Current Literature Review

Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial

Basaria S, Harman SM, Trivison TG, Hodis H, Tsitouras P, Budoff M, Pencina KM, Vita J, Dzekov C, Mazer NA, Coviello AD, Knapp PE, Hally K, Pinjic E, Yan M, Storer TW, Bhasin S. JAMA 2015;314:570-581.

Editorial Comment: Basaria et al assessed the long-term effect of testosterone administration on common carotid artery intima-media thickness and coronary artery calcium in older men with low or low-normal testosterone levels. They failed to identify significant differences between testosterone treated patients and controls, and one of their first conclusions was that testosterone administration for 3 years did not result in a significant difference in the terms of subclinical atherosclerosis progression. The results are very interesting since many observational studies have shown that low testosterone level is associated with an increased risk of adverse cardiovascular outcomes and more pronounced signs of atherosclerosis. The European cardiovascular prevention guidelines recommended (class IIa) both common carotid artery intima-media thickness and coronary artery calcium for cardiovascular risk assessment in asymptomatic adults at moderate cardiovascular risk. Subjects are considered to be at moderate risk when their 10-year risk of a first fatal atherosclerotic is comprised between 1% and 5%. Many middle-aged subjects belong to this category. Conversely, the role of both techniques on patients at high cardiovascular risk such as old patients with a high prevalence of cardiovascular risk factors may be questionable since they may already have an advanced atherosclerosis. Unfortunately, the authors did not report the cumulative cardiovascular risk (for example using the Framingham risk score or the European heartscore). Looking at baseline characteristics, most patients were hypertensive and taking statins suggesting a high baseline risk. In addition, obesity, hyperlipidemia and diabetes mellitus were common and the mean age was around 70s. Indeed, recent studies have shown that the coronary artery calcium score detected by multidetector-row computed tomography (MDCT) include two different calcium types: an intimal deposition and a medial accumulation of calcium across the coronary wall. While the former has been associated with coronary plaque rupture, the latter seems a passive and age-related accumulation of calcium. For this reason, the MDCT-derived coronary artery calcium score has a better prognostic role in young patients, when the contribution of medial calcium accumulation is less interfering.

For all these considerations the present study cannot exclude that in younger, low-risk subjects, hypogonadism may prevent or delay atherosclerosis. Yet, the study is important, because, although not primarily addressing CV safety (as none of other previous studies, including the TOM trial), it seems to confirm the safety of testosterone use in the settings of randomized controlled trials, as recently shown.

As a secondary outcome, the authors also investigated sexual function and health-related quality of life assessed using the International Index of Erectile Function (IIEF-15) and the Medical Outcomes Study 36-item short form health survey (SF-36). The authors concluded that sexual desire, erectile function, overall sexual function scores, partner intimacy, and health-related quality of life did not significantly differ between testosterone treated patients and controls. However, the results are difficult to interpret because of controversial enrollment criteria and baseline characteristics of participants. In fact, the population was not selected for signs or symptoms of hypogonadism, nor sexual dysfunction. Therefore, as expected no changes was expected in these domains.

These findings confirm, once more, that replacement is not an age-reversal drug, rather it is a replacement therapy that should be given to men with biochemical and clinical evidence of androgen deficiency to prevent sexual and systemic complications of hypogonadism, especially in young and middle-aged men before these complications become irreversible.

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Androgen therapy in women: A reappraisal: an endocrine society clinical practice guideline
Wierman ME, Arlt W, Basson R, Davis SR, Miller KK, Murad MH, Rosner W, Santoro N. J Clin Endocrinol Metab 2014;99:3489-510.

Editorial Comment: The decline of circulating androgens in pre- and post-menopausal women can be associated with a decrease in sexual function, and an increase in personal distress and anxiety. A replacement with testosterone in women has been a matter of controversies for almost two decades. The skepticism is mainly driven by the lack of valid reference ranges, very low accuracy of assays measurement of testosterone in the low (female) range and missing data on its safety.

Given this, the Endocrine Society commissioned a task force to develop clinical practice guidelines for the use of androgen in postmenopausal women.

The major advancement of the Task Force has been to provide a clear indication—and limitation—for testosterone therapy in women, that is only in postmenopausal women suffering from sexual dysfunction due to hypoactive sexual desire disorder (HSDD). According to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the definition of HSDD was deficient or absent sexual fantasies and desire for sexual activity causing marked distress or interpersonal difficulty. Since it has been established that low sexual desire and low arousal are codependent, the two have been combined in DSM-V as “desire—arousal disorder.” Thus, the diagnosis of HSDD includes the presence of both reduced interest in sexual activity and absent arousal from external sexual/erotic cues.

At the moment, the evidence is not strong enough for testosterone use for any other indication outside the treatment of HSDD. Moreover, the actual randomized controlled trials, that have studied the effect of testosterone on women, had a short follow-up duration and do not allow to wave any safety concern. In addition, the positive effects were lost when treatment was continued for longer periods, suggesting a transient mechanism of action. In light of these evidences, testosterone therapy should be prescribed as trial, for 3- to 6-month period. Treated women should be monitored carefully measuring testosterone levels at baseline and after 3–6 weeks to assess patient misuse or abuse, and signs of androgen excess such as acne and hirsutism. Therapy cessation should be considered in all women who have not responded to treatment by 6 months.

Most studies, investigating testosterone therapy for women, used a transdermal testosterone patch changed twice a week. This formulation is known for releasing approximately 300 μg of testosterone for day. Other transdermal testosterone formulations and a skin spray have not obtained the final approval for women, yet. A transdermal 1% testosterone cream for women is available in Australia. It has been shown to be effective and to have consistent pharmacokinetic properties in small studies. Testosterone undecanoate, in a dose of 40 mg either daily or on alternate days, is used in many countries. Unfortunately, this compound has highly variable absorption and can results in levels in the normal male range.

The best available evidence demonstrates that the use of testosterone either alone or with hormonal replacement therapy has statistically significant beneficial effects on multiple domains of sexual function in postmenopausal women. These outcomes include the number of satisfying sexual episodes, frequency of sexual activity, libido, orgasm, arousal, pleasure or enjoyment of sex, sexual responsiveness, sexual self-image, and sexual or relationship satisfaction.

Despite the improvement in sexual function associated with testosterone use in postmenopausal women, important considerations for implementation of recommendation are needed. Firstly, the length of treatment and monitoring procedures are not well established. No safety and efficacy data for testosterone therapy are available for more the 24 month treatments. Secondly, physiological testosterone preparations for clinical use in women are not available in many countries, including the United States.

Rigorously designed prospective observational studies could have a major role in evaluating the safety profile of testosterone therapy together with specifically designed testosterone formulations for women are welcome.

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Prevalence of sexual dysfunction after risk-reducing salpingo-oophorectomy
Tucker PE, Bulsara MK, Salfinger SG, Tan JJ, Green H, Cohen PA. Gynecol Oncol 2016 Jan;140:95-100.
Editorial Comment: It is well established that menopausal status is associated with increased rates of sexual dysfunction.\(^1\) Further, numerous studies have shown that bilateral salpingo-oophorectomy is associated with increased rates of sexual dysfunction.\(^2\) Quality of life for cancer patients is an increasingly important topic and sexual health has received a lot of attention from multiple disciplines.\(^3\) Survivorship has many ways become its own area of concentration within oncology and for associated specialists, especially the sexual medicine provider.

An important subset of women affected by cancer is women who undergo bilateral salpingo-oophorectomy \textit{not} for cancer treatment but rather for cancer prevention. This surgery has gained significant attention in recent years based on what has been dubbed the “Angelina Jolie” effect,\(^4\) which encompasses women who undergo risk reducing mastectomy and salpingo-oophorectomy based on a genetic predisposition to breast and ovarian cancer.

The term “risk reducing” is usually associated with such women who do not have cancer but are at high risk. There is evidence that salpingo-oophorectomy does itself help treat breast cancer in premenopausal women with hormone sensitive cancers. For these women the term “risk reducing” is less applicable.

The focus on these definitions is critical in interpreting the results of this study, which purports to assess the sexual function in women undergoing risk reducing bilateral salpingo-oophorectomy (RRSO).

This study is a cross sectional analysis of a cohort of women at a tertiary care center in Western Australia. Women who underwent RRSO were contacted and invited to complete a very comprehensive set of validated questionnaires related to sexual health and quality of life. Indeed, one of the greatest strengths of this article is that is actually incorporates the FSFI and FSDS, with which all specialists in sexual medicine are familiar. The authors had a high response rate (58%) and a large number of women (119) to include in this study. They found that there was a high rate of risk for FSD and HSDD (74% and 73%) and sexual distress rates were also high (49%). The majority of women (80%) were sexually active but many (41%) reported dissatisfaction with their sex lives. Most interesting was that the main complaint for these women related to lubrication. Thus is was not surprising that in the multivariable analysis self-reported pain and less use of vaginal estrogen were most associated with this effect,\(^4\) which encompasses women who undergo risk reducing mastectomy and salpingo-oophorectomy based on a genetic predisposition to breast and ovarian cancer.

What should be taken away from this study is that a large number of women experience sexual dysfunction, and there may be an effect from gynecologic surgery in exacerbating their symptoms. Thus all providers who care for these women can and should assess sexual function and work to help improve this very important health concern.

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Differences in pornography use among couples: associations with satisfaction, stability, and relationship processes
Willoughby BJ, Carroll JS, Busby DM, Brown CC. Arch Sex Behav 2016 45:145-58.

Editorial Comment: Pornography has been described as “a driving force behind the technological development and deployment of almost every type of media” (a quote attributed to Jenkins in Feona Attwood’s book Porn.com.) There is little doubt that use of pornography is very common, likely more so in the modern era where it is readily accessible via the internet. In this context, research on how porn affects sexuality (in the context of both individuals and dyads) is of great relevance.

This unique study studied use of pornography in the context of a large sample of heterosexual couples. A great deal of existing literature has suggested that communication and sexual difficulties within the dyad are associated with pornography use but, to date, few studies have examined pornography use/opinions in both partners of a couple.

The authors of this scale developed a metric to assess use of and acceptance of pornography within partners of a dyad;
Identification with stimuli moderates women’s affective and testosterone responses to self-chosen erotica

Goldey KL, van Anders SM. Arch Sex Behav 2015. In press.

**Editorial Comment:** Erotic material (most commonly audio-visual sexual stimulation or AVSS) is widely utilized in sexuality research, particular in studies of arousal patterns as a factor of mental and physical state. Much of the AVSS used in sexuality research is selected for its depiction of sexual activities generally regarding as appealing by the majority of likely viewers (eg, consensual foreplay, oral sex, and coitus in the context of heterosexual viewers) with the intent of being as universal as possible. While such selections may be generally appealing to most viewers, individual sexual preference is so varied that no researcher-selected AVSS can possibly evoke a standardized level of expected response in every subject exposed.

The authors of this study attempt to study variation in affective response to researcher versus subject selected erotica. Women were assigned to one of three types of erotic stimuli: (1) using erotic material entirely of their own choosing; (2) choosing from a selection of erotic materials provided by the researchers; and (3) having erotica assigned by the researchers.

As expected, women given control and choice about the erotic material to which they were exposed endorsed greater degrees of arousal. While this finding is not surprising, what was of particular interest was that women using self-selected erotica were more likely to report embarrassment and feelings of guilt. This effect was most pronounced when the participant women reported low or moderate levels of identification with the performers in the erotic materials.

In this research setting all subjects were aware that they were to be exposed to sexually explicit media and reported comfort with that type of material. Is actively “choosing” the type of erotica (rather than having it simply provided) the reason for negative feelings such as guilt? The association between lack of identification and guilt is particularly intriguing. It may be hypothesized that this low identification leaves the woman viewing feeling more like a voyeur than a participant in an erotic encounter; alternatively, it may sometimes be the case that the woman viewing finds the activity sexually arousing but mentally/emotionally unappealing and hence rejects it by refusing to identify with it.

These findings are relevant and interesting to investigators who utilize AVSS or other erotic stimuli in research settings and to clinicians who are influenced by their findings. In the future it may be the case that some form of “pre-screening” for sexual preferences and selection of concordant AVSS may facilitate maximal arousal without invoking feelings of guilt in this type of research.

Shame, catastrophizing, and negative partner responses are associated with lower sexual and relationship satisfaction and more negative affect in men with Peyronie’s disease.

Davis S, Ferrar S, Sadikaj G, Binik Y, Carrier S. J Sex Marital Ther 2016. In press.

**Editorial Comment:** Nelson et al have reported on the long term psychological and interpersonal consequences of Peyronie’s disease (PD); importantly, these researchers have determined in cross-sectional studies that duration of PD does not materially impact upon degree of psychological distress. While these studies are not longitudinal and hence causation cannot be gleaned, it is reasonable to postulate that the psychological burden of PD does not diminish over time as some other may occur with other ailments to which men become habituated.

Another interesting finding in the existing PD literature is that degree of deformity is only weakly correlate to subjective distress. It can be deduced that the emotional and psychological burden of PD is mediated in large part by how the man (and his partner) react to the diagnosis. This paper explores inter and intrapersonal factors that mediate the relative burden of PD in a given man. The authors used a combination of validated and non-validated metrics (eg, catastrophizing was measured using the Pain Catastrophizing Scale with the phrase “Peyronie’s Disease” put in place of “pain” for all questions and partner negative and solicitous responses were measured using an adapted version of the West-Haven-Yale multidimensional pain inventory).

The authors conclude that a tendency to catastrophize (ie, treating negative events as inordinately traumatic), negative partners responses to PD, and shame were associated with worse emotional, sexual, and relationship functioning related to PD. There was a range of response, with some men reasonably well adapted to their PD condition.
Given that existing treatments for PD may not reliably and consistently lead to complete reversal, attention to these psychological components of the diagnosis are essential for practitioners. Involvement of a mental health specialist and/or careful attention to catastrophizing, body image, and relationship issues by the primary treating physician are essential to optimizing outcomes in PD patients.

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