

Management of treatment quality in menopausal patients with acne by hormonal therapy

Abstract

Acne starts to represent an important condition treated by physicians worldwide, especially at menopausal patients. Although it can occur independently, sometimes could be accompanied by hyperandrogenism features followed by hormonal abnormalities. When most menopausal patients showed to be unresponsive to conventional treatment, hormonal therapy represent a better alternative option. Hormonal evaluation represents a prerequisite for hormonal therapy, either replacing the unresponsive cases, either to identify the cause of hyperandrogenism. Considering that the aim of hormonal therapy in menopausal patients tend to be the reduction of sebum production, in the present review, the hormones implicated in sebum production (i.e. androgens, estrogens, insulin and insulin growth factor-1) are discussed including the management of the hormonal therapy for acne.

Keywords: acne, sebum, hormones, menopause, therapy, management

1. Introduction

Acne represents the most common skin injury which affects more than 80% of people⁽¹⁾. In some conditions, it was showed to spontaneously remit usually before 30 years. Into the 6th decade of life, it has an unpredictable course, persisting for a longer time⁽²⁾.

The main implications were seen by the follicular epidermal hyperproliferation, excess of the sebum and inflammation⁽³⁾. In this respect, many topical or systemic drugs have been developed in order to achieve a better course of the injury over the last 25 years⁽⁴⁾. Although many clinical trial studies have been developed in this aim, the monitoring of the acne by the physician has still remain a debate, especially in menopausal patients^(5,6).

Some studies showed that many adult women who suffer from acne do not respond well at the systemic treatment either with antibiotics, either with isotretinoin⁽⁴⁾. Therefore, in such case, an alternative treatment is needed, especially who can offer acceptable negative effects⁽⁷⁾. Knowing that hormones have an important role in enhancing sebum production, a hormonal treatment could be an alternative⁽⁸⁾. Usually, such therapies are indicated in cases with hyperandrogenism signs, but could be used also in the cases with resistant acne⁽⁹⁾.

There are many physiological forms of acne characterized by lesions along the jawline, menstrual acne, cystic acne which lead to menstrual irregularities and hirsutism. The androgens fluctuation levels could lead to pre-menstrual disorders⁽¹⁰⁾.

The persons which are not affected by the androgens showed not to produce sebum in excess and they will not develop any type of acne⁽¹¹⁾. Some syndromes showed to be produced by the hormonal imbalance and to conduct at acne⁽¹²⁾.

Therefore, hormonal treatments can be applied not only in cases when the common treatment have been

failed, or when the patients present hyperandrogenism, but also in resistant cases and which have unpredictable course of this injury.

2. The Hormones Implicated in Acne Pathogenesis

2.1. Androgens

The production of the androgens can be seen in the ovary, under the influence of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and in the adrenal gland under the adrenocorticotrophic hormone level and in the skin^(13,14).

The main representative androgen is C-19 steroid which is biosynthesized from ovaries and adrenal gland⁽¹⁵⁾. In ovaries the biosynthesis take place in the mature follicle and in adrenal cortex the biosynthesis is due mainly on zona reticulate⁽¹⁶⁾. The androgenic hormones are based on strong androgens, like testosterone and androgens like dehydroepiandrosterone (DHEA) which are considered weaker. The androgens are usually converted at testosterone from adipose tissue. Then, testosterone are transformed to dihydrotestosterone by 5 α reductase^(17,18).

The higher activity of androgens showed to increase sebum production, which represents the first step in developing acne. In the same context, the hypersensitivity of sebaceous gland even at the normal or lower level of androgens causes the increase sebum production^(19,20). Therefore, the level of androgens could intensify the follicular hyperkeratosis. The biosynthesis of androgens act on the androgen receptors bases which are also present in the follicle and this could represent the mechanism by which acne could develop⁽²¹⁾. With this knowledge in mind, an anti-androgenic hormonal treatment has been considered as an alternative treatment for the acne.

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2.2. Estrogens

The roles of estrogens are to decrease the size of sebaceous gland and reducing the sebum by enhancing androgen production through a negative feedback⁽²²⁾.

The synthesis of estrogens are taking place from testosterone which is made when LH stimulate the theca cells of the ovary. The higher dose of estrogens showed to suppress the sebum production, being much higher than the ovulation dose⁽²³⁾. Interestingly, until present, the dose of ethinyl estradiol which is found mainly in oral contraceptive pills (OCPs) is still not enough to act on the sebum reduction. Although the OCP showed to be an elective treatment in acne, the mechanism through which it helps the organism to maintain the skin balance is not represented by the sebum reduction. The OCPs inhibit gonadal testosterone production by suppressing the pituitary gonadotropin release⁽¹⁰⁾. By this mechanism, the sex hormone binding globulin (SHBG) showed to be increased at the liver level which decreases the testosterone production which will lead in the end at the lipid suppression⁽¹¹⁾.

2.3. Insulin

Higher amount of insulin showed to promote the androgen biosynthesis especially in ovaries, increasing the sebum production. Both insulin and insulin growth factor-1 (IGF-1) have been showed to be involved in acneogenesis⁽²⁴⁾.

In the same manner, insulin regulates growth hormone receptor and showed to stimulate ovarian and adrenal production. In addition, insulin represents the main factor in lipid enzymes through stimulation of ovarian and adrenal production⁽²⁵⁾.

2.4. Insulin like-growth factor-1

It has been noted that the androgens are stimulated by the IGF-1, inhibiting SHBG production. The receptors of IGF-1 showed to be expressed mainly in sebaceous gland which will stimulate the sebum production and lipogenesis⁽⁵⁾.

Moreover, considering the higher glycemic index found in the diet, will result in insulin release which will lead to sebum production. This fact could explain the link between the diet and the acne production⁽²⁶⁾.

The levels of IGF-1 showed to be increased in polycystic ovary syndrome and acromegaly^(27,28). For example, IGF-1 is also used in the treatment of children disorders which will result in androgenesis and acne production^(27,28).

3. Management and Treatment Quality of Hormonal Therapy

When androgen excess occur, many features like cysts, nodules, and different lesions of the acne could be present. In such cases, the hormonal imbalance should also be taken into consideration, even in women which are closer of menopausal period⁽²⁹⁾. However, many studies suggested that the hormonal therapy alone is not indicated, in which the objectives are the androgen production suppression together with its receptors from the sebaceous gland⁽³⁰⁾.

Beside hormonal treatment for acne, the European guidelines suggested the combination with the topical or systemic antibiotics, especially in pustular or nodulocystic features which represent an extremely forms of acne.

In other mild types of acne, the use of hormonal treatment is contraindicated⁽³¹⁾.

The main drugs used in the hormonal treatment can be classified as: suppressors of androgen production, suppressor of adrenal androgen secretion, androgen receptor blockers and enzyme inhibitors⁽³²⁾.

3.1. Suppressors of androgen production

■ **OCPs:** like estrogen or ethinyl estradiol (EE) shows to suppress the androgens production through a negative feedback effect. In the same time it shows to negatively stimulate SHBG synthesis inhibiting 5 α -reductase. Therefore, it is indicated that estrogen to be combined with progestins, in order to avoid the risk of endometrial cancer⁽³³⁾.

■ **Cyproterone acetate (CPA):** which has an anti-androgen effect which blocks also the receptors. It has been showed an improvement in patient treated with CPA, especially when was combined with EE⁽³⁴⁾.

■ **Gonadotropin releasing hormone (GnRH) analogs:** it was showed to inhibit the androgen production by negatively inhibiting the release of FSH and LH⁽³⁵⁾. The drugs can be found as nasal sprays which can be easily administrated, or as subcutaneous injections. Until present, there are only few studies regarding the GnRH use in acne conditions, either alone or in combination with other drugs. It has some side effects like rapidly developing of menopausal symptoms regarding the bone loss and rheumatic imbalance. The abnormal vaginal bleeding represents the main contraindications for GnRH treatment⁽³⁵⁾.

3.2. Suppressor of adrenal androgen secretion

■ **Glucocorticoids:** the advantages of glucocorticoids are the fact that it can be used in low doses. Those indications are for the menopausal women with higher DHEA doses which will decrease 11-or 21-hydroxylase level. Low doses of dexamethasone can also be used for androgen suppression⁽³⁵⁾.

3.3. Androgen receptor blockers

■ **Spiranolactone:** which inhibits 5 α reductase, showed to be an aldosterone antagonist. It is usually used in resistant type of acne and can be used for a long period of time until 24 months⁽³⁶⁾;

■ **Flutamide:** It can be used for 6 months period of time alone, or in combinations with OCPs. It showed to be limited in used, especially for its side effects like hepatitis⁽³⁷⁾;

■ **Ketoconazole:** represent an antifungal drug, and at higher doses showed to have antiandrogenic and anti-glucocorticoid effects, inhibiting cytochrome P450 synthesis. It has limitation in its used, having a week effect and being a lower antiandrogen. Its side effects are mainly represented by hepatitis and thrombocytopenia⁽³⁸⁾.

3.4. Enzyme inhibitors

- **5 α reductase inhibitor:** used in hormonal imbalance when acne is present, especially in menopausal age. It can be used alone or in combination with OCPs⁽³⁹⁾.

4. Conclusions

In conclusions, the hormonal therapy showed to be a better alternative at the common treatment used for acne, even if the androgen level is normal. The selection of the patients for this treatment seems to be better understanding those effects, although a combination

with other therapies like antibiotics, glucocorticoids or androgen suppressors could be also enterprise.

Therefore, it is important to know the available hormonal treatments option for acne, their optimal modes of use, and absolute contraindications. The physicians should prefer a hormonal treatment option, especially in menopausal patients, supporting its potential beneficial role. ■

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