Section A-Research paper

An Outline of Acne Vulgaris and Possible Role of Spironolactone in Management

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Abstract

Background: Acne is a chronic inflammatory disease characterized by open or closed comedones and inflammatory lesions in the form of papules, pustules or nodules. It is considered as one of the most common skin diseases affecting mostly young individuals. Acne vulgaris is characterized by open and closed comedones (non-inflammatory lesions) and by papules, pustules and nodules (inflammatory lesions). The pathogenesis of acne is multifactorial in nature. It is characterized by excess sebum production, hyperkeratosis of follicular epithelium. Rupture of follicular epithelium occurs leading to increase in the release of inflammatory mediating agents. More than 25 different grading systems for the assessment of acne severity have been published in literature. However, the presence of this large number of grading systems indicates a lack of consensus on this issue. Therefore, no grading system is considered to be a global standard for assessment. Several factors may influence the choice of therapy including age of the patient, extent, severity of the disease and sites involved. Topical treatment can be used alone or with combination to other topical or oral agents.

Keywords: Acne Vulgaris, Spironolactone

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Introduction

Acne is a chronic inflammatory disease characterized by open or closed comedones and inflammatory lesions in the form of papules, pustules or nodules**.** It is considered as one of the most common skin diseases affecting mostly young individuals ***(1).***

Acne's incidence is over 90% among adolescents and it could persist into adulthood in 12% - 14% of cases. This may result in high psychological and social implications**.** However most cases are seen during early teenage years ***(2).***

Seborrhea, comedones, papules and pustules are characteristic features of this disease. Equal incidence of this disease occur in males and females, however the more severe form usually appears in men from the hormonal effect ***(1).***

Acne vulgaris is characterized by open and closed comedones (non-inflammatory lesions) and by papules, pustules and nodules (inflammatory lesions). A white head (closed comedo) is formed when the opening of hair follicle is blocked by oil and skin cells. This presents on the skin as small, whitish bumps and

under the surface of the skin. A blackhead (open comedo) is a non-inflammatory acne lesion that is filled with excess oil and dead skin cells. Black heads called an open comedo because the surface of the skin remains open with a dark appearance such as black and brown color ***(3).***

Acne variants:

A. Acne infantum:

Transplacental stimulation of adrenal gland results in transient high levels of DHEA (Dihydroepiandrosterone) in infancy ***(***Transplacental stimulation of adrenal gland results in transient high levels of DHEA (Dihydroepiandrosterone) in infancy ***(4).***

B. Acne cosmetic:

Adult onset acne can be caused by comedogenic cosmetics. Cessation of cosmetic products results in resolution of lesions ***(5).***

C. Acne excoriee:

In young adult females with psychological morbidity, compulsive scratching may complicate mild acne. It may cause a crust or scar***(5).***

D. Acne agminata:

It presents as papulopustular eruption affecting cheeks, eyelids, periorbital area sand occasionally limbs. It resolves spontaneously without scarring within 2 to 6 weeks ***(5).***

E. Acne conglobata:

It is a severe form of nodulocystic acne presenting with nodules and abscesses on trunk, back and buttocks, less often on the face. ***(5).***

F. Acne fulminans:

It occurs more commonly in males. It is caused by sudden rupture of microcomedones resulting in widespread necrosis leading to formation of painful, sterile, hemorrhagic nodules and plaques. This results in truncal and facial ulcers and scars which are severe. ***(5).***

Pathogenesis:

The pathogenesis of acne is multifactorial in nature. It is characterized by excess sebum production, hyperkeratosis of follicular epithelium. Rupture of follicular epithelium occurs leading to increase in the release of inflammatory mediating agents. Pro-inflammatory cytokines as interleukin 1α (IL-1α) and tumor necrosis factor α (TNF α) are considered as one of the factors responsible for further follicular hyper keratinization and the characteristic inflammatory acne lesions**.** Propionibacterium acnes (P.acnes) bacterial colonization was found to have a role in the pathology**.** P. acnes are gram positive, nonmotile, opportunistic pathogens, growing under different oxygen tension ***(6).***

Propionibacterium acne was found to be localized and proliferates in pilosebaceous unit favoring the lipid rich environment of it forming the inflammatory lesions of acne by releasing chemotactic factors by stimulating the secretion of IL-6& IL-8 from the follicular keratinocytes and by stimulating monocytic cells to produce IL-1 α, TNF –α, IL-8 and IL-12 in a Toll like receptor2 dependent manner ***(7).***

P. acne may activate keratinocytes and sebocytes through TLR (Toll Like Receptors), CD 14, CD1 molecules. In acne lesions the pilosebaceous follicles are surrounded with macrophages expressingTLR2 on their surface. TLR2 activation leads to transcription of nuclear factor triggering production of cytokines/chemokines, phenomena observed in acne lesions. Moreover, P. acnes induces IL-8 and IL-12 release fromTLR2 positive monocytes ***(8).***

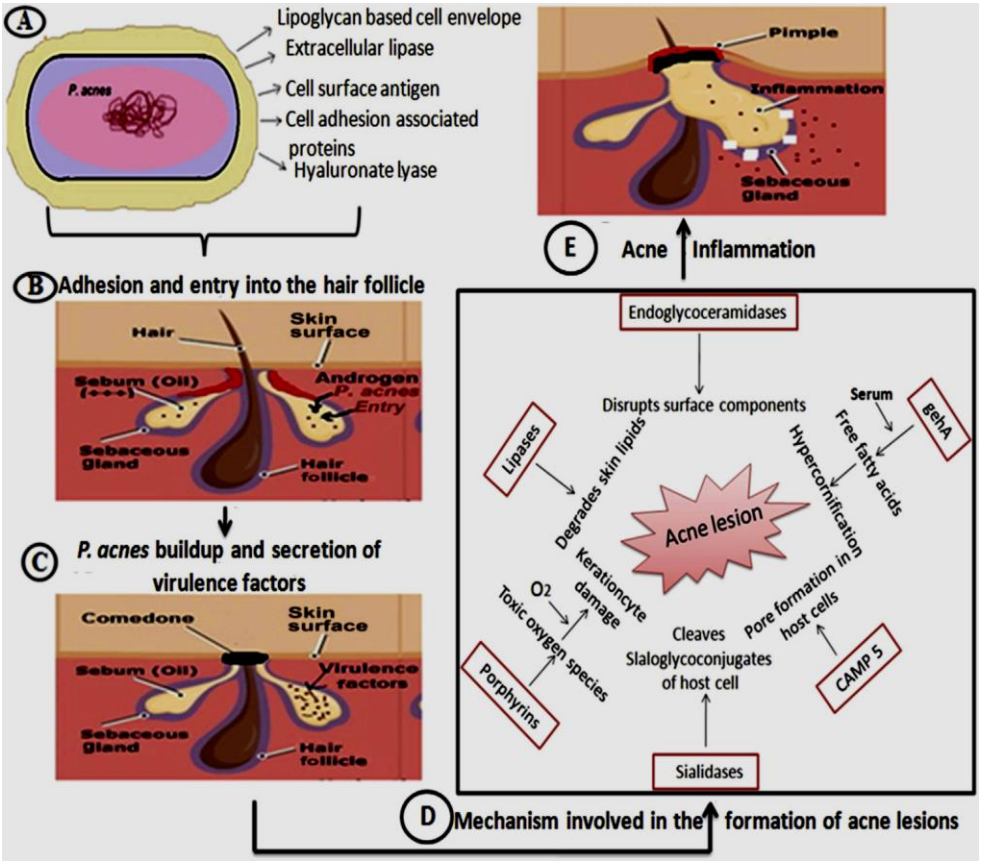

Figure (1) shows a schematic representation of the steps involved in the pathogenesis of Propionibacterium acnes in acne disease progression.

(A) important factors within P. acnes contributing acne pathogenesis; (B) adhesion and entry into the hair follicle; (C) P. acnes buildup and secretion of virulence factors; (D) mechanism involved in the formation of acne lesions; and (E) acne inflammation ***(7).***

Acne is affected by hormones and growth factors (particularly insulin-like growth factor (IGF-1)) which acts on the sebaceous glands and the keratinocytes lining the pilary canal. Dairy products and some other foods which contains 5α -reduced steroid hormones and other steroid precursors of dihydro testosterone (DHT) drive sebaceous gland (and likely pilar keratinocyte) function***. (9)***.

Hormones as androgens control the sebaceous gland size and affect sebum secretion. In cell culture, androgens only promote sebocyte proliferation, where asPPAR ligands are required for induction of differentiation and lipogenic activity. ***(10).***

Assessment of acne:

More than 25 different grading systems for the assessment of acne severity have been published in literature. However, the presence of this large number of grading systems indicates a lack of consensus on this issue. Therefore, no grading system is considered to be a global standard for assessment. ***(11).***

In 1997, Doshi, Zaheer and Stiller devised a global acne grading system (GAGS). This system divides the face, chest and back into six areas (forehead, each cheek, nose, chin and chest and back) and assigns a factor to each area on the basis of size as in [Table 1]

Table 1: The global acne grading system

Location	Factor
Forehead	2
Right cheek	2
Left cheek	2
Nose	1
Chin	1
Chest and upper back	3

Note: Each type of lesion is given a value depending on severity: no lesions = 0, comedones = 1, papules = 2, pustules = 3 and nodules = 4.The score for each area (Local score) is calculated using the formula: Local score = Factor × Grade (0-4). The global score is the sum of local scores, and acne severity was graded using the global score. A score of 1-18 is considered mild; 19-30, moderate; 31-38, severe; and >39, very seve

Treatment of acne vulgaris:

Several factors may influence the choice of therapy including age of the patient, extent, severity of the disease and sites involved. Topical treatment can be used alone or with combination to other topical or oral agents ***(12).***

Topical treatment:

It includes;

- ***Topical retinoids***

They are comedolytic agents. They are used as a first line therapy in cases with comedonal and inflammatory lesions. They help in reducing keratinocytes abnormal mitosis, inflammation and hyper keratinization. However, they have local side effects including erythema, dryness, photosensitivity and peeling. The most commonly used available agents are adapalene, tretinoin and tazarotene ***(13).***

- ***Benzoyl peroxide:***

It is an antibacterial agent. It helps in reducing number of lesions in cases of mild to moderate acne. It is less photosensitizing than topical retinoids so it may be applied at the morning. ***(14).***

- ***Topical antibiotics:***

They are found to accumulate in the follicle and found to have anti-inflammatory and antibacterial effects. Using topical antibiotics as monotherapy is not recommended as there is increased risk of antibiotic resistance. Examples of topical antibiotics are clindamycin 1%, erythromycin 2%. ***(12).***

They both suppress P. acnes growth and decrease lesion count. However, there is increasing resistance of P. acnes to erythromycin which resulted in decreased efficacy of erythromycin. Erythema, dryness and burning sensation are common side effects ***(15).***

Combined topical treatment:

Combination of topical therapies are more effective than monotherapy as they target multiple pathogenic mechanisms**.** Combination of clindamycin or erythromycin with benzoyl peroxide, tretinoin or adapalene show greater efficacy than monotherapy. ***(16).***

Oral treatment:

It includes;

- ***Oral antibiotics:***

Antibiotics are best used in combination with a topical retinoid or benzoyl peroxide due to their limited effect on comedogenesis and increasing antimicrobial resistance **.** Antibiotics have both antimicrobial and anti-inflammatory activity. ***(17).***

- ***Oral isotretinoin:***

Oral isotretinoin is the most effective medication when given for around 20 weeks which results in clinical cure in about 85% of cases**.** Relapse rates are around 21% and are dose-dependent, the best responses being seen with daily doses of 1 mg/kg per day or a total of 150 mg/kg over the treatment duration ***(18).***

Isotretinoin is used in cases with severe nodulocystic scarring acne resistant to other forms of treatment. ***(18).***

Hormonal therapy:

Oral contraceptive pills (OCP) significantly reduces inflammatory and non-inflammatory lesion counts and severity of acne. ***(19).***

Chemical peel:

Chemical peel has been used in treatment of mild to moderate papulopustular acne .A wide variety of agents have been used as superficial peel as α-hydroxy acid, Jessner solution, resorcinol, and Trichloroacetic acid (TCA). ***(20).***

Physical Treatment

A. Lesion removal

Comedones mechanical removal of both open and closed comedones can be done using comedone extractor and a fine needle or a pointed blade ***(20).***

B. Lasers, light sources, and photodynamic therapy:

including photodynamic therapy, infrared lasers, broad-spectrum light sources, pulsed dye lasers, intense pulsed light, and potassium titanyl phosphate laser. ***(21).***

Complications of acne vulgaris:

Postinflammatory hyperpigmentation is a common complication of acne vulgaris, particularly in pigmented skin. Spironolactone is structurally similar to the progesterone molecule as its non-selective for mineralocorticoid, as well as androgen and progesterone receptors and this results in the increased prevalence of anti-androgenic and progestonal adverse effects**.** Spironolactone is a competitive mineralocorticoid receptor antagonist that was synthesized initially as a diuretic to inhibit renal transport of sodium leading to salt and water excretion with potassium sparing. **(22).**

Pharmacokinetics:

- **Absorption**

Spironolactone is a poorly water-soluble drug **(23).**

Spironolactone has excellent oral bioavailability with food as food increases its absorption **(23).**

Metabolism

Spironolactone is converted rapidly in the liver by deacetylation, dethiolation, and thiomethylation to its metabolites **(24).**

- **Active metabolites**

Spironolactone pharmaco-dynamically active metabolites include canrenone, canrenoate, 7-α-thiomethylspirolactone and 6-hydroxy-7athiomethylspirolactone with clinically insignificant first-pass effect **(24).**

Onset of action 2–4h. Maximum effect 7h (single dose), 2–3 days (multiple doses).

- **Time to peak plasma concentration** 2–3h and its active metabolites 3–4.5h after oral intake.
- **Plasma half-life** 1–1.5h and its active metabolites 14–17h (multiple doses).
- **Duration of action** >24h (single dose), 2–3 days (multiple doses) **(25).**
- The active metabolites are excreted in both bile and urine **(22).**

Pharmacodynamics:

Spironolactone is a competitive inhibitor of the physiologic effects of the adrenocortical hormone aldosterone, the final product of the renin-angiotensin-aldosterone system, that binds to the mineralocorticoid receptors rendering aldosterone transcriptionally inactive. As a consequence, Spironolactone blocks the effects mediated via mineralocorticoid receptors activated by aldosterone on the epithelial cells of the renal distal convoluted tubule and the collecting duct this blocks reabsorption of Na+ and water and the subsequent elevation of blood pressure indirectly by expanding extracellular fluid volume. Spironolactone has been found to inhibit lipopolysaccharide -induced production of proinflammatory cytokines, TNF-α, interleukin(IL)-6, PGE2 and interferon γ in human peripheral blood mononuclear cells and human whole blood cultures via inactivation of IkB kinase/ nuclear factor (NF)-kB (IKK/NF-kB) in macrophages thus spironolactone is suggested to have beneficial effects on metabolic disorders such as atherosclerosis and obesity-linked type 2 diabetes through the anti-inflammatory effect **(26).**

Indications:

Spironolactone is licensed as a potassium-sparing diuretic for the treatment of hypertension, primary hyperaldosteronism, volume-overload states and hypokalemia in addition to patients with chronic congestive heart faliure having diminished ejection fraction and in post-myocardial infarction. It is also indicated as a diuretic in patients with cirrhosis and ascites, in whom secondary hyperaldosteronism is present, and hypokalemia is detrimental. Spironolactone reduces aldosterone-induced renal damage and decrease proteinuria in hypertensive patients **(27).**

As spironolactone binds to the androgen receptor and to a lesser extent estrogen and progesterone receptors, the resultant anti-androgenic effect is used to treat acne and hirsutism in women, particularly when associated with polycystic ovary syndrome although it can also result in undesirable antiandrogenic effects**.** Spironolactone is also indicated in treatment of peripheral edema associated with portal hypertension and nephrotic syndrome **(25).**

Side effects of oral spironolactone:

Impotence, decreased libido, and gynecomastia are side effects that limited male use of spironolactone; however, it is generally safer and well accepted to use in women. Gastrointestinal side effects like nausea, vomiting, anorexia, and diarrhea are not infrequent among users. Common side effects include: breast tenderness, menstrual irregularities, headache, fatigue, blood pressure reduction (with mean decrease of

5 mmHg systolic, 2.6 mmHg diastolic blood pressure) and a minimal rise in serum potassium levels with no cardiovascular or renal sequelae **(27).**

The risk of hyperkalemia increases (~3 to 4-fold) especially in the elderly and in patients with chronic kidney diseases, diabetes mellitus, extracellular fluid volume contraction, infrequent monitoring of serum electrolytes or receiving high doses of mineralocorticoid receptors antagonists, drugs producing hyperkalemia or K+ supplements **(28).**

Drug interactions of spironolactone:

Antihypertensives, vasodilatory drugs, alcohol, tricyclic antidepressants and neuroleptics increase the risk of hypotension in patients treated with spironolactone and requires monitor for blood pressure **(27).**

Enzyme inhibitors like clarithromycin, itraconazole and ketoconazole increase the risk of hyperkalemia thus; their combination with spironolactone is contraindicated, while enzyme inducers like rifampicin, carbamazepine, phenytoin, phenobarbital, cyclosporine and tacrolimus causes decrease in spironolactone plasma levels so drug dose should be increased **(28).**

Spironolactone increases the plasma concentration of digoxin up to 25% and can interfere with digoxin plasma concentration assay so reduction of digoxin dose and monitor of its plasma levels is recommended **(29).**

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, heparin, trimethoprim, sulfamethoxazole, non-steroidal anti-inflammatory drugs (NASIDs), Tacrolimus, I.V. penicillin G potassium and K+ salts or supplements can precipitate serious hyperkalemia in patients treated with mineralocorticoid receptor antagonists, particularly in older individuals or in patients with chronic kidney disease who require monitor for serum K+ levels. Additionally, NSAIDs reduce the antihypertensive effects of spironolactone and increase the risk of acute renal failure, thus reduction of the dose of NASIDs and monitor creatinine plasma levels is needed **(29).**

Contraindications of oral spironolactone:

Concurrent use of spironolactone with potassium supplements and potassium-sparing diuretics are the main contraindications of oral spironolactone intake, while other contraindications include hyperkalemia, Addison's disease, anuria and sever renal impairment **(30).**

- ***Topical spironolactone***

As spironolactone is poorly absorbed from the gastrointestinal tract and to minimize the unnecessary systemic side effects associated with the oral spironolactone, it has been shown that the topical spironolactone can allow high drug levels at the site of action which can lessen the systemic side effects and also patient compliance can be improved **(31).**

Mechanism by which topical spironolactone acts:

Topical spironolactone acts as an anti-androgen in human sebaceous glands, competing with dihydrotestosterone (DHT) receptors and producing a decrease of DHT level causing a significant decrease in sebum content, which is overproduced in acne patients **(31).**

Forms of topical spironolactone:

Clinical studies with topical formulation of spironolactone is previously reported and the results demonstrated beneficial effects in patients with acne without any systemic hormonal changes in the form of significant decrease in skin sebum, increased skin hydration which may be attributed to the retention of water content of the skin. There were no serious adverse experiences that were related to the treatment **.** Also, various approaches have been performed to increase spironolactone dissolution rate, such as complexation with spironolactone nanoparticles, spironolactone loaded nano capsules, liposomes and solid lipid nanoparticles which seems to be well-suited formulations for use on inflamed and damaged skin. Solid lipid

nanoparticles contain non-irritative and non-toxic lipids that ensure close contact with the stratum corneum; enhances transdermal penetration and increases the amount of encapsulated compounds penetrating into the skin **(32).**

Efficacy of topical spironolactone in treatment of acne vulgaris:

Kelidari et al reported that the efficacy of spironolactone gel 5% in the treatment of facial acne showed that total lesion count and acne severity index is reduced significantly **(32).**

Previous studies proved that local topical spironolactone is more effective in non-inflammatory elements (comedones) than in inflammatory ones (papules and pustules) **(32).**

This finding is due to non-penetration of the spironolactone because of the specific micro environmental conditions in the inflammatory acne lesions. Additionally, the presence of secondary bacterial agents and their products in the inflammatory lesions may deactivate the spironolactone. The third hypothesis is that destruction of the hair follicles, followed by destruction of the androgenic receptors during the inflammatory process, can interfere with the spironolactone efficacy via the androgenic receptors as topically administered spironolactone appears to have only a local skin impregnation without any systemic hormonal changes **(32).**

Adverse reactions

Topically prepared spironolactone formulations show some side effects including; hyperpigmentation localized to the treatment site, scaling, dryness, burning sensation, itching and erythema **(32).**

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