

ACNE VULGARIS — an update on pathophysiology and treatment

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Acne vulgaris is the most common of all skin disorders, though rarely life threatening, it is a bane of almost every adolescent face. Acne begins at puberty, the role of androgens in the pathogenesis of acne, probably came from Aristotle as early as the fourth century BC. The four major areas of pathophysiology are increased sebum production, follicular hyperkeratinisation, proliferation of *Propionibacterium acnes* and production of inflammation.

Androgen production begins at adrenarche, when there is increased production of serum dehydroepiandrosterone sulphate (DHEAS). DHEAS is an adrenal precursor for the synthesis of the more potent androgenic hormones: testosterone (T) and dehydroepiandrosterone (DHT). Although serum androgen levels correlate to the severity of acne, yet acne can occur in people with normal serum androgen levels.^{1,2} This raises the possibility of increased androgen production within the pilosebaceous follicle. The pilosebaceous unit possesses the steroid metabolizing enzymes that convert DHEAS to T and DHT. The skin like the other steroidogenic organs can synthesize androgens *de novo* from cholesterol or by locally converting weaker androgens to the more potent ones.^{1,3}

Steroid sulphatase is widely distributed in human tissues; it is present in the lesional skin of acne patients, but not in the unaffected skin. The enzyme converts DHEAS to DHEA. The enzyme 3 β -hydroxy steroid dehydrogenase (3 β -HSD), acts on DHEA and converts it into androstenedione. The conversion may take place in the adrenal glands and tissues such as sebaceous glands. There are two forms of 3 β -HSD; type 1 isoenzyme is active in the skin and type 11 in the adrenal glands and gonads.⁴

Another important hormone found in the skin is 17 β -hydroxy steroid dehydrogenase (17 β -HSD). This is a reversible enzyme that can oxidize and reduce androgens and estrogens. There are many types of 17 β -HSD; type 2 is most active within the sebaceous glands, where it oxidizes testosterone back to androstenedione. This enzyme thus plays an important protective role in acne, converting potent androgens to weaker androgens. The reduction step is responsible for the formation of testosterone from androstenedione. 17 β -HSD types 3 and 5 are responsible for this reduction. Thus 17 β -HSD can provide each cell with a means of controlling intracellular concentration of each sex steroid according to the local needs.^{3,4}

Testosterone is then converted to the more potent androgen dehydrotestosterone (DHT) by the enzyme 5 α - reductase. Two isoenzymes of 5 α - reductase have been identified. Type 1 is active within the sebaceous glands and keratinocytes present in the infundibular portion of the pilosebaceous unit. Type 2 isoenzyme is active in the prostate gland.^{3,4}

The activity of these enzymes shows regional differences on the skin of acne patients. In the skin that is prone to acne as the facial skin, activity of 17 β -HSD type 3 and 5 and 5 α -reductase type 1 is greater than in non-acne prone skin. In contrast action of 17 β -HSD type 2 is greater in sebaceous glands from non-acne prone skin, as this enzyme converts the potent testosterone to the less potent testosterone androstenedione.²⁻⁴

It is not known whether androgens act alone or in combination with growth factors, such as fibroblast growth factor, epidermal growth factor or insulin like growth factor.⁵

Comedogenesis. The hallmark of a pre-clinical lesion of acne vulgaris is the micro-comedone. The lesion may evolve to a clinically non-inflamed lesion or into an inflammatory lesion. The microcomedone represents a distension of sebaceous follicles and accumulation of a large number of corneocytes which appear to be shed in layers that are tightly compact.⁶

Another factor associated with comedone formation is reduction in the level of linoleic acid in the sebum of acne patients. Deficiency of linoleic acid causes hyperkeratinization of the epidermis.³ Comedone formation is due to the hyperkeratinisation of the pilosebaceous duct or due to the increased cohesiveness of keratin. The control of keratinization of the pilosebaceous duct is poorly understood, due to technical difficulties, in contrast to the identification and biochemical analysis of keratin in the inter-follicular region.^{3,6}

Skin in acne prone areas is colonized by *Staphylococcus epidermidis* and *Propionibacterium* (P) *acnes*. The main organism is P *acnes*. The bacteria have nothing to do with comedone formation, but are responsible for the initiation of inflammation. Ductal rupture is not a prerequisite for inflammation, but it is due to the release of cytokines from the duct into the dermis. The source of these cytokines, are P *acnes* or their extracellular products. Severe acne results in scar formation. Why are some scars

hypertrophic others atrophic is not known.⁷

One of the enigmas of acne is why does it improve in the early twenties, when there is no reduction in the amount of sebum production, nor is there no reduction in the amount of P acnes. It is perhaps due to the changes in the pilosebaceous follicle. They no longer produce hyperkeratinization, or hypercornification. Or the improvement in acne may be due to the reduction in the inflammatory response seen in acne patients. Both inflammatory and non-inflammatory lesions disappear; it seems most likely that this is related to changes in the duct function.⁶

Basic information on the pathogenesis of acne has led to rational therapies. For mild acne, topical preparations are the treatment of choice. More than 50% of acne patients belong to this group.⁸ For moderate acne systemic antibiotics are the mainstay of treatment, if these fail then antiandrogens or dianette may be considered. Retinoids are used in moderate to severe acne. Retinoids revolutionized the treatment of acne in the early 1970s. It acts on all four areas of pathogenesis.

The ideal topical therapy should be able to have an impact on the microcomedone, which is the precursor of all acne lesions. This would potentially arrest the development of non-inflammatory and inflammatory lesions of acne. Research has indicated that topical retinoids have an impact on the comedones, and should be considered early in any treatment regime for acne.^{9,10}

Recently, a combination of topical preparations, have shown to have greater efficacy than monotherapy. Adapalene 0.1% and benzyl peroxide 2.5% preparation was used in a fixed dose preparation in a randomized double blind controlled study. It showed greater efficacy for treatment of acne vulgaris, with a fast onset of action as early as after 1 week of treatment, relative to monotherapy with adapalene or benzyl peroxide. The penetration of benzyl peroxide is likely to be enhanced when combined with a retinoid, which alters the follicular microclimate.¹¹ Similarly combinations of clindamycin and benzyl peroxide have been tried. But most of these trials are either small or inconclusive, and therefore not very informative for use in general practice.

Topical androgens have shown to suppress sebaceous gland activity in animals but their study on humans has been disappointing in most studies. This is probably due to the difficulty in delivering the active substance to the target cell.^{12,13}

Moderate to severe acne requires systemic therapy. Oral antibiotics are the mainstay of treatment. The choice of the drug depends upon adverse effects, resistant, previous treatment, exposure to sun and cost.

Oral tetracycline is the most commonly used antibiotic. The preferred choice of cyclines varies from

country to country, from physician to physician. However there is lack of evidence-based data on their relative efficacy and dosage. In a systematic review of clinical trials from 1962-2006, it was found that all tetracyclines are equally effective against acne.¹⁴ Although minocycline has a greater antimicrobial effect on P acnes, than the first generation tetracycline, and doxycycline has greater lipid solubility, favouring its bioavailability in pilosebaceous units. However very few randomized studies have been done to compare efficacy with lesion count reduction. Minocycline can cause a number of rare but severe side effects, including hypersensitivity reactions, systemic lupus erythematosus, autoimmune hepatitis, thyroiditis and polyarteritis nodosa. Because of the lack of advantage over other tetracycline, an uncertain safety profile, there is no justification in continuing to use minocycline as the first line of therapy. Doxycycline is more likely than other cyclines to cause phototoxicity.¹⁴ Further studies are required to support the effect of one tetracycline over the other.

Erythromycin and other antibiotics are best reserved when tetracycline have failed. Retinoids have revolutionized the treatment of acne. Retinoids act on all areas of acne pathology. Oral retinoids are the drug of choice in nodular cystic acne, acne excoriee, moderate acne that is producing scars, or acne that is not responding to antibiotic therapy, gram-negative folliculitis, acne fulminans and acne conglobata. Being teratogenic it should only be prescribed by a dermatologist.

Evidence based reviews on lasers, light sources and photodynamic therapy in treatment of acne vulgaris have concluded that optical treatment possess the potential to improve inflammatory acne on a short-term basis, with the most convenient outcomes for photodynamic therapy.¹⁵ Interventions included were photodynamic therapy, infrared lasers, broad spectrum light sources, pulse dye lasers, intense pulse light and potassium titanyl phosphate laser. The supposed mechanisms for the action for optical treatments are photothermal heating of sebaceous glands and photochemical inactivation of P acnes which produces coproporphyrins and protoporphyrins. Photoimmunological reactions may also contribute in improving acne. These are not the first line treatments.¹⁵

Acne scarring can be treated today by a number of new treatment options, such as collagen injections, autologous fat transfer, laser resurfacing and surgical techniques. Each type of scar has an optimal treatment method.

Future medications would focus on enzymes in the skin that produce androgens locally. Androgens therapies that could block the action of these enzymes may be useful in the treatment of acne. Since DHT is the most potent

androgen, that directly influences acne, so enzymes that synthesize DHT from DHEAS (steroid sulphatase, 3 β -HSD, 17 β -HSD or 5 α -reductase), or those enzymes detoxify DHT (aromatase or 3 α -HSD), can be targeted or modified as a potential means of treating acne.² But since the proximal path of androgen metabolism may affect the synthesis of other steroid hormones, it would be safe to target the downstream enzymes as 5 α -reductase type 1.¹ Testosterone binds to type 1 5 α -reductase at micromolar concentrations, whereas affinity for type 2 5 α -reductase is in the nanomolar range. This implies that much higher doses may be required to inhibit this isoenzyme.⁴ Type 2 5 α -reductase enzyme inhibitor (finasteride) is used to treat prostate hypertrophy; it also acts on the external root sheath of terminal hair follicles, and so is effective in androgenetic alopecia.⁴ Studies have shown that type 1 5 α -reductase can also be inhibited by green tea extract catechins, zinc, azelaic acid and suramin.³

Although acne therapy has improved tremendously since the last two decades, yet we see a number of patients with severe acne and scars in our daily outpatient clinics. Both doctors and patients should understand how the disease should be managed. Patient compliance is very important. Both the primary care physician and the specialist should realise that acne is the most treatable skin disorder, and there is no justification for acne patients to suffer today.

References

1. Thiboutot D, Gilliland K, Light J, Lookingbill D. Androgen metabolism in sebaceous glands from subjects with and without acne. *Arch Dermatol* 1999; 135: 1041-5.
2. Chen CW, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspectives. *J Invest Dermatol* 2002; 119: 992-1003.
3. Thiboutot D, Bayne E, Thorne J, Gilliland K, Flanagan J, Shao O, et al. Immunolocalization of 5 alpha-reductase isozymes in acne lesions and normal skin. *Arch Dermatol* 2000; 136: 1125-9.
4. Thiboutot D, Ellen B, Thorne J et al. Immunolocalization of 5 α -reductase in Acne lesions and normal skin. *Arch Dermatol* 2000; 136: 1125-9.
5. Denilen Ko DM, Ring BD, Yanagihara D, Benson W, Wiemann B, Starnes CO, et al. Keratinocyte growth factor is an important endogenous mediator of hair follicle growth, development, differentiation. Normalization of the nu/nu follicular differentiation defect and amelioration of chemotherapy-induced alopecia. *Am J Pathol* 1995; 147: 145-54.
6. Cunliffe JW. Pathogenesis of acne: summary. In: *Acne*. Martin Dunitz Publication 1989; pp 250-1.
7. Leyden JJ. Advances of Acne therapy. In: *Dermatologic Therapy in Current Practice*. Marks R, Leyden JJ eds. Martin Dunitz Publication 2002; pp 35-43.
8. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology* 1998; 196: 119-25.
9. Alirezai IM, George SA, Coutts I, Roseeuw DI, Hachem JP, Kerrouche N, et al. Daily treatment with adapalene gel 0.1% maintains initial improvement of acne vulgaris previously treated with oral lymecycline. *Eur J Dermatol* 2007; 17: 45-51.
10. Thielitz A, Sidou F, Gollnick H. Control of microcomedone formation throughout a maintenance treatment with adapalene gel 0.1%. *J Eur Acad Dermatol Venereol* 2007; 21: 747-53.
11. Thiboutot D, Weiss J, Bucko A, Eichenfield L, Jones T, Clark S, et al. Adapalene - benzyl peroxide, a fixed dose combination for the treatment of acne vulgaris: results of a multicentre, randomized double-blind, study. *J Am Acad Dermatol* 2007; 57: 791-9.
12. Gruber MD, Sator MO, Joura EA, Kokoschka Em, Heinze G, Huber JC. Topical cyproterone acetate treatment in women with acne a placebo - controlled trial. *Arch Dermatol* 1998; 134: 459-63.
13. Lookingbill DP, Abrams BB, Ellis CN, Jegasothy BY, Lucky AW, Ortiz-Ferrer LC, et al. Inocoterone and acne. The effect of a topical antiandrogen: results of a multicentre clinical trial. *Arch Dermatol* 1992; 128: 1197-200.
14. Simonart T, Dramaix M, De Maertelaer V. Efficacy of tetracyclines in the treatment of acne vulgaris: a review. *Br J Dermatol* 2008; 158: 208-16.
15. Haerdersdal M, Togsve Bo K, Wulf HC. Evidence based reviews of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris. *J Eur Acad Dermatol Venerol* 2008; 22: 267-78.