

# The importance of the evaluation of androgen levels in adult women with acne: Brazilian casuistic report

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## Abstract

### Introduction

Acne in adult women is a hard-to-manage frequent disease with many relapse cases. It mostly interferes with the quality of life and causes major social and metabolic losses for patients. This is a transversal retrospective study whose aim is to identify the androgen profile in patients who were treated at the Acne-in-Adult-Women Ambulatory Clinic in the Dermatology Department of Faculdade de Medicina do ABC (FMABC) from 2008 to 2012, and who presented altered frequency and profile of the hormones.

### Materials and methods

In this study, we reviewed 201 medical records of women above 15 years of age, with the onset or worsening of acne cases, treated at the ambulatory clinic. The levels of the hormones DHEA-S, DHEA, DHT, androstenedione and total and free testosterone were measured in all patients.

### Results

The evaluation of the hormonal profile showed that 60% of the patients had hyperandrogenemia, and the levels of DHEA were the most frequently elevated.

### Conclusion

Therefore, in the face of the importance of the hyperandrogenemia in the

pathogenesis of acne, the standardization of circulating androgen levels and the early detection of hyperandrogenic states prove to be useful for a more precise evaluation of each patient and for the choice of the best therapeutic conduct.

To establish a model for the research of hormonal profile is paramount for relapse control in the event of a surge of acne breakouts in a woman's adult life.

### Introduction

Acne complaints are very common in dermatological offices. Although it is a typical disease among adolescents, an expressive rate of patients still bears acne lesions throughout adulthood<sup>1</sup>. Despite the same etiopathogeny, some authors consider these lesions a nosologic entity that is different from the acne vulgaris.<sup>2,3</sup>

Acne vulgaris is basically an alteration in the pilosebaceous follicle, which starts in puberty, among other factors, as a result of the androgen production increase<sup>4,5</sup> that leads to the excessive production of sebum, the abnormal detachment of keratinocytes and the obstruction of the follicle opening, resulting in the development of microcomedones.<sup>6</sup>

The sebum accumulation stimulates the proliferation of the gram-positive bacterium *Propionibacterium acnes* in individuals with genetic predisposition. This, in return, leads to the release of not only cytokines, like the interleukins IL-6 and IL-8, by the infundibular keratinocytes and of IL-8 and IL-12 by the macrophages, but also of pro-inflammatory mediators which cause the onset of the inflammation in the follicle and in the adjacent derm<sup>7,8</sup>. In the beginning of adolescence, the hormonal trigger

induces the hypersecretion of sebaceous glands and the possible modification of the sebum composition, influencing pro-inflammatory events.<sup>6</sup>

In the female sex, from the moment ovulation is fully established, around two years after the menarche, oestrogen levels favour the acne improvement. Nonetheless, after this period some patients still bear lesions or report acne breakouts, a fact that is referred to as acne in the adult woman<sup>2</sup>. In this context, hyperandrogenism plays an essential role.<sup>9</sup>

The human skin is the target for a large number of chemical messengers, including a wide range of hormones. Hormonal effects on the development of secondary sexual characteristics starting at puberty and the capacity of the pilosebaceous unit to produce and release hormones are vastly known<sup>10</sup>.

Human skin cells produce IGF-1 and IGF-BP, melanocortin derivatives, catecholamines, steroids and vitamin D from cholesterol; retinoids from dietary carotenoids; eicosanoids from fatty acids.

Hormones like steroids exert biological effects on the skin through high-affinity receptors not only in the cytoplasmic, but also in the nuclear membrane. Human skin is also capable of activating or inactivating hormones.

Most of circulating androgens is produced by the gonads<sup>11</sup> and by the adrenal glands<sup>12</sup>. Androgens may also be produced locally within the sebaceous gland itself from the hormones DHEA and androstenedione<sup>10</sup>. Testosterone (T) and dihydrotestosterone (DHT) are the main androgens that interact with nuclear and cytoplasmic androgen receptors located in the basal layer of

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the sebaceous gland and in the keratinocytes from the outer root sheath of the hair follicle<sup>10,13</sup>.

DHEA is the precursor hormone of other androgens and oestrogens, and it is primarily metabolized from cholesterol<sup>14</sup>. DHEA-S is a hormone abundantly produced in the reticular zone of the adrenal cortex, and it circulates in the blood at relatively high levels when compared with other hormones<sup>14</sup>.

Through the action of the enzyme 3-beta-hydroxysteroid-dehydrogenase, it is converted into androstenedione (A). This conversion may occur in the adrenal and in the sebaceous glands, sites where this enzyme activity can be found<sup>15</sup>. Besides DHEA-S and DHEA, other androgens like testosterone, dihydrotestosterone and androstenedione affect several functions of the human skin. Their effects are mediated by nuclear receptors, and androgen activation and deactivation are mainly intracellular events<sup>16</sup>.

In peripheral tissues like the skin, DHT is produced from T through the action of the enzyme 5-alpha-reductase. There are two isoenzymes: number 1 is active within the sebaceous gland and in the keratinocytes of the infundibular region of the pilosebaceous follicle whereas number 2 is more active in the prostate and hair follicles.<sup>16</sup>

T androgens, especially DHT, form complexes with androgen nuclear receptors. The complex androgen-receptor then interacts with the DNA in the sebaceous cell nucleus in order to regulate the genes involved in cellular growth and in the lipid production.<sup>10</sup>

Androgens affect several functions of the human skin, like the sebaceous gland growth and its differentiation, hair growth, epidermal barrier homeostasis and cicatrization. Such effects are mediated by the binding to nuclear receptors. Alterations in the isoenzymes and/or androgen

receptors may have important implications in the development of hyperandrogenism signs, which may be associated with the onset of acne. The fact that the 5-alpha-reductase also acts in the infundibular region reinforces the suspicion that androgens may also influence follicular keratinization.<sup>16</sup>

Diseases that present an increase in androgen production are associated with acne. Among them, two of the most common diseases are the polycystic ovary syndrome (PCOS) and the congenital adrenal hyperplasia (CAH). Androgen-secreting tumours and acromegaly are other examples of endocrine causes of acne.<sup>17</sup>

PCOS is the most common hormonal disorder among young women<sup>17</sup>. Its diagnosis is based on the conjunction of two out of the three following criteria: oligo- or amenorrhea, hyperandrogenism (clinical evidence of excessive androgens) or hyperandrogenemia (biochemical evidence of excessive levels of androgens) and polycystic ovaries shown in pelvic or transvaginal ultrasound images<sup>18</sup>. Nearly 23-35% of women with PCOS have acne, and 83% of the women with the late onset of severe acne breakouts have PCOS.<sup>18</sup>

The primary abnormality of PCOS is an overproduction of androgens by the ovaries caused by the abnormal regulation of 17-hydroxylase. In the peripheral adipose tissue, excessive androgens are converted to oestrogens in an acyclic way, generating an increase in the hypophysis secretion of luteinizing hormone (LH). The peripheral resistance to insulin is also evident, and it results in hyperinsulinemia which stimulates androgen hypersecretion and the production of more LH.<sup>18</sup>

The physical exam focus on the presence of signs and symptoms of excessive androgens, which include acne, hirsutism or hypertrichosis, relapsing seborrheic dermatitis,

obesity or increase in waist circumference due to the deposition of adipose tissue in the area and female androgenetic alopecia<sup>19,20</sup>. Cases of acne are usually accompanied by menstrual irregularity.

Congenital adrenal hyperplasia results in alterations in adrenal steroid synthesis caused by a genetic deficiency of enzymes. The 21-hydroxylase deficiency is the most common disorder followed by the 11-hydroxylase deficiency in a smaller scale. The deficiency of these enzymes leads to the substitution of steroid biosynthesis from cortisol for the production of androgens from cholesterol<sup>19</sup>. The 21-hydroxylase deficiency is classified as classical and nonclassical. In its nonclassical form, the deficiency is partial with late manifestation. Its phenotype is similar to PCOS<sup>19,20</sup>, and acne may be the only symptom.

In addition to the acne cases, adult female patients are more likely to have an increase in the total cholesterol and LDL levels in the bloodstream and to develop resistance to insulin, both risk factors responsible for the appearance of type II diabetes and cardiovascular diseases.<sup>3</sup>

Although androgens are related to the pathogenesis of acne, reports that correlate the elevation of androgens in women at a fertile age with acne are inconsistent in the literature, varying from 30 to 90% in some groups of patients until the absence of androgen alterations in others<sup>5,21</sup>.

There are few evidences of which endocrine tests should be prescribed in cases of acne in adult women. As the hormonal evaluation is not standardized, studies alternate the standards based on small samples of patients<sup>22</sup>.

Some studies recommend the research on dehydroepiandrosterone sulphate (DHEA-S), dehydrotestosterone (DHT) and testosterone<sup>8</sup>, or androstenedione and testosterone<sup>9,21,23</sup>, or still, DHEA-S, testosterone and free testosterone<sup>3</sup> or DHEA-S and free testosterone<sup>5,24</sup>. It may

be noticed thus that there is no consensus on the literature concerning which hormones should be researched. This fact makes the comparison of the data from the numerous available reports very hard, once each report indicates distinct exams.

Given the great number of adult patients above 15 years of age with acne or exacerbation of acne and whose androgen levels are normal, the systematic research of the complete serum androgen profile was chosen according to the available literature. DHEA-S, DHEA, DHT, androstenedione and total testosterone<sup>25</sup> were included in order to verify the percentage of androgen concentration tests whose results showed levels above normal in adult patients with acne.

### Materials and methods

This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

This is a retrospective transversal study conducted at the Acne-in-Adult-Women Ambulatory Clinic, dermatology department from the Faculdade de Medicina do ABC in Santo André, SP between the years 2008 and 2012. We included 276 female patients with appearing or aggravation papule-pustule or cystic acne cases after 15 years of age.

A questionnaire was applied at the first attendance to provide basis for data collection. The questionnaire included questions on age, clinical classification of lesions (comedonic acne – grade I; papule-pustule acne – grade II; nodule-cystic acne – grade III) and the areas of their major concentration (face, chest and back). The adopted classification is based on the morphological characteristics: the comedonic acne presents open

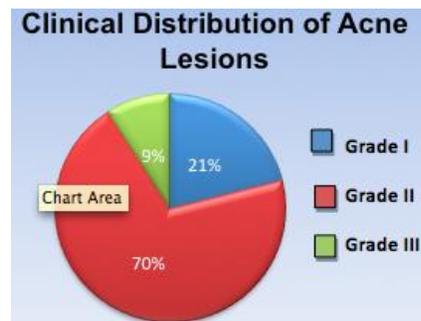


Figure 1: Clinical distribution of acne lesions according to their grades.



Figure 2: Relative distribution of acne affected area.

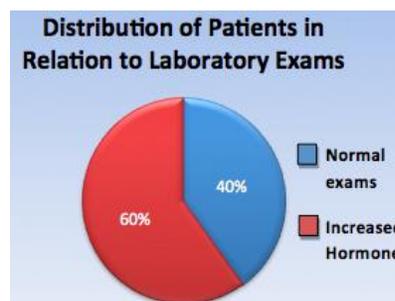


Figure 3: Distribution of patients in relation to laboratory exams (total of 201 patients).

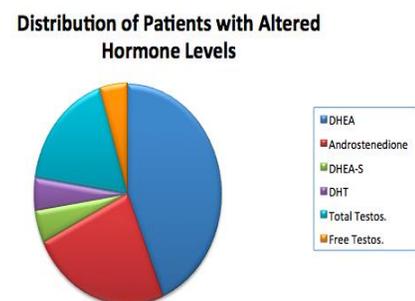


Figure 4: Distribution of patients in relation to altered hormone levels (total of 122 patients).

(follicular dilatation of 1-2 mm) and closed comedones. The papule-pustule acne is characterized by the predominance of red and sensitive papules of 1-5 mm in diameter, with or without whiteheads.

As to the nodule-cystic acne, there are deep inflammatory lesions bigger than 5mm in diameter<sup>24</sup>. Concerning the number of lesions, they were classified as mild (up to 5 lesions), moderate (from 5 to 10 lesions) and severe (above 10 lesions or spreading beyond the face).

A full androgen profile was requested from these patients containing the following exams: DHEA, DHEA-S, DHT, androstenedione, total testosterone and its free fraction. Laboratory exams were performed regardless of the menstrual cycle phase since it does not interfere with the obtained values.

### Inclusion Criteria

Women aged between 15 and 18 with severe comedonic acne, severe papule-pustule acne, mild papule-pustule acne associated with other

signs of hyperandrogenism (hypertrichosis and/or hirsutism, hard-to-control seborrheic dermatitis and central obesity) and nodule-cystic acne.

Women above the age of 18 years who had severe comedonic acne, papule-pustule acne or cystic acne, regardless of the gravity or extension of the lesions.

### Exclusion Criteria

Patients between 15 and 18 years of age with mild cases of papule-pustule acne with no sign of hyperandrogenism, so that the possibility of a delayed puberty manifestation could be eliminated. Patients with mild and moderate comedonic acne, once such lesion may be triggered by occlusive external agents, like the inadequate topical use of comedogenic products. Pregnant patients or patients undergoing systemic corticosteroid therapy, making use of steroids, vitamin supplements or anticonvulsants.

### Hormonal evaluation

Hormone measurements were requested systematically at the first attendance before the beginning of the

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treatment, and they were performed at the Clinical Analysis Laboratory at the FMABC. The adopted measurement methods followed international rules which were in consonance with standardizations established according to the good practice guidelines in clinical analysis.

## Results

Among the 276 analysed medical records, 201 met the study inclusion criteria. The median age of the patients was 28 years (range, 15-58 yr), and the clinical predominance was of acne grade II (142 patients), followed by grade I (41 patients) and grade III (18 patients) as seen in figure 1.

The area with major incidence of lesions was the face in 79% of the cases, followed by the chest and the back in 11 and 10% of the cases respectively (Figure 2).

The number of patients with altered hormone levels was analysed (122 patients) in relation to the patients who presented normal results (79 patients) totalling 201 patients (Figure 3).

In the cases where there was more than one hormonal alteration (43 patients), the combination most frequently observed was the association of androstenedione and DHEA (18 patients), followed by the increase in total testosterone and DHEA (15 patients) (Figure 4 and Table 1).

## Discussion

The study proposal was to determine the prevalence of serum levels of DHEA, androstenedione, free and total testosterone, DHEA-S and DHT in a sample of adult female patients with acne. It is of major importance to define the hyperandrogenism state, once many studies point to the fundamental role of the androgens in the pathology of acne.<sup>2,6,7</sup>

In most published studies it can be observed that researches focus on the

**Table 1: Distribution of altered hormones in total of patients and in patients with altered levels.**

Discrimination of Altered Hormones		
Hormones	Total no of Patients (201)	In Patients w/ Hormonal Alterations (122)
DHEA	78 (29%)	78 (64%)
Androstenedione	43 (22%)	43 (35%)
Total Testosterone	32 (16%)	32 (26%)
Free Testosterone	8 (4%)	8 (7%)
DHEA-S	8 (4%)	8 (7%)
DHT	8 (4%)	8 (7%)

evaluation of some androgenic hormones and not on the analysis of a complete hormonal profile, as it is proposed in this retrospective study.

Another point that should be taken into consideration is the age from which the androgenic hormone research is indicated. In patients aged 15 years and over, with extensive severe acne cases or with other signs of androgenization, the early diagnosis allows the control of the symptoms and prevents not only the cutaneous, but also the harmful metabolic consequences these women are subjected to.<sup>17,25</sup>

A substantial number of studies show the increase of androgens in women with acne, ranging from 30 to 90%. In our series we found at least one type of hormone with altered levels in 60% of the cases. The main hormones found at high levels in the group of patients with acne were DHEA (39%), androstenedione (22%) and total testosterone (16%). Some studies recommend the free salivary testosterone measurement due to the fact it is more sensitive to the detection of hyperandrogenism. However, as shown in this study, the free testosterone measurement result alterations were found in only 4% of the cases, a fact that is consonant with many researches that defend the total testosterone measurement as a more reliable method.<sup>3,5,8,9,13,26,27</sup>

Factors like stress, smoking, heredity, premenstrual acne aggravation and the use of medications are correlated to the onset or worsening of acne in this group. Given the difficulty found

in the retrospective analysis of medical records, these data were not taken into consideration. Nevertheless, they should be systematically included in future studies on the theme.

## Conclusion

The early and complete laboratory evaluation of women with acne is of great importance for the detection of hyperandrogenic states so that the early diagnosis of conditions that are closely related to reproductive and metabolic complications can be made.

By providing a fast and effective approach, a decrease in the morbidity and mortality rates among such patients is expected. The antiandrogen therapy should be included in the treatment in order not only to minimize aesthetic complications, like scars and dyschromias, but also to raise these women's self-esteem.

Therefore, in the face of the importance of hyperandrogenism in the pathogenesis of acne, standardizing the research of the hormone profile is paramount for the treatment and control of relapses in the event of a surge of acne breakouts during a woman's adult life.

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