



REPRODUCTIVE X MEDICINE CORNER

Testosterone Replacement Therapy for Sexual Dysfunction in Postmenopausal Women

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THERE IS ONGOING DEBATE over testosterone therapy for aging women to address problems related to sexual health. Fundamental obstacles and controversy have precluded general recommendation of this therapy. First, it is still contentious whether there is actually a constellation of clinically identifiable signs and symptoms characteristic of androgen insufficiency in women, especially without an underlying etiology leading to absolute reduction in androgens (i.e., hypopituitarism or adrenal insufficiency). Proposed symptoms of low androgens are reduced sexual desire, lethargy, decreased motivation and altered mood. However, most evidence has shown that serum androgens do not correlate with such symptoms in various populations of women (1). This may have to do with a number of factors, including the lack of sensitive and specific assays to measure androgens in women and no reliable normal reference intervals across women's lifespan. In addition, androgen production, action and metabolism is extremely complex and not fully understood. One major complexity has to do with the intracrine action of DHEA, a precursor hormone. Cells which possess the required enzymes directly convert DHEA to more potent androgens, which are then used and metabolized within the cell with minimal leak of active hormones into the circulation. Therefore, the "total body store" of androgen exposure is difficult to quantify. Another layer of complexity has to do with individual and cell specific differences in enzymatic activity converting androgen prohormones to hormones (i.e., 5 alpha reductase activity). In one recent study, the testosterone metabolite androsterone glucuronide (ADT-G) was measured with mass spectrometry in order to take into account the total systemic androgen pool (2). This study compared testosterone, precursor hormones and the ADT-G metabolite in women with hypoactive sexual desire disorder (HSDD) to sexually healthy controls and found that this metabolite did not correlate with sexual health. Therefore, because neither testosterone levels nor its major metabolite ADT-G reliably predict symptoms of sexual

dysfunction, it seems difficult to assert that a cause and effect relationship definitively exists. In order to recommend therapy with testosterone replacement to treat sexual dysfunction, ideally we should know that a hormone deficiency has actually caused the symptom.

Empiric treatment with testosterone therapy has been proposed by some authors due to the inherent limitations of a conclusive biochemical diagnosis of androgen insufficiency in women. Proceeding with treatment in this way will inevitably result in many women being treated with testosterone to supra-physiologic levels rather than replacement therapy. Therefore, a clear understanding of the risks versus benefits of testosterone therapy is even more essential under these conditions. Benefit of testosterone therapy on sexual function has been shown in specific populations of women, primarily in surgically menopausal women. One recent study assessed the efficacy over 6 months of use of transdermal testosterone in naturally menopausal women and found that it was effective in treating HSDD and improving sexual function both with and without concurrent estrogen repletion (3). The primary endpoint of total satisfying sexual episodes was increased by a mean of 1.69 episodes over a 4-week period in the group receiving 300ug/day of testosterone versus 0.53 mean increased episodes in the placebo group. Secondary endpoints of sexual desire and personal distress were also statistically significantly improved in the testosterone group.

A major issue is that the risks of testosterone therapy (and particularly supraphys-

iological therapy) are not well understood and generally have not been evaluated over long treatment periods. One recent study published adverse events data for up to four years of transdermal testosterone use in surgically menopausal women and showed very few overall serious adverse events and there was no increase in number of events over time (4). In addition, there were no clinically meaningful changes in lipid profile and glucose parameters with increased duration of exposure.



A particularly concerning issue with androgen therapy is a potential increased risk of cardiovascular disease. Epidemiologic evidence appears to show that higher endogenous androgen lev-

els are associated with higher risk of cardiovascular disease even within a range of normoandrogenemia (5, 6). In addition, women with polycystic ovary syndrome (PCOS) characterized by hyperandrogenemia are generally considered to be at higher risk of cardiovascular disease. The hyperandrogenism itself has been implicated to contribute to the elevated risk of cardiovascular disease in women with PCOS and although androgen levels do decrease with age, postmenopausal women with persistent PCOS are thought to have a higher risk of both cardiovascular events and type 2 diabetes due in part to ongoing hyperandrogenemia (7). A recent study has shown that higher levels of advanced glycation end-products (known atherogenic molecules) are positively associated with higher androgen levels (also still within normal ranges) in otherwise healthy postmenopausal women (8). Primarily due to the lack of long term safety data especially related to a potential increased risk of cardiovascular disease, supplementary treatment with

testosterone therapy in postmenopausal women should be seriously questioned. Patients should be advised of these issues when considering use of compounding pharmaceuticals or using testosterone treatments off label.

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