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The Link between Acne Vulgaris and Metabolic Syndrome

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Abstract
Background: Acne vulgaris is a common inflammatory pilosebaceous disease affecting over 80% of young adults and adolescents. The relationship between acne vulgaris and metabolic syndrome (MetS) has been a subject of increasing interest in recent years. **Objective:** This article aims to review the link between metabolic syndrome and acne vulgaris and its correlation with acne severity. **Data Sources:** The literatures on the causes, pathogenesis, clinical pictures of acne vulgaris, discuss role of metabolic syndrome in patients with acne vulgaris and its correlation with the disease's severity decline up to 2024 was sourced via a search of the Medline databases (Pub Med and Medscape). **Data Extraction:** If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment factors included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and well-defined evaluation measures. Data from each eligible study were independently abstracted using a data collection form to capture information related to our concerned study outcomes. **Conclusions**: Both acne vulgaris and MetS are associated with hormonal changes, insulin resistance, oxidative stress and chronic inflammation. Studies have shown that individuals with MetS are more likely to have severe acne.

Keywords: Acne Vulgaris; Obesity; Diet; Metabolic Syndrome

Introduction

Acne vulgaris is a common inflammatory pilosebaceous disease affecting over 80% of young adults and adolescents. Acne is characterized by open and closed comedones and lesions with inflammatory nodules, pustules, and papules, which typically affect the face, chest, and back [1].

Acne vulgaris can be one of symptoms of polycystic ovary syndrome, Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women during their reproductive ages, associated with a plethora of cardiometabolic consequences, with obesity, insulin resistance and hyperandrogenemia playing a major role in the degree of such manifestations [2].

Materials and Methods

Data Sources: The literatures on the causes, pathogenesis, clinical pictures of acne vulgaris, discuss role of metabolic syndrome in patients with acne vulgaris and its correlation with the disease's severity decline up to 2024 was sourced via a search of the Medline databases (Pub Med and Medscape).

Study Selection: All studies were independently assessed for inclusion. They were included if they fulfilled the following criteria: 1. Written and published in English language. 2. Published in peer-reviewed journals. 3. Review the causes, pathogenesis, clinical pictures of acne vulgaris, and discuss role ofmetabolic syndrome in patients with acne vulgaris and its correlation with the disease's severity.

Data Extraction: If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment factors included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and well-defined evaluation measures. Data from each eligible study were independently abstracted using a data collection form to capture information related to our concerned study outcomes.

Prevalence of Acne Vulgaris

Acne vulgaris is a common cutaneous disorder of the pilosebaceous unit with a high prevalence in the general population. A global burden of disease identified acne vulgaris as the eighth most common skin disease, with an estimated global prevalence of 9.38 [3]**.** Estimates continue to change as the prevalence of acne decreases secondary to improved treatment modalities. Acne vulgaris affects approximately 650 million people globally or around 9.4% of the population [4].

Pathogenesis of Acne Vulgaris:

Sebaceous glands secrete excess sebum under the effect of hormones, found in huge amount in entire body surface but cover

larger portion in upper trunk area, chest, and back, they are absent where hair follicle is absent such as the palm, sole and dorsum area of feet. Excess production of sebum interferes with the normal follicular keratinization process leading to blockage of the pore of sebaceous gland, and the development of acne is started. The events of pathogenesis is carried in following steps. 1) The excess production of sebum from sebaceous glands, 2) hyperkeratinisation leading to microcomedo that enlarges into comedo, 3) growth of anaerobic bacteria leading to colonization of the follicle. 4) finally the inflammatory responses [5].

1) Genetics:

Family and twin studies have shown that genetics have a role in the development of acne. Several genetic polymorphisms that impact gene expression and/or function have been studied. The insulin like growth factor (IGF1) (CA) 19 repeat polymorphism, the Pro12Ala polymorphism of peroxisome proliferator activated receptor gamma (PPARG124), the interleukin (IL6 572) G/C polymorphism, and the IL1A 889 C/T polymorphism were all linked to acne [6].

2) Hormonal factors:

During puberty, under the influence of androgens, sebum secretion is increased as 5-alpha reductase converts testosterone to more potent DHT, which binds to specific receptors in the sebaceous glands increasing sebum production. This leads to an increased hyperproliferation of follicular epidermis, so there is retention of sebum. Distended follicles rupture and release pro-inflammatory chemicals into the dermis, stimulating inflammation. C. acnes, Staphylococcus epidermis, and Malassezia furfur induce inflammation and induce follicular epidermal proliferation [7].

Menstrual cycles and pregnancy period seem to contribute to the increase in the female sex hormone production especially (oestrogens, oestradiol and oestrone), and subsequently influencing acne vulgaris. The levels of DHEA are most frequently elevated [8]. By contrast, 17α-hydroxyprogesterone levels are not different in women with or without acne. Furthermore, high oestradiol levels in women have a protective effect [9].

3) Role of sebum:

Sebaceous glands together with the hair follicles form the pilosebaceous unit with a primary role to produce sebum. Changes in their lipid metabolism, resulting in an altered amount and composition of sebum, is associated with skin diseases such as acne vulgaris and atopic dermatitis as well . Moreover, sebocytes are also capable of exerting inflammatory responses via the secretion of pro-inflammatory cytokines, chemokines and antimicrobial peptides upon activation by pathogens (e.g. different P. acnes strains) and pathogen-associated molecular pattern recognition receptor (like TLR2 and TLR4) ligands [10].

4) Role of Inflammation:

Inflammation plays an important role in the onset, development, and resolution of acne vulgaris. IGF-1 and virulent P. acnes are the most important factors to induce inflammatory response in acne. IGF-1 is sufficient to induce pro-inflammatory cytokine expression in primary human sebocytes. Increased expression of NF-κB, IL-1β, IL-6, IL-8, and TNF-α in cultured sebocytes was observed after stimulation with IGF-1 [11].

In addition to IGF-1, androgen might have similar effects, since androgen can increase IGF-1 level in serum in normal men. After the stimulation of IGF-1, sebocytes release cytokines and Matrix Metalloproteinases (MMPs) and recruit inflammatory cells into the pilosebaceous unit. MMPs are capable of breaking the follicular membrane, causing fatty acid spillage to the dermis and dissolution of the extracellular matrix [12].

***5*) Bacterial factor:**

Propionibacterium acnes (P.acnes) are gram-positive, facultative, anaerobic rod-shaped bacteria that is a main inhabitant of the human skin accounting for 87% of the clones with other *Staphylococcus, Corynebacterium, Streptococcus*, and *Pseudomonas species.* P. acnes remains dormant prior to puberty, but with the onset of puberty, androgenic hormones increase the levels of sebum by which bacteria get activated and react by proliferating. It lives primarily on fatty acids in sebum, secreted by sebaceous glands. In the follicles, bacteria use sebum, cellular debris and metabolic by-products from the surrounding skin tissue as their primary sources of energy and nutrients. Hence, blockage of the follicle can create appropriate environment for bacteria to flourish [13].

6) Diet:

The hyperglycemic food, induces the insulin like growth factor signaling, is the central line of endocrine pathway of sexual

maturation, and play the primary role in development of acne. The western diet contains huge amount of glycemic carbohydrate, saturated fat and dairy products that promote the sebaceous lipogenesis and sebum secretion. Dietary intake of dairy products adds to the pathogenesis of acne vulgaris. Positive association was reported between the prevalence of acne and the consumption of full-fat, skimmed and low-fat milk. There is strong support for the reduction of acne with regular consumption of omega-3 fatty acids and low glycemic index diets [14].

Three major food classes that promote acne are: 1) hyperglycemic carbohydrates, 2) milk and dairy products, 3) saturated fats including *trans*-fats and deficient ω-3 polyunsaturated fatty acids (PUFAs). Diet-induced insulin/insulin-like growth factor (IGF-1)-signaling is superimposed on elevated IGF-1 levels during puberty, thereby unmasking the impact of aberrant nutrigenomics on sebaceous gland homeostasis [12].

7) Role of linoleic acid:

Linoleic acid is an essential fatty acid in the normal composition of sebum. Deficiency of linoleic acid impairs the hair follicle barrier that will lead to entry of other free fatty acids produced from bacterial lipases. These foreign fatty acids will lead to further deficiency of linoleic acid creating a vicious circle ending with production of abnormal thick sebum that obstructs the sebaceous gland duct [12].

Apparently, sebaceous gland selectively utilizes fatty acids, whereas, linoleic acid only appears to be subjected to β-oxidation. It is transformed into precursors (two carbon units) for the generation of acetyl-CoA that is incorporated into different metabolic route such as the biosynthetic pathway leading to squalene and wax esters synthesis. The reduced linoleic acid content in the sebum affects sphingolipids composition in the follicle. Sphingolipids in human epidermis maintain a barrier between the environment and the human body. The sphingolipids with reduced linoleic acid have been postulated to be involved in the follicular hyperkeratosis, which is an essential incident in the comedo formation [15].

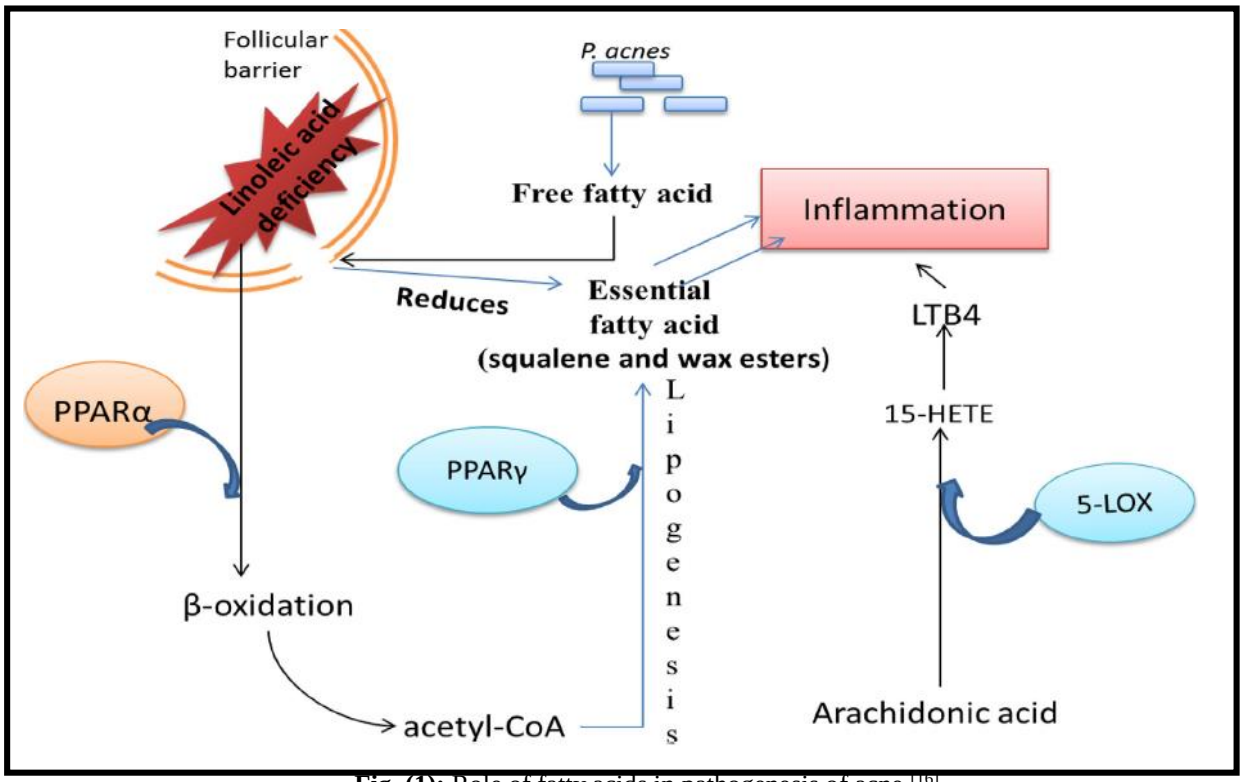


Fig. (1): Role of fatty acids in pathogenesis of acne [16]

Clinical picture and grading of acne vulgaris:

The primary lesion in acne is the comedon (either open or closed). White-head comedons

are the closed and black-head comedons are the open ones. Acne lesions also might include pustules and/or nodules. The typical distribution involves the sebaceous gland–rich areas of the face, upper back, chest, and shoulders. Secondary lesions are scarring, post inflammatory hyperpigmentation, or erythema [17].

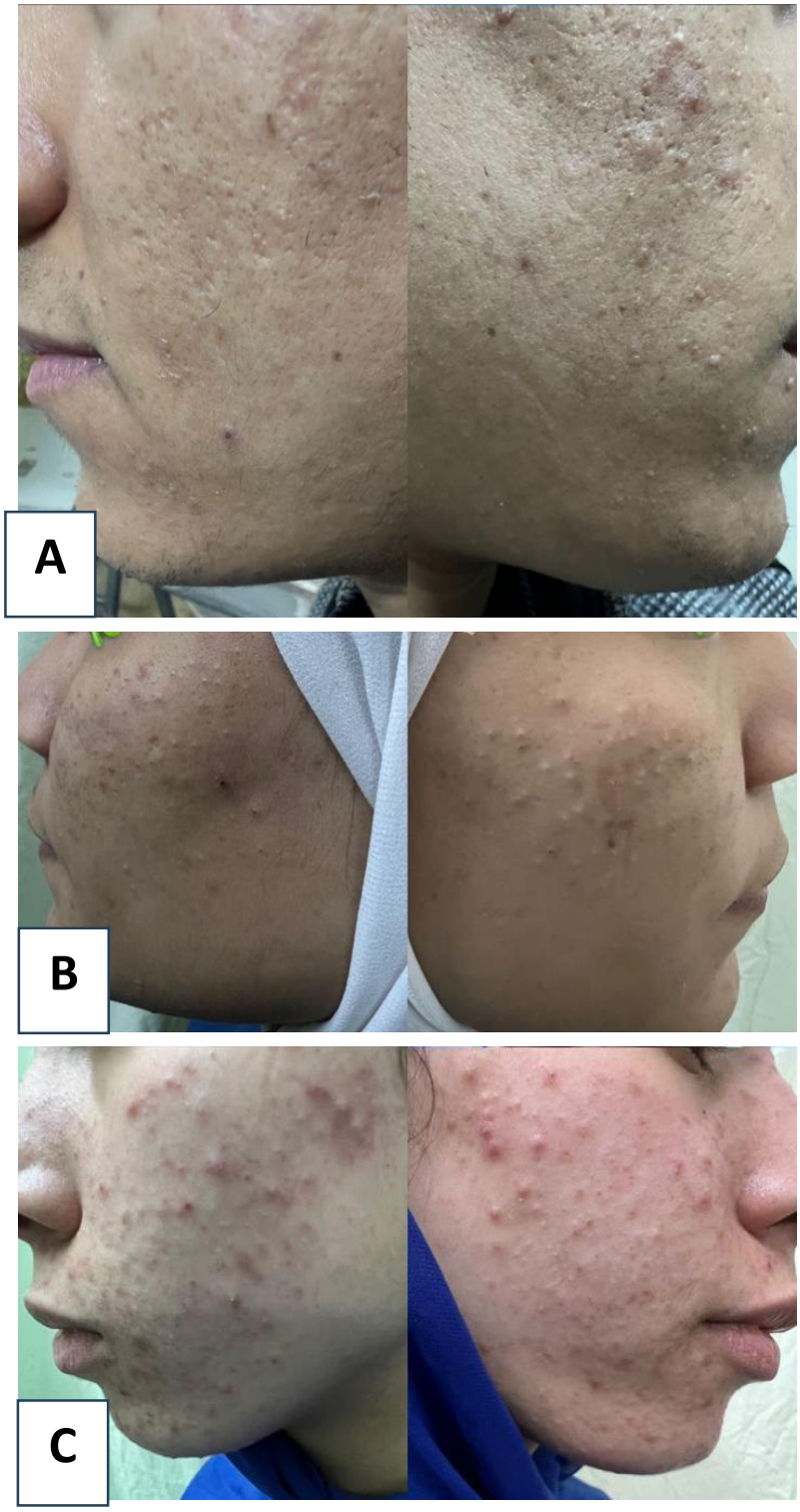
- **Grading of acne:**

Methods of measuring the severity of acne vulgaris include simple grading based on clinical examination, lesion counting, and those that require complicated instruments such as photography, fluorescent photography, polarized light photography, video microscopy and measurement of sebum production. The two commonly used measures are grading and lesion counting. Dating back to 1956, Pillsbury, Shelley and Kligman published the earliest known grading system then several systems were introduced with one of the most popular is Global Acne Grading System (GAGS) [18].

Global Acne Grading System (GAGS): The GAGS is a quantitative scoring system to assess acne severity. It was first developed by Doshi and colleagues in 1997. The total severity score is derived from summation of six regional sub scores. Each is derived by multiplying the factors-2 for forehead, 2 for each check, 1 for nose, 1 for chin, 3 for both chest and back by the most heavily weighted lesion within each region (1 for ≥ one comedon, 2 for ≥ one papule,3 for ≥ one pustule, and 4 for ≥ one nodule) [19].

Table (1): Global Acne Grading System [20]

Location	Factor X Grade (0-4) = local score	
Forehead	2	[Global score = 0 = None 1-18 = Mild 19-30 = Moderate 31-38 = Severe > 39 = Very severe]
Right cheek	2	
Left cheek	2	
Nose	1	
Chin	1	
Chest & upper back	3	



A: Mild acne vulgaris, B: Moderate acne vulgaris, C: Severe acne vulgaris.

Acne vulgaris and metabolic syndrome

Metabolic syndrome has a cluster of risk factors, including central obesity, high triglyceride levels, low high-density lipoprotein cholesterol (HDL-C) levels, glucose

intolerance, and hypertension hat increase the risk of heart disease, stroke, and diabetes [21].

The relationship between acne vulgaris and metabolic syndrome (MetS) has been a subject of increasing interest in research. Inflammatory, hormonal, and environmental factors are implicated in the acne-metabolic syndrome correlation [22].

Both acne vulgaris and MetS are associated with chronic inflammation. Inflammatory markers such as TNF-α, IL-17, and IL-23 are elevated in both conditions [23].

Elevated androgen levels, which increase sebum production, play a crucial role in acne development. Similarly, hormonal imbalances are a key feature of MetS. In addition, increased oxidative stress is observed in both acne and MetS. This stress can exacerbate inflammation and contribute to the pathogenesis of both conditions. Patients with MetS and acne vulgaris have higher levels of OS indicators, such as malondialdehyde (MDA), than healthy controls, according to experimental Investigations [24].

Studies have shown that individuals with MetS are more likely to have severe acne. For instance, a study found that severe acne was more common in patients with MetS compared to those without. Insulin resistance, a hallmark of MetS, has been linked to acne severity [25]. Insulin resistance can lead to hyperinsulinemia, which increases androgen production and sebum secretion. Obesity, another component of MetS, is associated with more severe acne. The increased adipose tissue can lead to higher levels of inflammatory cytokines and androgens [22].

Adipokines are synthesized and secreted by adipocytes in response to various stimuli and related to acne pathogenesis. They include IL-6 and other small molecular weight bioactive proteins such as adiponectin, resistin, leptin, serpin E1 [also known as plasminogen activator inhibitor 1 (PAI1)], visfatin (also known as nicotinamide phosphoribosyltransferase), apelin, chemerin, retinol binding protein-4 (RBP4), and monocyte chemoattractant protein 1 (MCP1) [26].

Potential mechanisms also include the mechanistic target of rapamycin complex 1 (mTORC1) pathway. It is a key regulator of cell growth and metabolism. Overactivation of this pathway, often due to a Western diet high in hyperglycemic carbohydrates and dairy, can contribute to both acne and MetS [27].

Recent research suggests that biogenic amines and glutathione peroxidase may play a role in the pathophysiological link between acne and MetS. These compounds are involved in oxidative stress and inflammation [28].

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