bombs," referring to this early stage as the "embryonic stage of acne." The numerous intracellular lipid inclusions found within keratinized and granular cells are what Knutson [75] identified as the most obvious distinction between comedones and typical follicles. According to his theory, three potential pathways might cause improper keratinization: synthesis of an abnormal lipid, lack of an enzyme for the normal lipid's normal breakdown, or production of an atypical 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, however, that it was still unclear what had happened to cause the comedones' altered follicular keratinization.

Some scepticism was voiced by Cunliffe and Shuster [76] regarding the significance of follicular keratosis as the primary cause of the acne process. They published a study on the role of sebum in acne and came to the conclusion that acne is caused by two factors—"the interaction between an enhanced sebum secretion and a second factor"—in addition to a blockage in the follicular duct (increased organic blockage resistance or increased sebum viscosity barrier to sebum flow).

In other types of acne (aestivalis, steroid acne), the inflammatory lesions were primary and the production of horny cells was subsequent, according to Plewig [74], who noted that the preservation of epidermal cells may be minimal., even though he defended follicular hyperkeratosis as the primary initiating component. 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 " not the cause of the seborrhea, but the comedone," according to Withfield [80]. He proposed that the microbacillus would be handled by the follicle's epithelium in the same manner as the epidermis always handles foreign objects, mainly by encrusting it with horny cells, describing the comedo development. Additionally, no researcher was able to support Koch's postulates, which outline a order of requirements that must be met in order to demonstrate that a particular microorganism is the cause of a particular infectious disease. These requirements include the organism being continuously present in the diseased tissue, being grown in pure culture, and inducing the disease when the pure culture is injected into an animal.

The effectiveness of medicines, particularly tetracyclines, on acne lesions reemphasized the significance of microorganisms. [81] In tetracycline-treated acne patients, a significant fall in C. acnes was seen along with a rise in free fatty acids. [82-84] Last but not least, Kligman et al. [85] proposed that If triglyceride hydrolysis could be stopped, either by inactivating lipases or by inhibiting the bacteria that caused it, sebum would be less comedogenic. Following syndrome further highlights the importance of infection in the pathogenesis of acne

SAPHO Syndrome

Chamot et al. first identified the syndrome of synovitis (S), acne (A)-typically affecting the face and back, pustulosis (P) of the palms and soles, hyperostosis (H), and osteoitis (O) in 1987.. [86] Acral pustulosis and bone and joint involvement is similar to pustular psoriasis and hence has to 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:-

1. **PAPA Syndrome**

PAPA syndrome or acne is an autosomal dominant hereditary autoinflammatory disorder that is sometimes referred to as pyogenic arthritis, pyoderma gangrenosum, and pyogenic arthritis. [89] On chromosome 15, a recently discovered relevant gene has been located. [90] A protein known as CD2 binding protein 1 has two mutations (CD2BP1). [91] Doxycycline or isotretinoin can cure severe nodulocystic acne, which is the most common type.

2. **Apert Syndrome**

Acrocephalosyndactyly, a congenital condition marked by deformities of the head, face, hands, and feet, takes the form of Apert syndrome. More data bolsters the notion that the aetiology of acne

depends on the combination of forkhead box class O (FoxOs)-mediated transcriptional regulation with androgen receptor transactivation and insulin/insulin-like growth factor-1 (IGF-1) signalling. Apert syndrome and the Munro acne nevus both have FGFR2 mutations that gain-of-function.

Conclusion

Both sexes produce more sebum as a result of the androgen-mediated stimulation of the sebaceous gland that occurs at the onset of puberty. 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. A typical member of the skin flora, Propionibacterium acnes lives in the pilosebaceous units and feeds on lipid-rich sebum. It is significant to emphasise that acne is not brought on by high amounts of hormones, but rather by an aberrant response to these hormones' normal adolescent levels, 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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