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Comparable amounts of sex steroids are made outside the gonads in men and women: Strong lesson for hormone therapy of prostate and breast cancer

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ABSTRACT

The objective of this study was comparison of circulating androgens and their metabolites as well as estrogens measured for the first time by a validated mass spectrometry technology in 60–80-year-old men and women of comparable age.

Castration in men ($n = 34$) reduces the total androgen pool by only about 60% as indicated by the decrease in the serum levels of the glucuronide metabolites of androgens compared to intact men ($n = 1302$). Such data are in agreement with the 50 to 75% decrease in intraprostatic dihydrotestosterone (DHT) concentration after castration. Most interestingly, the same amounts of androgens and estrogens are found in postmenopausal women ($n = 369$) and castrated men of comparable age.

The most significant therapeutic implication of these findings is the absolute need to add a pure (non-steroidal) antiandrogen to castration in men with prostate cancer in order to block the action of the 25 to 50% DHT left in the prostate after castration. Not adding an antiandrogen to castration in men treated for prostate cancer is equivalent to not prescribing a blocker of estrogens in women suffering from breast cancer because they are postmenopausal and have low circulating estradiol.

1. Introduction

The ovaries and testicles have usually been considered the exclusive sources of estrogens and androgens in women and men. For example, the fall in serum estradiol (E_2) to extremely low levels at menopause coupled with the beneficial effects of exogenous estrogens on menopausal symptoms [1] has focused the efforts of hormone replacement therapy almost exclusively on various forms of estrogens to compensate for the cessation of estrogen secretion by the ovaries. In men, on the other hand, the 95% fall in serum testosterone induced by castration and the clinical benefits of this procedure in men with advanced prostate cancer [2] has led the urological community to generally believe that castration eliminates 95% of androgens and is thus a sufficient treatment for prostate cancer.

The scientific findings recently provided by endocrinology are quite different [3–5]. For example, in postmenopausal women with breast cancer, the high rate of response to aromatase inhibitors and antiestrogens [6] is a consequence of the relatively high levels of estrogens which remain in breast cancer tissue after menopause [7]. On the other hand, in men, the finding that 25% to 50% of androgens are left in the prostate after castration [3,5,8,9] explains why the addition of a pure (non-steroidal) antiandrogen to castration has been the first treatment shown to prolong life in prostate cancer [3,10–12]. The androgens remaining at a relatively high level after castration also explain why the same treatment (combined androgen blockade) can provide cure for most patients when the treatment is started at the localized stage of prostate cancer [13–15], thus clearly demonstrating the major role of extratesticular androgens.

The immunoassays so-far used to measure serum E_2 and testosterone lack sufficient sensitivity and specificity at the low levels found in postmenopausal women and castrated men [16,17]. However, the recent mass spectrometry assays validated under Good Laboratory Practice criteria [18,19] offer the opportunity to perform the first reliable measure of the estrogens and androgens of ovarian, testicular and peripheral origins in women and men. Only such accurate and validated data can provide the scientific basis required for the proper design of improved approaches for a more efficient blockade of sex steroids for breast and prostate cancer treatment and for adequate replacement therapy in postmenopausal women.

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2. Subjects, materials and methods

2.1. Subjects

Steroid levels were measured in elderly normal intact men as well as in castrated men with prostate cancer using mass spectrometry [18–20]. Blood samples of 69–80-year-old men were obtained from the Mr OS study. The Mr OS study is a multicenter study including men from Sweden ($n \cong 3000$: ≅1000 in Malmö, ≅1000 in Göteborg and ≅1000 in Uppsala), Hong Kong (≅2000) and the United States (≅6000). In the present study, we used blood samples from a subsample of the population-based Swedish part of the MrOS ($n = 911$ intact men; $n = 34$ castrated men). Among the castrated men, 31 subjects were chemically castrated using GnRH agonists while 3 subjects were surgically castrated. The demographic characterization of the MrOS Göteborg cohort can be found in Vandenput et al. [20]. The study was approved by the ethics committee of Göteborg, University. An informed consent was obtained from all study participants.

For comparison, steroid levels were also measured in blood samples of 48–86-year-old intact men obtained from a randomized sub sample ($n = 391$; average age = 67 years) of a large prospective randomized and controlled prostate cancer study of 46 193 men performed in Quebec City [21]. The demographic characterization of the study population can be found in Labrie et al. [21]. The study was approved by the Laval University Hospital Ethics Committee and all men have signed informed consent.

Three hundred and seventy seven (377) healthy postmenopausal women aged 55–65 years participated in this study after IRB approval and having given written informed consent. No subject had taken hormone replacement therapy during the previous 6 months. No subject was suffering from an endocrine disorder, and none was under treatment with lipid- or glucose-lowering agents. The others inclusion/exclusion criteria are described in Labrie et al., [18]. All subjects had a medical history, complete physical examination, serum biochemistry as well as complete blood and urinalysis. Blood sampling was performed under fasting conditions between 08:00 and 10:30 h.

2.2. Quantitation of steroids in human serum: human blood sample collection for measurement of steroids

Extraction and analysis of conjugtated and non-conjugated steroids were performed as described [18,19]. The serum steroid levels of testosterone (testo), estrone (E_1) and estradiol (E_2) were analyzed by GC-MS while androsterone glucuronide (ADT-G), androstane-3α, 17β-diol-3-glucuronide (3α-diol-3G), androstane-3α, 17β-diol-17-glucuronide (3α-diol-17G) and estrone-sulfate (E_1S) were analyzed by a LC/MS/MS method using TurboIonSpray.

Table 1
Intra- and inter-assay coefficients of variation (%) for steroids measured by GC/MS and LC-MS/MS in human samples (endogenous steroids).

Steroid	LLOQ ng/mL	Conc ng/mL	Coefficient of variation	
			Within runs	Between runs
Testo[a]	0.05	0.48	2.9	3.4
ADT-G[b]	2.00	22.8	3.1	3.7
3α-Diol-3G[b]	0.50	0.79	10.3	10.7
3α-Diol-17G[b]	0.50	1.65	4.6	5.3
Steroid	**LLOQ pg/mL**	**Conc pg/mL**	**Coefficient of variation**	
			Within runs	Between runs
E_1[a]	8.00	60.8	1.8	1.8
E_2[a]	2.00	19.2	3.5	3.7
E_1S[b]	75.0	279	4.5	6.0

[a] GC/MS.
[b] LC-MS/MS.

2.3. Coefficients of variation of steroid assays by mass spectrometry

The intra- and inter-assay coefficients of variation obtained from 3 different assays performed with 6 replicates in each assay as well as the lower limit of quantification (sensitivity) for steroid assays are indicated in Table 1.

2.4. Statistical analysis

The means and standard errors of the mean (SEM) of steroid concentrations were calculated for each subpopulation (Table 2, Figs. 1 and 2).

3. Results

While the serum levels of testo are reduced by 97.4% following castration in 69–80-year old men (Fig. 1A), the sum of the metabolites of androgens, the only accurate and valid parameter of total androgenic activity measurable in the circulation [18], is only reduced by 58.9% (Table 2, Fig. 1B), thus indicating that a very important amount (41.1%) of androgens is still present in men after complete elimination of testicular androgens. Such data are in close agreement with the concentration of intraprostatic DHT that shows an average of 39% of DHT left in the prostate after castration in various studies, namely 45% [3], 51% [5], 25% [8] and 35% [9].

Table 2
Serum steroid levels in intact and castrated elderly men and in postmenopausal women.

	Testo[a]	ADT-G[a]	3α-diol-3G[a]	3α-diol-17G[a]	ADT-G + 3α-diol-3G + 17G	E_1[b]	E_2[b]	E_1S[a]
Population-based Swedish cohort (69–80-year-old)								
Intact men ($n = 911$)	4.57 ± 0.05	32.12 ± 0.89	1.46 ± 0.04	2.67 ± 0.07	36.26 ± 0.95	37.4 ± 0.5	21.5 ± 0.3	0.470 ± 0.011
Castrated men ($n = 34$)	0.12 ± 0.01	12.84 ± 1.99	0.52 ± 0.06	0.35 ± 0.04	14.89 ± 1.56	20.8 ± 1.4	3.0 ± 0.3	0.178 ± 0.020
Castrated Swe/intact Swe × 100	**2.6%**	**40.0%**	**35.6%**	**13.1%**	**41.1%**	**55.6%**	**13.8%**	**37.9%**
Population-based Canadian cohort								
Intact men ($n = 391$) (48–86-year old)	4.47 ± 0.08	30.37 ± 0.96	1.52 ± 0.05	3.57 ± 0.11	35.46 ± 1.04	30.2 ± 0.6	19.2 ± 0.3	0.515 ± 0.019
Castrated Swe/intact Can × 100	**2.7%**	**42.3%**	**34.2%**	**9.8%**	**42.0%**	**68.9%**	**15.5%**	**34.6%**
Intact women ($n = 377$) [18] (55–65-year-old)	0.14 ± 0.004	15.83 ± 0.65	0.64 ± 0.03	0.57 ± 0.02	17.04 ± 0.68	17.8 ± 0.5	4.2 ± 0.2	0.222 ± 0.011
Castrated men/intact women × 100	**85.7%**	**81.1%**	**81.2%**	**61.4%**	**87.4%**	**117%**	**71.2%**	**80.2%**

Data are presented as mean ± SEM. Percentages are in bold to highlight these data.
[a] ng/ml.
[b] pg/ml.

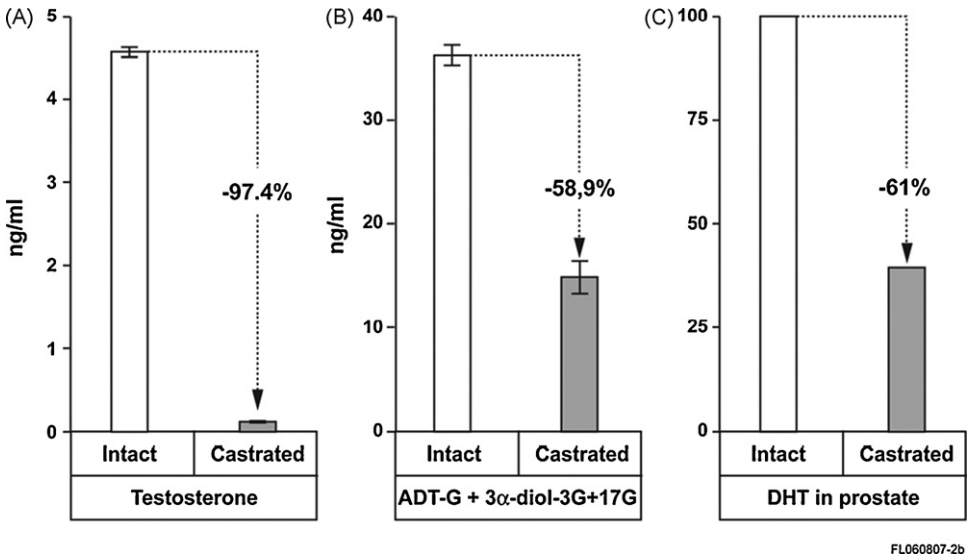

Fig. 1. Effect of castration on the concentration of serum testo (A), total androgen pool (sum of serum ADT-G, 3α-diol-3G and 3α-diol-17G) (B) and intraprostatic DHT, the predominant androgen in the prostate (C). Data in C are the average of values published in Labrie et al. (1985) [3], Bélanger et al. (1989) [5], Nishiyama et al. (2004) [8] and Mostaghel et al. (2007) [9]. Data are presented as means ± SEM.

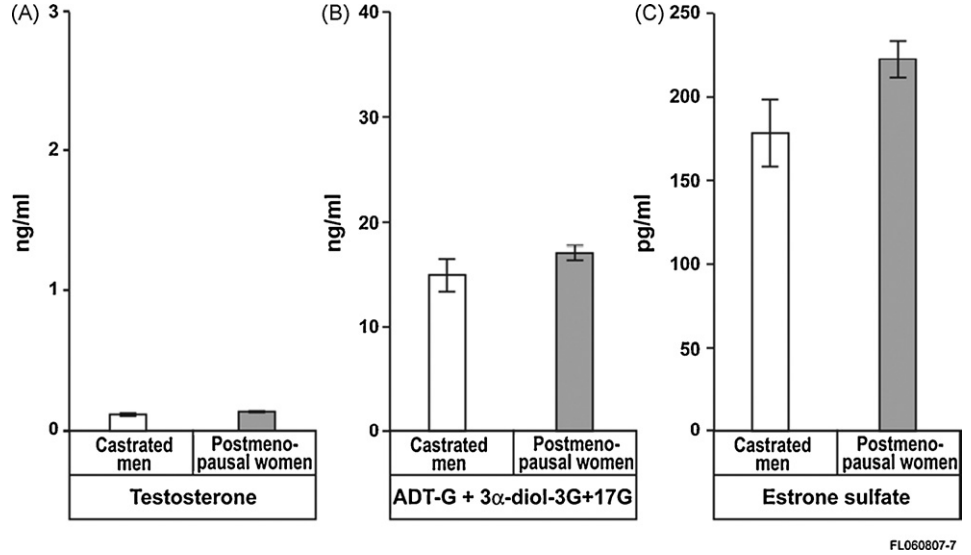

Fig. 2. Comparison of the serum concentrations of testo (A), total androgenic pool (sum of ADT-G, 3α-diol-3G and 17G) (B) and E_1S (C) in castrated 69–80-year-old men ($n = 34$) and intact 55–65-year-old postmenopausal women ($n = 377$) [18].

Knowing the major importance of androgens of adrenal origin in both sexes, it is of interest to compare the data obtained in men with the serum levels of the same steroids measured in intact postmenopausal women. As can be seen in Table 2 and Fig. 2A and B, the serum levels of testo and of the total androgen metabolites are almost superimposable in castrated men and postmenopausal women of comparable age. In fact, serum testo levels are measured at 0.12 ± 0.01 ng/ml and 0.14 ± 0.004 ng/ml while total androgenic activity, namely the sum of serum ADT-G, 3α-diol-3G and 3α-diol-17G are measured at 14.89 ± 1.56 ng/ml and 17.04 ± 0.68 ng/ml, respectively, in castrated 69–80-year-old men and 55–65-year-old postmenopausal women.

Most interestingly, it can also be seen that the serum levels of E_1S are also comparable at 178 ± 20 pg/ml and 222 ± 11 pg/ml in castrated men and postmenopausal women, respectively (Fig. 2C and Table 2). It can also be seen in Table 2 that the serum levels of E_1 and E_2 are also comparable, thus indicating that similar amounts of estrogens of adrenal origin are found in both men and women.

4. Discussion

The present observations based upon validated parameters of androgenic and estrogenic activities measured by the mass spectrometry technology show that:

(1) Approximately 40% of androgens are made in peripheral tissues in the absence of testicles in 69–80-year-old men. Since serum DHEA decreases markedly with age starting in the thirties [22], and testicular androgen secretion decreases only slightly, it is most likely that androgens of adrenal origin have an even greater relative and absolute importance at younger ages. The same conclusion applies to women with respect to the androgens synthesized from DHEA.
(2) Postmenopausal women synthesize androgens and estrogens in quantities similar to castrated men of comparable age.
(3) Intact postmenopausal women synthesize approximately 50% as much androgen as men of similar age, the 50% higher andro-

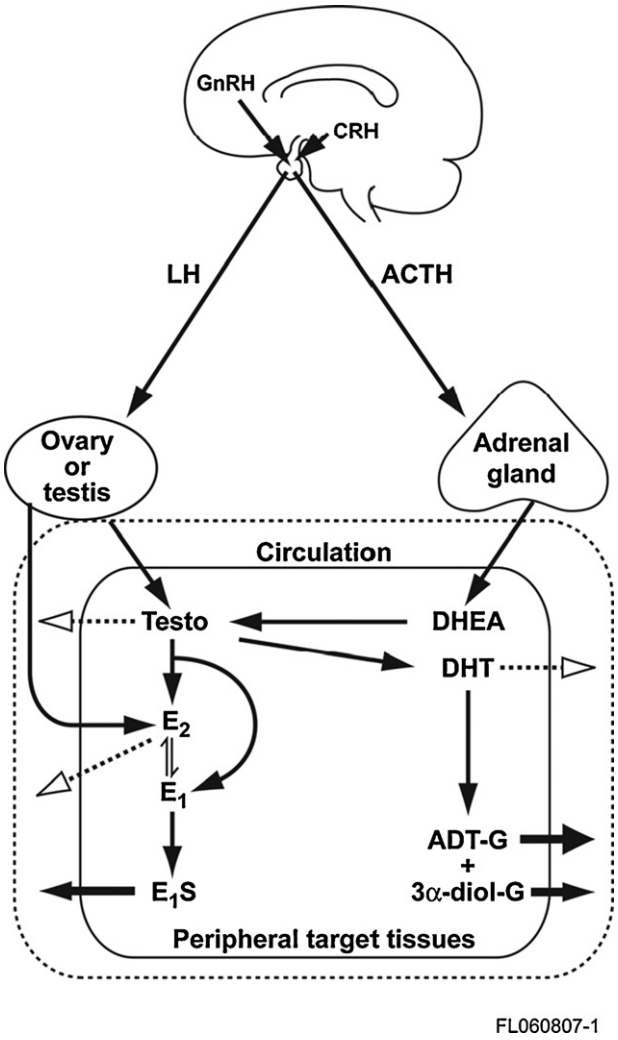

Fig. 3. Schematic representation of the ovarian, testicular and adrenal sources of sex steroids in women and men. After menopause, the secretion of E_2 by the ovaries ceases, and then all estrogens and nearly all androgens are made locally in peripheral, target intracrine tissues. The pre- and postmenopausal ovary secretes small amounts of testo directly into the circulation, where it has an inhibitory effect (−) on GnRH secretion in the brain. Much larger amounts are secreted by the testis. Conversely, the adrenal glands – as well as secreting cortisol that decreases CRH secretion, which otherwise stimulates ACTH levels – secrete large amounts of DHEA; this is converted in specific target tissues into androgens and/or estrogens via the process of intracrinology. Only small amounts of these peripherally made sex steroids diffuse into the circulation. The androgens are metabolized into the metabolites ADT and 3α-diol which are then further transformed into the more water soluble glucuronide derivatives and released into the blood where they can be measured as parameter of total androgenic activity. Abbreviations: ACTH, adrenocorticotropin; CRH, corticotrophin-releasing hormone; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; E_1, estrone; E_1S, estrone sulfate; E_2, estradiol; GnRH, gonadotropin-releasing hormone; LH, luteinising hormone; testo, testosterone; ADT-G, androsterone glucuronide; 3α-diol-G, androstane-3α-diol-3 or 17-glucuronide.

gen formation in men being essentially attributable to the androgens of testicular origin (Fig. 1B).

The androgens testo and DHT as well as E_2 made in peripheral tissues from DHEA of adrenal origin exert their action locally in the same cells where synthesis takes place with only minimal release in the circulation (Figs. 1 and 3). Under normal physiological conditions, this sophisticated mechanism permits to maintain biologically active levels of intracellular estrogens and androgens in specific tissues in need of these sex steroids while the same steroids are present at very low levels in the blood. Following their local formation and immediate availability for local intracellular action, testo and DHT (the most active natural androgen) are inactivated and transformed in the same cells into water soluble glucuronide derivatives which can then diffuse quantitatively into the general circulation where they can be measured by mass spectrometry before their elimination by the kidneys (Fig. 3).

This recently identified mechanism of steroid formation and action has been named intracrinology [4,23]. Although similar detailed knowledge is not yet available for estrogens, the serum E_1S concentration is likely to reflect adequately the changes in the total estrogen pool. This hypothesis is well supported by the parallelism of the changes in serum E_1S, E_1 and E_2 following DHEA administration in postmenopausal women where all estrogens are made in peripheral tissues from DHEA [18,19,24].

The above-described data have major therapeutic implications for the management of very important hormone-sensitive diseases, especially:

1- Prostate cancer: As mentioned above, data from different laboratories have shown that 25% to 50% of androgens remain in the prostate after castration, namely 45% [3], 51% [5], 25% [8] and 35% [9]. With the discovery that 40% of total androgens are left after castration, it is reasonable to conclude that limiting androgen blockade for the treatment of prostate cancer to surgical or medical castration, as originally proposed [2], is equivalent to refusing to administer estrogen blockade to postmenopausal women based upon the observation of very low serum levels of E_2. Not treating postmenopausal women with estrogen blockade would imply that at least 75% of postmenopausal women suffering from breast cancer (those with tumors having positive estrogen and/or progesterone receptor) would not receive an aromatase inhibitor, tamoxifen or fulvestrant, while these treatments are well known to have major clinical benefits [6].

The importance of blocking the action of the androgens made locally in the prostate is further supported by the finding of increased local formation of androgens during evolution of prostate cancer [25]. Unfortunately, the observation of very low levels of circulating testosterone after castration has resulted in inadequate androgen blockade for the treatment of prostate cancer in the majority of cases around the world. Today's knowledge of the physiology of androgen formation in men should rapidly convince the urological world to block the action of the androgens of adrenal origin and not limit androgen blockade to castration alone or an antiandrogen alone.

The well known observation that a pure antiandrogen added to castration prolongs life by 6 to 12 months in advanced prostate cancer can only be interpreted by the effect of blockade by the antiandrogen of the action of the androgens made locally in the prostate from DHEA [3,10–12]. A recent finding having major implications is that the same combined androgen blockade or the simple addition of a nonsteroidal antiandrogen to castration started simultaneously at the localized stage of prostate cancer can probably cure more than 90% of cases [12–15,26] while monotherapy is unlikely to cure prostate cancer at any stage of the disease.

2- Breast cancer: Proof of the importance of the extraovarian source of estrogens is provided by the finding of elevated concentrations of E_2 in the breast cancer tissue of postmenopausal women similar to the values found in premenopausal women [7]. In analogy with the observation of high levels of DHT in the prostate cancer tissue after castration in men, the high levels of E_2 found in breast cancer tissue after menopause explain the positive response of a large proportion of breast cancer patients following blockade of peripheral estrogen formation (aromatase inhibitor) or action (tamoxifen or fulvestrant). See Labrie (2007) for review [27].

3- Women's health: The finding that women make approximately 50% as much androgens as men has important implications for the design of the most appropriate hormone replacement therapy for women at menopause and postmenopause. This issue is particularly important since approximately 60% of the androgens present at the age of 30 years in women are already lost at time of menopause in parallel with the decrease in serum DHEA. The important clinical issues facing women's health at menopause pertain to hot flushes, vaginal atrophy, bone loss, loss of muscle mass and strength, fat accumulation and type 2 diabetes. It is of particular interest that all these medical problems have been found to respond positively to androgens and, in most cases, to the administration of DHEA when used at the proper dose [28–31]. See Labrie (2007) for review [27].

Conflict of interest

The authors declare no conflict of interest.

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