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## Letter to the Editor NOT referring to a recent journal article

### Elevated Serum Estradiol Is Associated with Higher Libido in Men on Testosterone Supplementation Therapy

Testosterone has always been considered to be a *male hormone*, whereas oestrogen has typically been discussed in the context of being a *female hormone*. Conventionally, the goal of testosterone supplementation therapy (TST) in men was to raise serum testosterone levels and lower oestrogen levels. A recent study by Finkelstein et al. highlighted an important role for oestrogen in regulation of sexual function in men on TST [1]. In that study, dramatic declines in libido were observed in conjunction with decreased levels of serum oestrogen. Although oestrogen is associated with male sexual behaviour [2], the distinct roles of testosterone and oestrogen on sexual function in men on TST are controversial. We thus sought to elucidate the associations between serum testosterone, estradiol, and libido in men undergoing TST for symptomatic hypogonadism (total testosterone <300 ng/dl and three or more symptoms on the Androgen Decline in Aging Male [ADAM] questionnaire).

Men on TST (injections or gels;  $n = 423$ ) presenting to a large-volume, tertiary referral andrology clinic were asked to rate the quality of their libido using 5-point Likert scales (1 = terrible, 5 = excellent) as part of the validated, quantitative ADAM questionnaire [3]. Men were categorised as having low (0.5–5.0 ng/dl) or high (>5.0 ng/dl) estradiol and low (<300 ng/dl) or high (>300 ng/dl) testosterone. Serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), serum testosterone, and sex hormone-binding globulin (SHBG) were collected on the same day that men completed their ADAM questionnaires. We subsequently performed univariate ( $t$  test, chi-square) and multivariate analyses (ordinal logistic regression) to evaluate factors that predicted libido.

Men with serum testosterone levels >300 ng/dl reported greater libido than men whose levels were <300 ng/dl (3.46 vs 2.92;  $p < 0.01$ ). Men with serum estradiol levels >5 ng/dl reported greater libido than men with estradiol levels <5 ng/dl (3.70 vs 3.23;  $p < 0.01$ ). In total, 60.4% of men with a serum testosterone level >300 ng/dl and estradiol level >5 ng/dl reported very good or excellent levels of libido (scored as 4 or 5) compared with 31.3% of men with testosterone levels <300 ng/dl and estradiol levels <5 ng/dl ( $p < 0.01$ ).

Univariate analysis noted associations between libido and age, and FSH, LH (analysed as continuous variables), estradiol, and testosterone levels (analysed as categorical variables, and which remained significant even when analysed as continuous variables) (Table 1). Interestingly, on multivariate analysis, only estradiol at serum levels >5 ng/dl (2.13;  $p = 0.04$ ) was associated with greater libido (Table 2).

While this study highlights the importance of oestrogen in men on TST, the limitations include a lack of control group and no score comparisons before and after commencement of TST. Furthermore, a larger sample size may have unmasked a confounding relationship between testosterone and libido.

In summary, we have found that elevated serum levels of estradiol are associated with increased libido in men on TST. We recommend judicious use of aromatase inhibitors for indications such as gynaecomastia. Indiscriminate prescription for the sole purpose of reducing serum oestrogen may

**Table 1 – Predictors of libido in men on testosterone supplementation therapy: univariate analysis**

	Odds ratio (95% CI)	$p$ value
Age	1.02 (1.01–1.04)	0.001
FSH	1.07 (1.02–1.12)	0.004
LH	1.17 (1.06–1.28)	0.002
Estradiol level >5 ng/dl vs <5 ng/dl	2.22 (1.47–3.38)	<0.001
Testosterone level >300 ng/dl vs <300 ng/dl	2.37 (1.47–3.83)	<0.001
Free testosterone	1.00 (1.00–1.00)	0.282
SHBG	1.01 (1.00–1.02)	0.130

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinising hormone; SHBG = sex hormone-binding globulin.

**Table 2 – Predictors of libido in men on testosterone supplementation therapy: multivariable analysis**

	Odds ratio (95% CI)	$p$ value
Age	1.01 (1.00–1.03)	0.093
FSH	1.01 (0.93–1.10)	0.853
LH	1.10 (0.92–1.33)	0.290
Estradiol level >5 vs <5 ng/dl	2.13 (1.35–3.36)	0.001
Testosterone level >300 vs <300 ng/dl	1.63 (0.97–2.75)	0.064

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinising hormone.

be met with poor libido-decreasing satisfaction and quality of life. Carefully designed placebo-controlled trials to assess the risks and benefits of both testosterone and oestrogen are required.

**Conflicts of interest:** Larry I. Lipshultz has been a clinical trials participant, consultant, and speaker for Auxilium and Endo. The other authors have nothing to disclose.

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