

Adrenal Androgens and Intracrinology

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ABSTRACT

In postmenopausal women, all estrogens and nearly all androgens are made locally in peripheral target tissues from the inactive adrenal steroid precursor dehydroepiandrosterone (DHEA). In adult men, approximated 50% of androgens are made locally. This new section of endocrinology, which describes the local formation of sex steroids, has been named intracrinology. In fact, all the enzymes required to make androgens and estrogens are expressed in a cell-specific fashion, thus permitting local control of steroid formation and action. The local inhibition of sex steroid formation or action has shown important benefits in the treatment of hormone-sensitive cancers, including significant prolongation of survival and even curing localized disease. On the other hand, exogenous DHEA provides important advantages in postmenopausal women because it compensates for the declining secretion of DHEA by the adrenals with age. The benefits of DHEA include increased bone mineral density, muscle mass, well-being, and libido, as well as beneficial effects against skin atrophy, type 2 diabetes, and obesity.

KEYWORDS: Intracrinology, androgens, estrogens, peripheral target tissues

INTRACRINOLOGY

Humans, along with the other primates, are unique among animal species. They have adrenals that secrete large amounts of the inactive precursor steroid DHEA and especially its sulfate DHEA-S, which are converted into potent androgens or estrogens, or both, in peripheral target tissues.¹⁻⁴ The term intracrinology was first coined in 1988⁵ to describe the synthesis of active steroids that exert their action in the same cells in which their synthesis takes place, with minimal release of the active steroids into the extracellular space and general circulation (Fig. 1).¹ Plasma DHEA-S levels in adult men and women are 100 to 500 times higher than those of testosterone and 1000 to 10,000 times higher than those of estradiol, thus providing a large reservoir of substrate for conversion into androgens or estrogens, or both, in the peripheral intracrine tissues, which possess the enzymatic machinery necessary to transform DHEA into active sex steroids.¹

The marked reduction in the formation of DHEA-S by the adrenals during aging⁶⁻¹⁰ results in a dramatic fall in the formation of androgens and estrogens in peripheral target tissues, a situation that may be associated with age-related diseases, such as insulin resistance,^{11,12} obesity,¹³⁻¹⁵ and skin atrophy. Recently, much attention has been given to the benefits of DHEA administered to postmenopausal women, especially on the bone, skin, vagina, and well-being after oral^{16,17} and percutaneous^{18,19} administration of the precursor steroid.

Proof of the role of the intracrine formation of estrogens in peripheral target tissues is particularly well-illustrated in women. The important benefits for women with breast cancer were observed in postmenopausal women treated with aromatase inhibitors.²⁰ Moreover, because postmenopausal ovaries do not secrete estrogens, the recent observation that use of the antiestrogen raloxifene for only 3 years in postmenopausal women led to a

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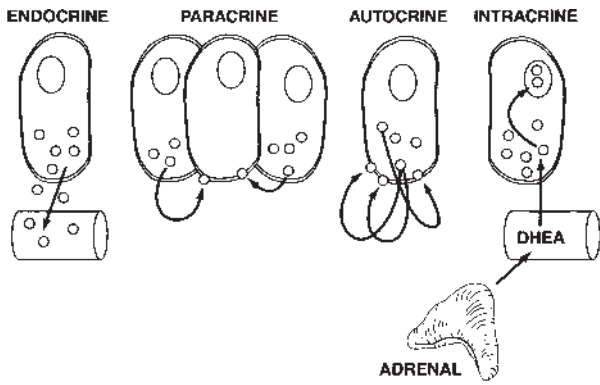


Figure 1 Schematic representation of (A) endocrine, (B) paracrine, (C) autocrine, and (D) intracrine secretion. Classically, endocrine activity refers to the hormones that are secreted in specialized glands, called endocrine glands. These hormones are released into the general circulation and are transported to distant target cells that possess the specific steroid receptors. On the other hand, hormones released from one cell can influence neighboring cells (paracrine activity) or can exert a positive or negative action on the cell of origin (autocrine activity). Intracrine activity or intracrinology describes the formation of active hormones that exert their action in the same cells where synthesis took place without release into the pericellular compartment. (From Labrie,¹ with modifications.)

76% decrease in the incidence of breast cancer is a clear demonstration of the crucial role of extraovarian estrogens in the development and growth of breast cancer.²¹

STEROIDOGENIC ENZYMES IN PERIPHERAL TISSUES

Contrary to the belief that the testes are responsible for 90 to 95% of total androgen production in men (as suggested by the decrease in serum testosterone after castration), it is now well-demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors DHEA-S, DHEA, and 4-dione into the active androgens testosterone and dihydrotestosterone (DHT) locally in peripheral tissues without significant release of the active androgens in the circulation. In fact, the prostate makes approximately 50% of its own androgens; the other 50% is of testicular origin.

The human steroidogenic pathway comprises 15 main steps, transforming cholesterol into the five classes of active hormonal steroids, namely androgens (testosterone and DHT), estrogens (estradiol and 5-androstenediol), progesterone, glucocorticoids (cortisol or corticosterone), and mineralocorticoids (aldosterone), as well as their inactive sulfate and glucuronide derivatives (Fig. 2). So far, 30 human genes have been found to encode enzymes of the steroidogenic pathway. Such a large number of steroidogenic enzyme isoforms allows tissue-specific expression and thus local control of steroid formation according to local needs dictated by intracellular and extracellular signals. These control mechanisms permit local regulation of steroid action independently from the circulating levels of these steroids.

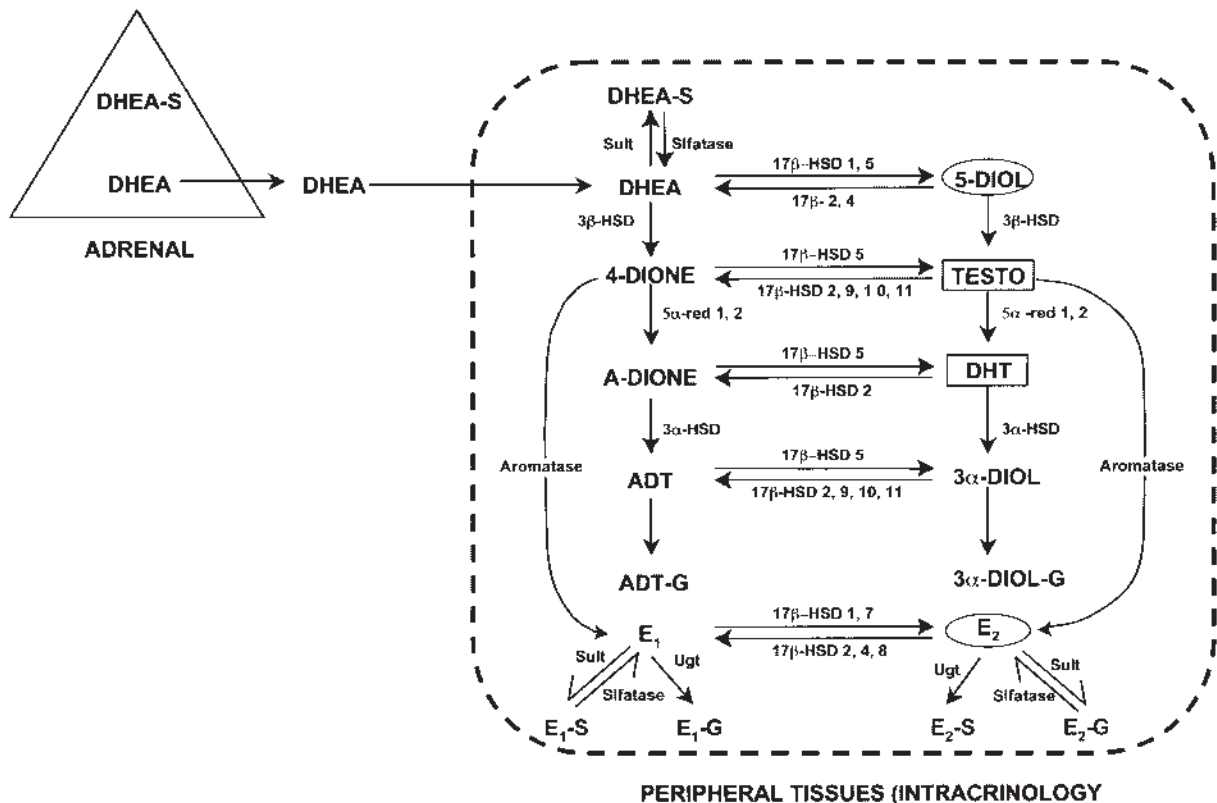


Figure 2 Human steroidogenic and steroid-metabolizing enzymes in peripheral target intracrine tissues.

The formation and inactivation of androgens and estrogens is under fine control by a series of enzymes that reduce (activate) or oxidize (inactivate) the C17 position of C19 (androgens) or C18 (estrogens) steroids. At the present time, 11 human 17 β -hydroxysteroid dehydrogenases (17 β -HSDs) are known and can be divided into two functional groups.^{4,22–26} Those of the first group are represented by types 1, 3, 5, and 7 17 β -HSDs, which prefer nicotinamide-adenine dinucleotide phosphate (NADPH) as cofactor and catalyze the reduction of 17-ketosteroids (inactive form) into 17 β -hydroxysteroids (active form) (Fig. 2). The members of the second group represented by types 2, 4, 6, 8, 9, 10, and 11 17 β -HSDs function as dehydrogenases or inactivating enzymes. These enzymes prefer NAD⁺ as cofactor and catalyze the oxidation of 17 β -hydroxysteroids. The following are some of the most appropriate examples.

Type 5 17 β -HSD: Like type 3 17 β -HSD, this enzyme catalyzes the transformation of 4-dione into testosterone, although its tissue distribution is very different.²⁷

It is believed that this enzyme plays a crucial role in the formation of testosterone in all tissues in women and in peripheral tissues in men.^{28,29} This enzyme is most likely responsible for the virilization of young adult men deficient in type 3 17 β -HSD.²⁴ The action of this enzyme is particularly evident at the time of puberty, when the secretion of DHEA by the adrenals increases.

Type 7 17 β -HSD: It is of interest that type 7 17 β -HSD,³⁰ the other enzyme that catalyzes the transformation of estrone (E1) into estradiol (E2) is expressed in all tissues at a somewhat higher level than type 1 17 β -HSD, including the ovary.

Types 9, 10, and 11 17 β -HSDs: These enzymes catalyze the oxidation of the 17 β -hydroxy 5 α -reduced steroids and can also transform 5 α -androstane-3 α ,17 β -diol (3 α -diol) into 5 α -androstane-3 α -ol-17-one (androstosterone).^{31–33} These enzymes could play an important role in the inactivation of DHT.

The best-known action of 5 α -reductase (5 α -red) is the transformation of the weak androgen testosterone into the most potent natural androgen, namely DHT. On the other hand, the best-known activity of 3 α -HSDs^{34,35} is the inactivation of the potent androgen DHT into 3 α -diol. It is generally thought that these enzymes are highly expressed in androgen-sensitive tissues, the prostate being the best example.³⁶

In our genomic profile or steroid action (ATLAS) program, we are measuring the levels of messenger RNAs encoding all of these enzymes in the mouse, which amounts to 45 steroidogenic and steroid-metabolizing enzymes. It is of interest to mention that all the enzymes found in the human are also found in the same peripheral tissues in the mouse. Thus, although the

evolutionary path of the mouse diverged from that of humans 75 million years ago, all the enzymes responsible for the formation and inactivation of androgens in human peripheral tissues are also expressed in some peripheral tissues of the mouse. This strongly supports the important role of these enzymes, not only in the human and the other primates but also in lower animal species.

The local biosynthesis and action of androgens in target tissues eliminates the exposure of other tissues to androgens and thus minimizes the risks of undesirable masculinizing or other androgen-related side effects. The same applies to estrogens, although we feel that a reliable parameter of total estrogen secretion (comparable to the glucuronides for androgens) is not yet available.

DECREASE OF DHEA WITH AGE

Because of assay difficulties, until recently, only a limited number of circulating adrenal and gonadal steroids have been measured during advancing age, thus limiting the evaluation of the relative role of different sources of sex steroids. This analysis is of special importance in postmenopausal women, in whom the sex steroids of adrenal origin gain particular importance after the complete arrest of estrogen secretion by the ovaries at menopause.¹

It is important to recall that in the 50- to 60-year-old age group, serum DHEA has already decreased by 70%, compared with the 20- to 30-year-old peak values (Fig. 3).²³ It is thus quite remarkable that most of the important decline in circulating DHEA, DHEA-S, androst-5-ene-3 β , 17 β -diol (5-diol), 5-diol-G, 4-dione, and the conjugated metabolites of androgens, namely androsterone glucuronide (ADT-G), 3 α -diol-G, and androstane-3 β , 17 β -diol glucuronide (3 β -diol-G), occurs between the age ranges of 20 to 30 years and 50 to 60 years, whereas relatively smaller changes occur after the age of 60 years.³⁷

HIGH LEVELS OF ANDROGENS IN WOMEN

Although the metabolic clearance rates of the three main androgen metabolites are likely to show differences between men and women, an estimate of the relative amount of total androgens in women and men calculated on the basis of the sum of the serum concentrations of these three metabolites indicates that total androgen production in women is more than two thirds, or 71%, that observed in men.^{37,38} This calculation is based on the knowledge that active androgens are inactivated to glucuronide derivatives before their diffusion from the intracellular compartment into the circulation, where they can be measured as ADT-G, 3 α -diol-G and 3 β -diol-G.

Such data showing the presence of relatively high levels of androgens in normal women strongly suggest

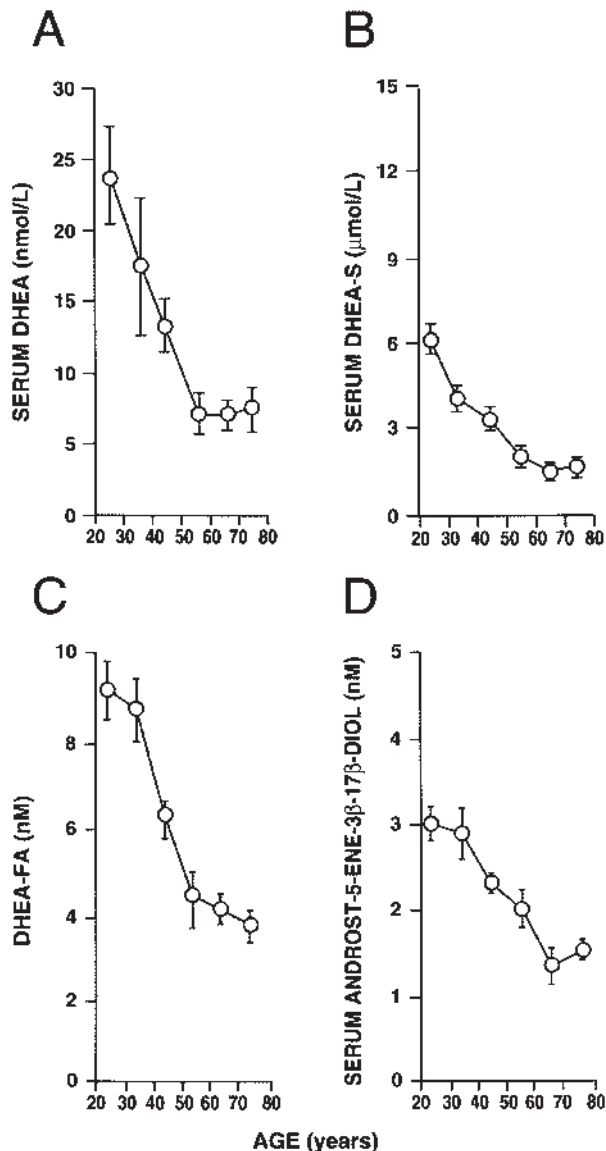


Figure 3 Effect of age (20 to 30 years old to 70 to 80 years old) on the serum concentration of (A) DHEA, (B) DHEA-S, (C) DHEA-fatty acid esters (DHEA-FA), and (D) 5-diol in women (Reproduced with permission: Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. From Labrie et al.³⁷

that the androgens play a major, but so far underestimated, physiological role in women. The 44.5% fall that occurs in serum DHEA in 20- 30-year-old to 40- 50-year old women could well explain the bone loss that precedes menopause.³⁸⁻⁴¹

MULTIPLE ROLES OF DHEA AND ANDROGENS IN WOMEN

The best-recognized fact about menopause is that it corresponds to a rapid and complete arrest of estrogen secretion by the ovaries, which is illustrated by the

marked decline in circulating E2 levels. The almost exclusive focus on ovarian estrogens at menopause has diverted the attention from the progressive and dramatic fall in circulating DHEA, which starts earlier, at the age of 30 to 40 years (see Fig. 3).^{6-10,37,42} Because DHEA is transformed into both androgens and estrogens in peripheral target tissues, such a fall in the serum concentration of the steroid precursors DHEA and DHEA-S explains why postmenopausal women, as discussed later, are lacking not only estrogens but also androgens. In fact, levels of serum follicle-stimulating hormone increase in premenopausal women even before serum E₂ shows a decrease.⁴³ On the other hand, age-related bone loss has been reported as beginning during the 4th decade, and changes in bone turnover have also been found before menopause.³⁹⁻⁴¹ In agreement with these findings, bone density was lower at all sites examined in women classified as perimenopausal compared with those who were premenopausal.⁴⁴ Moreover, women taking contraceptives or estrogen replacement therapy (ERT) have reduced ovarian androgen secretion attributable to inhibition of gonadotropin secretion, as well as reduced androgen bioavailability attributable to increased sex hormone-binding globulin levels.⁴⁵

It is likely that the androgens produced from DHEA have other beneficial effects in postmenopausal women. The detailed benefits of androgens added to ERT or hormone replacement therapy (HRT) have been described for general well-being, energy, mood, and general quality of life.^{46,47} Improvements in the major psychological and psychosomatic symptoms, namely irritability, nervousness, memory, and insomnia, have been observed after addition of androgens to ERT.⁴⁸

Loss of libido and sexual satisfaction are common in early menopause. The addition of androgens to HRT is known to have beneficial effects on these problems.^{47,49,50} Moreover, a positive correlation has been found in postmenopausal women between sexual behavior and circulating levels of androgens. In addition, androgenic compounds have been found to be beneficial for the treatment of the mastalgia frequently caused by HRT.⁵¹ In fact, ERT may result in severe breast pain, which may lead to discontinuation of therapy. Moreover, the androgenic effect of DHEA should also be useful in reducing hot flashes. In fact, androgen therapy is successful in reducing hot flashes in hypogonadal men.⁵² It has also been observed that the addition of androgens is effective in relieving hot flashes in women who had unsatisfactory results with estrogen alone.⁵³

The 70 to 95% reduction in the formation of DHEA and DHEA-S by the adrenals during aging results in a dramatic reduction in the formation of androgens and estrogens in peripheral tissues, which could well be involved in the pathogenesis of age-related diseases such as insulin resistance^{11,12} and obesity.¹³⁻¹⁵ Antitumoral effects of DHEA-S and DHEA have,

in fact, been found in a series of animal models.⁵⁴⁻⁵⁶ DHEA has also been shown to have immunomodulatory effects *in vitro*⁵⁷ and *in vivo* in fungal and viral diseases,⁵⁸ including human immunodeficiency virus.⁵⁹ On the other hand, a stimulatory effect of DHEA on the immune system has been described in postmenopausal women.⁶⁰

We have thus evaluated the effect of chronic replacement therapy with a 10% DHEA cream applied on the skin once daily for 12 months in 60- to 70-year-old women ($N = 15$). Anthropometric measurements showed no change in body weight but a 9.8% decrease in subcutaneous skinfold thickness at 12 months ($p < 0.05$).¹⁸ Bone mass density was increased by 3.75% at the Ward's triangle in the hip, and 2.2% at the lumbar spine level (all $p < 0.05$).¹⁹ These changes in bone mineral density were accompanied by significant decreases at 12 months of 38% and 22% in urinary hydroxyproline and in plasma bone alkaline phosphatase, respectively (all $p < 0.05$). An increase of 135% over control ($p < 0.05$) in plasma osteocalcin, a marked bone formation was observed concomitantly.

Measurements of midhigh fat and muscle areas by computed tomography have shown a 3.8% decrease ($p < 0.05$) of femoral fat and a 3.5% increase ($p < 0.05$) in femoral muscular area at 12 months.¹⁸ There was no significant change in abdominal fat measurements. These changes in body fat and muscular surface areas were associated with a 12% decrease ($p < 0.05$) of fasting plasma glucose and a 17% decrease ($p < 0.05$) in fasting plasma insulin levels. Treatment with DHEA had no undesirable effect on the lipid or lipoprotein profile. In fact, there was an overall trend for a 3 to 10% decrease in total cholesterol and its lipoprotein fractions. Plasma triglycerides were not affected.

The index of sebum secretion was 79% increased after 12 months of DHEA therapy with a return to pretreatment values 3 months after cessation of treatment. DHEA administration stimulated vaginal epithelium maturation in 8 out of 10 women who had a maturation value of zero at the onset of therapy; stimulation was also seen in the three women who had an intermediate vaginal maturation before therapy. Most importantly, the estrogenic stimulatory effect observed in the vagina was not found in the endometrium which remained completely atrophic in all women after 12 months of DHEA treatment,¹⁹ thus eliminating the risk of endometrial hyperplasia and cancer and the need for a progestin.

The present data clearly indicate the beneficial effects of DHEA therapy in postmenopausal women through its transformation into androgens or estrogens, or both, in specific intracrine target tissues without significant side effects. The absence of stimulation of the endometrium by DHEA eliminates the need for progestin replacement therapy, thus avoiding the fear of

progestin-induced breast cancer. The observed stimulatory effect of DHEA on bone mineral density and the increase in serum osteocalcin, a marker of bone formation, are of particular interest for the prevention and treatment of osteoporosis and indicate a unique activity of DHEA on bone physiology, namely on bone formation, whereas ERT and HRT can only reduce the rate of bone loss.

DHEA has been shown to have important effects on the skin of aged individuals, the most salient of which, as mentioned earlier, is an increase in sebum production.¹⁹ This has been shown in several studies performed in women, particularly those > 70 years old who are physiologically hyposeborrheic and thus found an improvement of their skin with DHEA administration. The DHEA-induced increase in sebum production observed in our study is probably due to the fact that the sebaceous glands contain all the steroidogenic enzymes necessary to catalyze the transformation of DHEA into the androgen DHT and that this androgen is the main stimulator of sebaceous gland activity.^{26,61}

Apart from sebum production, other beneficial effects of DHEA on the skin have been noticed. To date, evaluation of the dermatological aspects of DHEA administration has only been performed with some details in one study in which male and female subjects between the ages of 60 and 79 years were given 50 mg of DHEA orally, once daily for 1 year. In that study, Baulieu et al¹⁷ evaluated skin hydration, pigmentation, and thickness. Skin surface hydration significantly increased for the whole DHEA-treated population examined after 12 months of treatment. Skin surface hydration is considered a real benefit for the skin, especially in aged individuals because the dryness makes the skin rough in these subjects. DHEA also significantly decreased facial skin pigmentation (yellowness) for the entire population. This decrease was more pronounced in women > 70 years, who are more concerned with age-related pigment changes. The two other components of skin color remained stable during the duration of the study (i.e., lightness and redness).

The data obtained concerning DHEA in women strongly support the paradigm of intracrinology whereby the precursor steroid DHEA is transported in the bloodstream as DHEA and DHEA-S, which are metabolized into active estrogens and androgens in specific peripheral target tissues that possess the required enzymatic machinery.¹ These locally produced steroids then act in the same cells in which synthesis takes place before being inactivated and then released in the extracellular space and the general circulation as the more water-soluble sulfate and glucuronide derivatives.^{1,26} The active steroids, on the other hand, do not diffuse significantly in the general circulation, thus protecting the other tissues from the action of these steroids and avoiding the

potential side effects observed following systemic administration of estrogens and androgens.

ROLE OF DHEA IN MEN

Contrary to the previous belief that the testes are responsible for 90 to 95% of total androgen production in men (as suggested by the decrease in serum testosterone after castration), it is now well-demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors DHEA-S, DHEA, and 4-dione into the active androgens testosterone and DHT locally in peripheral tissues without significant release of the active androgen in the circulation. In fact, as mentioned earlier, the prostate makes its own androgens at a level comparable to the androgens of testicular origin.

An important point to make is that testosterone and DHT are made locally, and the amounts of testosterone and DHT that are found in the circulation are not reliable parameters of the true exposure to androgens in target tissues. In fact, DHT, as well as testosterone, is inactivated locally in the prostate tissue to glucuronosyl derivatives of testosterone, DHT, androstanediol, and androsterone. These compounds are more water soluble and are thus easily released into the circulation, from which they are then eliminated, mostly by the bile and then through the intestine. Accordingly, plasma sex steroid concentrations have very limited value for estimating what is going on in the peripheral tissues. The testis makes testosterone, which can be directly measured in the circulation, and it reaches the peripheral tissues through this vehicle. The adrenals, on the other hand, secrete a large amount of DHEA that is also released into the circulation, through which it reaches the peripheral target intracrine tissues where it is transformed into testosterone and DHT. However, very little testosterone or DHT made from DHEA comes back into the circulation. In fact, these two steroids act locally and are inactivated locally mainly by glucuronosyl transferases. These glucuronosyl derivatives are the steroids that can be easily measured in the blood, thus providing a proper estimate of the androgen milieu.

These explanations about the physiology of androgens in men are extremely important for choosing the appropriate androgen blockade for the most efficient treatment of prostate cancer. In fact, the understanding of the two sources of androgens in men and their relative importance is crucial for the best choice of androgen blockade for the prostate cancer patients. We know that prostate cancer is highly sensitive to androgens. Accordingly, we should choose the best way to take advantage of this very important characteristic of prostate cancer. In fact, prostate cancer is the most sensitive of all cancers to hormonal therapy, even more so than breast cancer, which is already highly sensitive to hormonal therapy. The most scientifically based approach is to use a

luteinizing hormone-releasing hormone (LHRH) agonist to block androgen secretion from the testicles or to remove the testicles surgically. At the same time, however, the action of the androgens made locally in the prostate must be blocked with a pure antiandrogen.

Contrary to the previous belief that the testes are responsible for 95% of total androgen production in men, as suggested by simple measurement of circulating serum testosterone, it is now well-demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors DHEA-S, DHEA, and 4-dione into the active androgen DHT. In fact, the prostate synthesizes its own androgens.

The first treatment shown to prolong life in men with prostate cancer is the combination of a LHRH agonist (blocker of androgen secretion by the testes) with a pure antiandrogen such as flutamide, nilutamide, or bicalutamide (at the proper dose, namely at least 150 mg daily). When associated with castration, which eliminates the androgens of testicular origin, these compounds—sometimes called nonsteroidal antiandrogens—block the action of the androgens produced locally in the prostate.⁶²⁻⁷⁰

Analysis of all the studies performed with flutamide and nilutamide associated with medical or surgical castration compared with castration plus placebo shows that overall survival is increased by an average of 3 to 6 months (Fig. 4).^{64-66,68,71-75} Because approximately 50% of patients in that age group die from causes other than prostate cancer, this 3- to 6-month difference in overall survival translates into an average of 6 to 12 months of life gained when cancer-specific survival is analyzed. These additional months, or sometimes years, of life can be obtained by simply adding a pure antiandrogen (flutamide, nilutamide, or bicalutamide at a proper dose) to castration. These data demonstrate the particularly high level of sensitivity of prostate cancer to androgen deprivation, considering that such statistically significant benefits on survival are obtained even at the very advanced stage of metastatic disease.

Bennett et al⁶⁶ have performed a meta-analysis of all peer-reviewed published randomized controlled trials comparing treatment with flutamide in association with medical (LHRH agonist) or surgical castration versus castration alone in advanced prostate cancer. Nine studies with 4128 patients were included in the analysis that demonstrated a statistically significant (10%) improvement in overall survival with the combination therapy using flutamide compared with castration alone. Similar benefits have been obtained in favor of flutamide plus castration versus castration alone in the Prostate Cancer Trialist's Collaborative Group (PCTCG).⁷⁵

In fact, as illustrated in Figure 4, all the meta-analyses of all the data have shown significant ($2p < 0.05$) or highly significant ($2p < 0.01$) advantages of

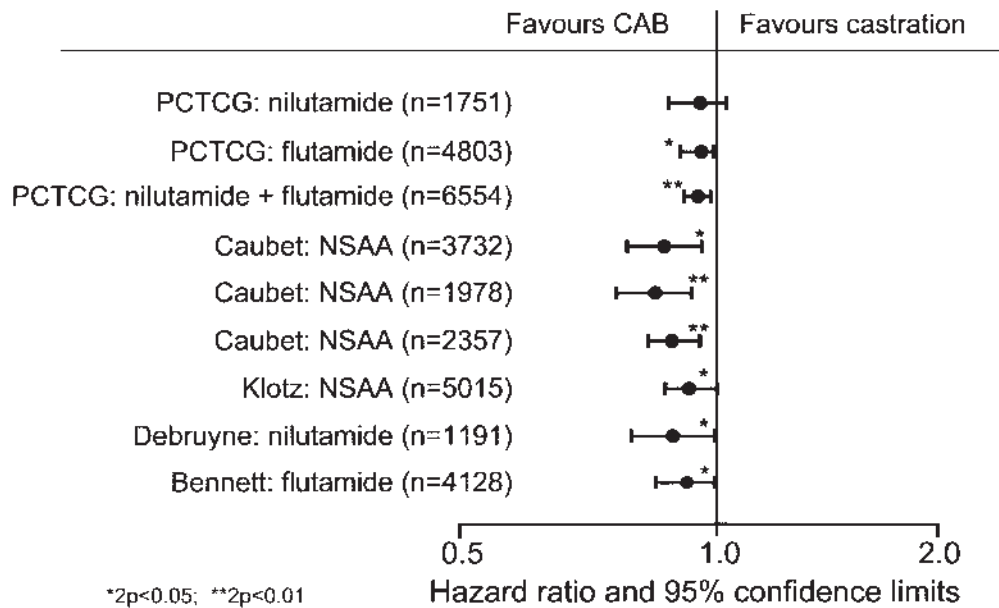


Figure 4 Summary of meta-analyses comparing CAB (combination of medical or surgical castration associated with a pure antiandrogen) versus medical or surgical castration alone. A pure antiandrogen refers to a nonsteroidal antiandrogen (NSAA), namely flutamide or nilutamide. (Adapted from Klotz.⁶⁶)

combined androgen blockade versus castration alone in advanced prostate cancer.^{66–68,72,75,76} However, when the studies providing the most rigorous data are analyzed, a 20% advantage in overall survival is observed.⁷²

It is of interest to recall, as recently published by Aprikian et al,⁶⁹ that the cost per month of prolonged survival in prostate cancer achievable with the simple addition of a nonsteroidal antiandrogen to castration (LHRH agonist or orchiectomy) is 50% that of vinorelbine for lung cancer, 10% of the cost of renotecan for colon cancer, and 10% of the cost of trastuzumab for breast cancer. Moreover, the nonsteroidal antiandrogens have minimal toxicity, whereas vinorelbine and irinotecan are associated with severe grade 3 and 4 clinical toxicities, and trastuzumab has cardiac side effects when associated with anthracyclines.

Despite the important advance observed with monotherapy (LHRH agonists) in localized prostate cancer, namely a one third to two thirds reduction in death from prostate cancer, can we achieve better results? Based on the observation that 50% of androgens are left in the prostate after castration alone,^{63,77} it is reasonable to suggest that better results can be achieved with the combination of an LHRH agonist with a pure antiandrogen. In fact, with long-term treatment of localized prostate cancer with combined androgen blockade, the evidence obtained even indicates that long-term control or cure of the disease can be obtained in most patients.⁷⁸

With a minimum of 5 years of follow-up after cessation of long-term combined androgen blockade (CAB), only two rises in prostate-specific antigen (PSA) occurred among 20 patients with stage T2/T3

cancer who stopped treatment after continuous CAB for more than 6.5 years, for a nonfailure rate of 90% (Fig. 5). On the other hand, for the 11 patients who received CAB for 3.5 to 6.5 years, the nonfailure rate was only 36%. The serum PSA increased within 1 year in all 11 patients with stage B2/T2 treated with CAB for only 1 year, thus indicating that active cancer remained present after short-term androgen blockade despite undetectable PSA levels. Most importantly, in all patients who had biochemical failure after stopping CAB, serum PSA rapidly decreased again to undetectable levels. When CAB was restarted, PSA remained at such low levels afterward. Of these patients, only 1 had died of prostate cancer as of the last follow-up.⁷⁸

The present results obtained in patients diagnosed with localized prostate cancer and treated continuously for many years with combined androgen blockade are not too different from the results that we have obtained recently with human breast tumors in nude mice in which complete estrogen blockade led to the disappearance or cure of the tumors in 61% of cases within a few months.⁷⁹ In fact, when the estrogens in breast cancer and the androgens in prostate cancer are blocked optimally, a cure of the disease can be achieved with hormonal therapy.

Knowing the particularly high sensitivity of prostate cancer to androgen blockade, especially at the localized stage, blockade of androgens appears to be a logical approach for the prevention of the disease. In fact, the 5 α -reductase inhibitor finasteride has been shown to reduce the prevalence of prostate cancer by 24.8% in the Prostate Cancer Prevention Trial.⁸⁰ Because only a 50% decrease in serum PSA is observed

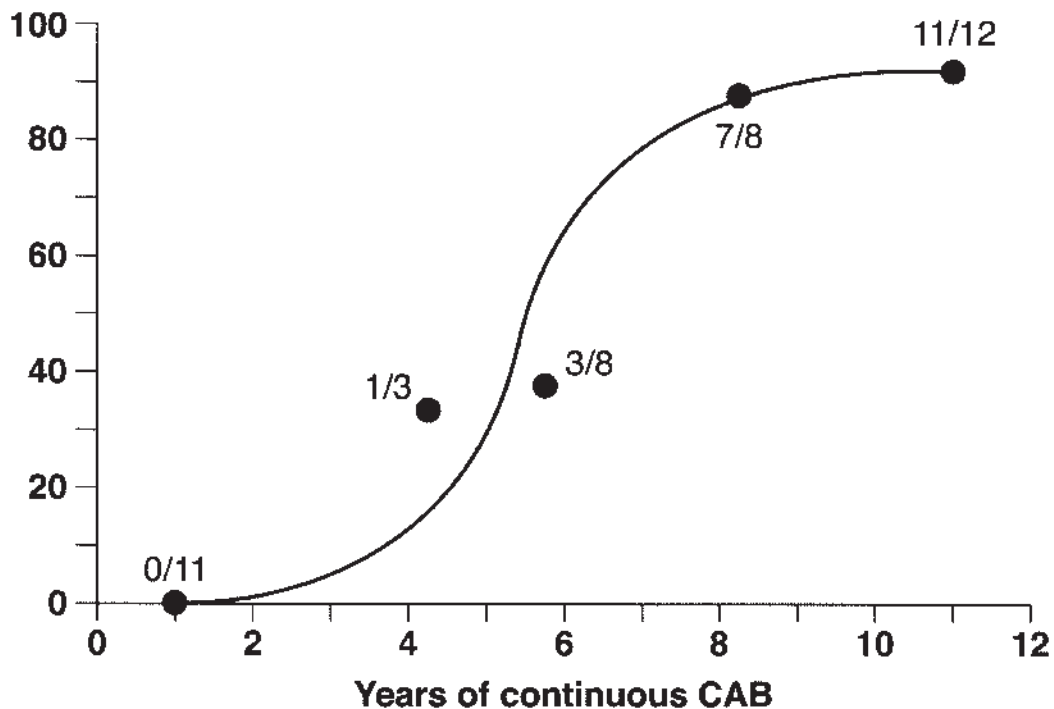


Figure 5 Effect of duration of treatment of localized prostate cancer with continuous CAB on the probability of long-term control or "cure of the disease" illustrated by no recurrence of a PSA rise for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the 3 patients treated with CAB for 3.5 to 5.0 years and followed for at least 5 years. The point at 5.75 years refers to the 8 patients treated continuously with CAB for 5.0 to 6.5 years before cessation of treatment. The point at 8.25 years refers to the 8 patients treated continuously for 6.5 to 9.0 years. The point at 11 years refers to the 13 patients treated for 10 to 11.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after cessation of continuous CAB or until PSA rise. Only 1 patient has died from prostate cancer; 18 have died from other causes.⁷⁷

with finasteride, thus indicating a relatively weak effect on prostate cell biology compared with castration alone and even less when compared with CAB, such data showing a positive effect on the prevalence of prostate cancer support the particularly high sensitivity of early prostate cancer to such partial androgen blockade. Tumors of Gleason grade 7, 8, 9, or 10 were, however, more common in the finasteride group (37.8% versus 22.2% in the placebo group). This phenomenon could well be related to the early observation that pretreatment low levels of serum testosterone were the most significant variable associated with early time to progression.⁸¹ Such data reinforce the importance of a maximal blockade of androgens in prostate cancer at all stages of the disease.

Because more complete blockade of androgens should lead to a more rapid and more complete inhibition of prostate cancer growth, the addition of finasteride to the combination of a pure antiandrogen and castration could be an interesting approach, as already supported by positive clinical data in localized disease.⁸² The challenge of such androgen blockade is related to the secondary effects on libido and sexual performance. The development of more potent antiandrogens or short-term administration of CAB could optimize the inhibition of cancer growth and induce maximal apoptosis while limiting the secondary effects.

It is very important to remember again that contrary to what can be found in most textbooks, orchiectomy or treatment with LHRH agonists does not reduce exposure of the tissues to androgens by 90 to 95%. In fact, removal of testicular androgens decreases DHT levels in the prostate by only 50 to 60%, thus leaving an important amount of androgens free to continue to stimulate prostate cancer. Most importantly, the presence of a significant concentration of androgens leaves the cancer exposed to additional mutations and the development of resistance to androgens and to hormonal therapy. In practical terms, and based on our current best knowledge of the endocrinology of the prostate, the only reasonable hormonal treatment for prostate cancer is the combined use of a LHRH agonist or orchiectomy in association with a pure antiandrogen, namely flutamide, nilutamide, or bicalutamide (150 mg or more daily).

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