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INVITED RESEARCH HIGHLIGHT

Male Endocrinology

The multiple actions of testosterone in men: nature knows best

John W Funder

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In male hormone replacement therapy Finkelstein et al. show that testosterone rather than synthetic "pure" androgens should be prescribed. Testosterone is converted to the superactive androgen dihydrotestosterone and to estradiol, and thus has actions via androgen receptors and both estrogen receptors (ERα, ERβ). Although muscle strength is androgen dependent, estradiol has major physiologic effects in men—on bone, cartilage, and together with androgens, on sexual functioning. Neither dihydrotestosterone nor 'pure' synthetic androgens can be converted to estradiol; those so treated thus risk missing out on the beneficial (and necessary) effects of estrogens in men.

In a recent issue of the *New England Journal of Medicine*, Finkelstein *et al.*[1] published a paper entitled "Gonadal steroids and body composition, strength, and sexual function in men". That their findings were of wide general interest was shown by the number of media reports and commentaries, over the week following the initial publication. In the same issue of the journal, David Handelsman, the noted andrologist, published an accompanying editorial, entitled "Mechanism of action of testosterone–unravelling a Gordian knot"[2].

The *New England Journal of Medicine* is an authoritative journal, read across the spectrum of medical practice, not just by andrologists. Given this readership, it might be reasonable to offer a commentary on the Finkelstein report from the viewpoint of someone interested in steroid hormone action across the board, rather than androgen action in particular. With this as both an apologia and a point of departure, here goes.

As David Handelsman began his commentary, it used to be simple. We were brought up on one gene, one protein; one hormone, one receptor: now we know neither to be the case. We used to have 'the estrogen receptor'; now there are ERα and ERβ, with different selectivity for natural and synthetic estrogens, plus different—and often opposing—actions. What for decades was 'the progesterone receptor' is now PRα and PRβ, with overlapping but not identical actions. Mineralocorticoid receptors (MR) are 'protected' in epithelia by the enzyme 11βhydroxysteroid dehydrogenase type 2, allowing selective activation by aldosterone in epithelia (kidney, colon *etc*.); in non-epithelial tissues, cortisol in the physiologic MR ligand, with roles essentially very lightly explored. Very recently, posttranscriptional phosphorylation of MR has been shown to allow its regulated and reversible inactivation.[3] In addition, there is excellent evidence for membrane-associated receptors for both mineralocorticoids and glucocorticoids, distinct from the classical nuclear transcription factors (MR and GR).

Much of this complexity is recapitulated for androgens and androgen action. The principal secreted androgen is testosterone (T) which in some but not all tissues is converted to the more potent androgen receptor activator 5α-dihydrotestosterone (DHT). What this does is thus to put tissues into one of two classes: those sensitive to circulating levels of T, and those which are supersensitive, reflecting conversion to DHT. What it means clinically is that inhibitors of this enzyme 5α reductase, which converts T to DHT, can reduce androgen action locally in otherwise 'supersensitive' tissues, such as the prostate and the skin, without affecting androgen action elsewhere.

But conversion to DHT is not this only fate of T; it can be, and is, converted by aromatization to estradiol, opening up a whole new ball game. In men, the testes (even the aging testes) are the main source of androgens, able to be converted to estrogens; in men, estrogens have major physiologic roles in brain, cartilage and bone (at least). In post-menopausal women the adrenal glands secrete relatively high levels of androgens, which is aromatized in various peripheral tissues to estrogens: it is for this reason, for example, that aromatase inhibitors are increasingly used in the follow-up treatment of ER-positive breast cancer.

So what we have here is complex, not simple. One major steroid hormone (T) acts as an androgen via androgen receptors, but in addition can go two ways. In some tissues it can be 5α-reduced to DHT, a super-androgen; in other tissues, T (but, interestingly not DHT) can be aromatized to estradiol—which in turn can act via ERα, ERβ or both. Instead of one ligand (T) and one receptor (AR) there are now three ligands (T, DHT and E_2) and three receptors (AR, ERα, ERβ)—different ligands, different receptors—and perhaps most importantly, different target tissues.

Into this complexity stepped Finkelstein *et al.*[1] with a classic hormone ablation-replacement study on ~400 healthy Boston men (interestingly, with a mean BMI of 27, classically in the overweight range, but in fact the now median or 'normal' weight). The subjects were aged between 20 and 50, and their endogenous (testicular) secretion of testosterone was suppressed by monthly injections of a gonadotropin releasing hormone (GnRH) analog. They were then assigned to five groups, receiving placebo or 1.25/2.5/5/10 g per day of transdermal (patch) T, to span the normal replacement dose (~5 g per day). In each group, half received an inhibitor of aromatization, to block conversion of administered T to E_2. Subjects were assessed at baseline, and at weeks 4/8/12 and 16 for changes in strength, muscle mass, fat mass (subcutaneous

Prince Henry's Institute, Clayton, Victoria, Australia.
Correspondence: Prof. JW Funder (john.funder@princehenrys.org)

and intra-abdominal) and what was loosely termed sexual function.

The headline results are not surprising. Muscle mass and strength are driven by an androgen receptor mediated action, subcutaneous and intra-abdominal fat by conversion to estrogen. The effects on 'sexual function' are complex, with low values for sexual desire and erectile function in the placebo plus GnRH analogue group progressively increasing towards normal with increasing doses of T: this effect was clearly largely reversed at the higher doses of T by aromatase inhibition. The take-home message is that 'sexual function' in men is dependent on both androgen and estrogen action.

What this means in practice is that androgen replacement therapy needs to take these findings into account and use testosterone, and not a non-aromatisable ('pure') androgen. Men need estrogen, not only for normal sexual function but also to close their long bone epiphyses. Severe congenital hypogonadism in men—with the consequent low androgen levels—leads to failure to fuse their long bone epiphyses, a situation which is also the case in the rare condition of men with congenital absence of ERα.

In the present study the authors measured but do not report on the effects on bone and the cardiovascular system of graded doses of replacement testosterone with and without aromatase inhibition. These data will be very welcome, particularly given the not altogether clear status of androgen/estrogen receptor activation as cardiovascular risk factors. Even without these data, the impact of the present study should be clear. First, androgen replacement therapy needs to be with testosterone, pure and simple and not with a non-aromatisable synthetic androgen. Second, as a consolation to aging males in the population with low testosterone levels, its replacement via a cutaneous gel appears to be an appropriate therapeutic option, in terms of muscle, fat and sex. It is possible that the findings from the cohort in terms of cardiovascular risk markers may either reinforce this option, or sound a note of caution; we thus await their publication with considerable interest.

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