Testosterone Insufficiency and Treatment in Women: International Expert Consensus Resolutions

Gary Donovitz, MD (Chairman), Erika Schwartz, MD, Charles Miller, MD Mickey Barber, MD, Florence Comite, MD, Ken Janson, MD, Jeffrey Leake, MD, Edwin Lee, MD, Jeffry Life, MD, Luis Martinez, MD, Douglas Woodford, MD

While it is general knowledge that testosterone is used to improve sexual function in women, its non-sexual effects in women require more in depth review and acknowledgement. To provide a broader scope for this discussion an expert consensus conference addressing Testosterone insufficiency (TI) in women was held in Orlando, Florida, USA on April 24, 2017.

Participants representing a wide range of specialties were invited on the basis of their clinical and/or research expertise with the usage of Testosterone therapy and diagnosis and treatment of Testosterone insufficiency (TI) in women

The goal is a review that provides reasonable and prudent rationale for the consideration of testosterone as part of a woman's disease prevention and hormone optimization program based on the present scientific and clinical evidence.

Historical Background

Clinical use of testosterone dates to 1939 but became popularized by Greenblatt in 1949[1]. Since then, testosterone therapy for women became a routine component of HRT in Europe and Australia but still limited in the United States.

Despite the plethora of data in support of the extensive benefits of testosterone supplementation in women, the lack of an F.D.A. approved testosterone product for women, has left medical education in the dark. In the most recent, Shifren and Davis[2], review of androgens in postmenopausal women the importance of testosterone therapy in premenopausal women remains limited primarily to sexual dysfunction.

Our Consensus panel with more than 100,000 patient YEARS experience with testosterone supplementation in women is excited to share the studies we reviewed and our clinical and evidence based recommendations.

The format of the consensus group followed Morgentaler et al.[3] on testosterone deficiency and treatment in men.

The goal of our review is to raise awareness, open discussion and focus researchers and clinicians on the broader scope for the use of testosterone and its effects on multiple organ systems.

As a consequence of the Women's Health Initiative (WHI) a 79% decline in utilization of hormone therapy occured.[4] The WHI study didn't consider differences in action and risk associated with various forms and routes of administration of hormones, the age of the participants or pre-existing conditions and omitted testosterone as a component of hormone optimization. In contrast Sherwin[5] conducted a randomized trial comparing estrogen, testosterone and placebo in 1985 with 115 pre-menopausal women post hysterectomy and oophorectomy. Testosterone treated group showed superior energy improvement, wellbeing, decrease in somatic complaints and psychological symptoms.

Terminology

Optimization of an individual's testosterone balance and replaces "Testosterone replacement therapy". "Testosterone insufficiency (TI)" replaces "low T" consistent with Morgentaler Consensus recommendations in men.

Participants

The panel consisted of ten international specialists in obstetrics and gynecology, endocrinology, internal medicine, age management medicine, and urology. Participants were invited on the basis of established clinical experience with women's health, TI and treatment. The choice of multiple specialties and geographic diversity was intentional contributing diverse opinions and minimizing regional and specialty-based biases. All experts volunteered their time.

Methods

Two months before the conference each participant was assigned one statement developed by a working group and asked to provide, 3 to 5 Pub Med, Medline, Cochrane review references pro and con to the statement. At the conference each participant presented his/her statement, interpretation and references. Collaborative discussion and debate led to the resolutions being unanimously agreed upon by the participants.

This review summarizes the resolutions followed by abstracts and supporting evidence.

RESOLUTION 1. Testosterone is Not a Male-Exclusive Hormone. It is the Most Abundant Gonadal Hormone Throughout a Woman's Life.

Although testosterone is known as the "male" hormone, in 2002 Dimitrakakis, et al.[6] stated testosterone (T) is the most abundant biologically active gonadal hormone throughout the female lifespan. According to Panay and Fenton[7] young women's ovaries produce approximately three- to four-times more testosterone than estrogen daily. Measured ranges of androgen precursors are similar in women and men.

Burger[8] noted that quantitatively, women produce more androgen than estrogen. Only T and DHT bind to the androgen receptor. Other androgens; DHEA, DHEA-S and Androstenedione are essentially pro-androgens.

In charting average estradiol (E2) and testosterone levels across the female lifespan, T consistently exceeds E2, usually by 250-300 pg/ml, and between ages 24-30 T levels are 400 pg/ml higher than E2. Both women and men have functional estrogen receptors (ERs) and functional androgen receptors (ARs), with the AR gene located on the X chromosome.[9]

Although T is the major substrate for E2, in proper balance with E2 it is equally important for health in both sexes. Testosterone was reported to effectively treat symptoms of menopause as early as 1937[10]. Oddly estrogen is the hormone of choice for "replacement therapy" in women despite lack of clear evidence to that fact.

RESOLUTION 2. Serum Testosterone Levels do not correlate with Symptoms of Testosterone deficiency in women. Optimal ranges of Serum Testosterone levels in women have not been established.

Established reference ranges for total testosterone, free testosterone and pre-androgens, below which a woman might be considered androgen "deficient" were not found in the literature. Biochemical definition of a "female androgen deficiency syndrome" is also lacking in the literature reviewed. Normal ranges posted by various labs reflect averages for a given population and do not correlate with clinical picture.

In 2002,[11] an expert panel published the Princeton consensus guideline on Female Androgen Deficiency. The recommended definition of androgen deficiency included: [1] a diminished sense of well-being or dysphoric mood; [2] persistent, unexplained fatigue; lethargy and [3] sexual function changes, including decreased libido, sexual receptivity, and pleasure. No biochemical marker diagnosing androgen deficiency was established.

In discussing androgen production in women, Burger noted that although women produce 200-300 micrograms testosterone per day, serum levels follow circadian, diurnal and menstrual cyclical variation making it difficult to define normal ranges. Other variations occur due to stress, sleep, exercise, insulin levels and more. According to Davison[12] there is a wide range of normal. Traditional medicine requires clinical practice to follow "normal" values for the "mean." However "normal" values do not always apply to the individual woman thus leaving reference levels unreliable. Seeking rigid guidelines for optimal T levels is also counter to the accepted concept that hormone optimization is not a "one size fits all" treatment (NAMS position statement 2013). Thus, TI is a clinical syndrome defined solely by clinical symptoms and its successful treatment measured solely by symptomatic improvement.

Carruthers et al.[13] also noted poor correlation between symptoms and serum levels of androgens. Kelleher and Handelsman[14] noted considerable variation among individuals in the serum levels of testosterone when deficiency symptoms exist.

Glaser[15] noted "higher doses of testosterone correlated with greater improvement in symptoms" in 300 pre and post menopausal women studied. No laboratory correlation was found.

Kratzik[16] reported neither the total AMS (Aging Male Score) nor the MRS (Menopause Rating Scale) score correlated with total testosterone serum levels.

Most testosterone in the blood is bound to sex hormone–binding globulin (SHBG). Circulating levels of SHBG are affected by genetics, aging, HRT and other factors[17].

Genetic variations in the androgen receptor (AR) gene were noted by Westberg.[18] The cysteine, adenine, guanine (CAG) terminal domain of the AR gene varies in both sexes. Longer chains represent less active receptors and lower levels of serum androgens. Serum levels of androgens in premenopausal women are influenced by variants in the AR gene. There is no "normal" testosterone level in women.

Due to the difficulty in establishing clear laboratory criteria for a deficiency syndrome, the consensus proposes the term "Female Testosterone Insufficiency" to represent symptom driven clinical syndrome.

RESOLUTION 3. Female Testosterone Insufficiency is a Clinical Syndrome that May Occur During Any Decade of Adult Life.

Guay et al.[19] demonstrated a precipitous age-related decline in all androgens (total T, free T, DHEA-S and Free Androgen Index) in premenopausal women without sexual dysfunction age 20 to 49 years old.

In a subsequent study, Guay[20] found that premenopausal women with complaints of sexual dysfunction had lower adrenal androgen precursors and testosterone than age-matched controls. No differences were noted in the ovarian androgen precursors between groups.

Turna et al.[21] demonstrated that low total testosterone, free testosterone and DHEA-S levels correlated positively with full-scale FSFI score and FSFI-desire, FSFI-arousal, FSFI-lubrication and FSFI-orgasm scores. Slemenda et al.[22] found hip bone loss associated with lower androgen concentrations in premenopausal women.

Zumoff et al.[23] noted declining testosterone levels in premenopausal women. By age 40 a woman has half the mean plasma testosterone levels of a 21-year-old.

Androgen insufficiency (AI) may explain why despite taking standard estrogen/progestin hormone replacement therapy, 67% of women with premature ovarian failure have diminished bone density associated with increased hip fracture risk as discussed by Kalantaridou and Calis.[24]

Pathophysiological states affecting ovarian and/or adrenal function may result in androgen insufficiency in premenopausal women. Young women with hypothalamic amenorrhea, premature ovarian failure, oophorectomy, premenstrual syndrome, acquired immunodeficiency wasting syndrome, adrenal insufficiency, hypopituitarism and on certain medications (oral estrogen, oral contraceptives and corticosteroids) may have testosterone deficiency. Additionally, testosterone insufficiency (TI) in young women may be under diagnosed because the symptoms are generally nonspecific, awareness of TI is low and the measurement of plasma total and free testosterone, not helpful.

RESOLUTION 4. Testosterone Therapy May be Breast Protective.

Studies have shown that testosterone may protect the breast from cancer. Hofling et al.[25] showed that addition of Testosterone to a standard estrogen/progestogen regimen may modulate the stimulatory effects of the estrogen/progestogen on breast cell proliferation.

As early as 1937,[26] it was recognized that breast cancer was an estrogen sensitive cancer; testosterone was 'antagonistic' to estrogen and was used to treat breast cancer as well as other estrogen sensitive diseases including breast pain, chronic mastitis, endometriosis, uterine fibroids and dysfunctional uterine bleeding.

Dimitrakakis and Glaser[27] stated "testosterone and DHEA-s levels in saliva were statistically significantly lower in breast cancer patients compared to controls and more profound in post-menopausal women with breast cancer."

Clinical trials in primates and humans[28] have confirmed that testosterone has a beneficial effect on breast tissue by decreasing breast cell proliferation and preventing stimulation by E2.

Although testosterone is breast protective, it can aromatize to E2 and have a secondary, stimulatory effect via estrogen receptor (ER) alpha.[29]

Friedman,[30] reports that testosterone down regulates the Estrogen alpha receptor and may inhibit the proliferative effect of estrogen through this process.

Starting in the 1940s, androgen therapy was used to induce regression of breast cancer metastasis with promising results. Over time the use of androgen-based hormonal therapies were largely abandoned primarily due to testosterone's masculinizing side- effects in some women albeit decreasing the dose or discontinuing use eliminated the side-effects.[31-39]

More recently, studies using exogenous Testosterone have shown that Testosterone in combination with estrogen may reduce, the risk of breast cancer. Dimitrakakis et al.[40] followed 508 postmenopausal women receiving testosterone in addition to customary HRT in South Australia and found the addition of Testosterone reduced breast cancer incidence—to numbers lower than those observed in the general population who never took hormones.

Glaser et al.[41] in the Dayton Study reported 8-year data using both testosterone and testosterone with anastrozole pellets finding a marked reduction in the incidence of breast cancer 76/100,000 women years in comparison to an age matched S.E.E.R. incidence rate of 297/100,000 women years.

RESOLUTION 5. Testosterone Insufficiency in Women Negatively Affect Sexuality, General Health and Quality of Life. Testosterone Supplementation May Positively Influence Sexuality, General Health and Quality of Life.

Maclaran and Panay[42] state testosterone has wide-ranging effects via androgen receptors, found throughout the body, including brain, skin, adipose tissue, vascular system and bone. Exogenous testosterone positively affects bone density, body composition, energy levels and psychological well-being.

Laumann et al.[43] evaluated over 1700 women and estimated sexual dysfunction at 43%. It is biologically plausible that androgen insufficiency may play a role in a portion of these women. The percentage of these women complaining of low libido was substantial and varied little between 27-32% at various decades.

Basson et al.[44] "It remains possible that testosterone deficit hinders desire and response but that its systemic production is of little relevance. Testosterone is produced de novo within the central nervous system starting from cholesterol. This production appears to be quite widespread within the central nervous system." The molecular structure of the androgen receptor in women with and without sexual disorders has not been studied. "Not only would relative resistance of the androgen receptor theoretically impair testosterone activity and contribute to sexual dysfunction, but this could be accompanied by relatively high serum testosterone levels due to lessening of the hypothalamic pituitary ovarian axis negative feedback." Goldblatt et al.[45] conducted a randomized, placebo controlled crossover efficacy study using testosterone crème (10 mg/day) in premenopausal females with low libido and serum testosterone levels in the lower third of the reproductive range. It included women on oral contraceptives aged 30 to 45 years with total testosterone levels less than 2.2 nmol/l. (62.8 ng/dl). The treatment group showed improvement in wellbeing, mood and sexual function and a corresponding increase in serum testosterone and FAI.

Davis et al.[46] showed that a daily 90ul dose of transdermal testosterone in sexually active women age 35 to 45 years with low libido and low circulating testosterone improved sexual satisfaction scores.

OCs reduce the level of free testosterone in a woman's body by suppressing the production of testosterone in the ovaries and adrenals. OCs increase SHBG (sex hormone-binding globulin) levels, inhibiting the conversion of free testosterone to dihydrotestosterone (DHT). Due to increase in SHBG levels, free T levels decrease twice as much as total Testosterone[47] according to a meta-analysis of the effect of combined OC on T levels in healthy women.

Glaser et al.[48] demonstrated beneficial effects of testosterone therapy on somatic, psychological, and urologic complaints in both pre- and post-menopausal women. The validated Menopause Rating Scale (MRS) showed significant improvement in all 11 symptoms on the screening questionnaire during treatment period.

RESOLUTION 6. Testosterone Insufficiency May Be Associated with an Increased Risk of CVD in Women.

Testosterone insufficiency may increase cardiovascular risk in women. In 2007, Debing et al.[49] reported on a study of endogenous sex hormone levels in postmenopausal women undergoing carotid artery endarterectomy. Significant association between low serum androgen levels and severe ICA atherosclerosis in postmenopausal women were found. Findings suggest that higher, yet physiologic levels of androgens in postmenopausal women may have a protective role against the development of atherosclerosis of ICA.

In their review of the literature, Glaser and Dimitrakakis[50] found substantial

evidence that testosterone is cardio protective and adequate levels decrease the risk of cardiovascular disease. Unlike anabolic and oral, synthetic steroids, there is no evidence that human identical testosterone supplementation has an adverse effect on the heart. In fact, testosterone appears to improve blood flow to the coronaries and reduces atherogenic inflammatory markers and improves lipid profiles.

Jones and Saad[51] note there is overwhelming biological and clinical evidence that testosterone supplementation is cardio protective.

Golden,[52] reported that total levels of testosterone in women correlated inversely with carotid atherosclerosis. Her data confirmed reports by Bernini et al.[53] showing women with highest endogenous testosterone levels had significantly lower risk for carotid atherosclerosis.

Møller and Einfeldt[54] note testosterone therapy has beneficial effects on lean body mass, glucose metabolism and lipid profiles in men and women; and has been successfully used to treat and even prevent CV disease and diabetes.

Rosano et al.[55] and Worboys et al.[56] report that testosterone acts as a vasodilator in both sexes, has immune-modulating properties that inhibit formation of atheromata with beneficial effects on cardiac muscle.

Low Testosterone is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure. Testosterone supplementation has been shown to improve functional capacity, insulin resistance and muscle strength in women with congestive heart failure. [57]

Miller et al.[58] provide data suggesting that physiological level testosterone replacement in women with hypopituitarism for 12 months may improve insulin resistance. Chronic low-dose testosterone administration does not increase cardiovascular disease markers.

Spoletini et al.[59] note in postmenopausal women, testosterone replacement within physiologic range is associated with improved overall wellbeing. A definitive explanation of how androgens impact cardiovascular health in postmenopausal women and whether they may be used as treatment has yet to be established. Evidence of favorable effect of androgens on surrogate cardiovascular markers in postmenopausal women, such as HDL cholesterol, total cholesterol, body fat mass, and triglycerides exists.

RESOLUTION 7. Testosterone Optimization May Be Brain Protective and May Enhance Cognitive Function.

C.J. Pike et al.[60] reported the loss of the sex steroids in women is associated with increased risk of Alzheimer's' disease. Like estrogen, testosterone has neuroprotective effects on the brain. Testosterone increases neuronal resistance to the insults of Alzheimer's disease and it reduces neuronal cell apoptosis preserving the life span of neurons as well as the reduction of beta amyloid production and accumulation.[61]

Arguments against the protective role of sex steroids stemmed from the Women's Health Initiative Memory Study (W.H.I.M.S.)[62] where the effects of CEE alone or combined with MPA showed no decline in incidence of dementia or Alzheimer's disease. Testosterone was not evaluated and HT (consisting of only CEE and MPA) was initiated 10 years after menopause while cognitive decline starts by the fourth decade.

In a study of changes in spatial cognition and brain activity in healthy women after a single Testosterone dose, Pintzka et al.[63] reported the Testosterone treated group had a significantly higher MRT (mental rotation task) score than the placebo group.

A pilot study[64] of healthy post menopausal women receiving testosterone spray and controls for 26 weeks showed $p<0.05$ statistically significant improvement in verbal, learning and memory scores in the treated group.

Laboratory studies[65] in rats have shown that "compared to normal females, partial motor neuron depletion was greatly attenuated by testosterone treatment. Findings suggest that testosterone has neuroprotective effects on morphology and is a neurotherapeutic agent in nervous system injuries."

Studies in animals and humans have suggested that poor spatial memory and navigational/spatial skills are correlated with low levels of testosterone.[66]

RESOLUTION 8. Testosterone Optimization May Be a Key Component for Improved Bone Health.

Current evidence suggests that circulating androgens and estrogens are bone protective.[67, 69] Cross-sectional epidemiologic studies[68] have demonstrated a positive correlation between endogenous androgens and BMD in both adolescent females and in premenopausal adult women.

An inverse relationship between SHBG and BMD in menstruating premenopausal and peri-menopausal women demonstrated that lower SHBG was associated with higher BMD at all measured sites. Experimental data suggest that androgens influence bone formation directly via interactions with androgen receptors, and indirectly via binding to ERα and ERβ after aromatization in adipose and other tissues. Both sex steroids—estrogen (E) and testosterone (T)— have receptors on osteocytes, osteoblasts, and osteoclasts. Androgen receptors are the dominant receptors. Endogenous androgens increase bone mineral density (BMD) in both adolescent and adult premenopausal women. Estrogen with androgen therapy increases BMD to a higher degree than estrogen therapy alone.[67]

Low total serum Testosterone has been associated with diminished vertebral bone mass in post-menopausal women as reported by Davidson et al.[70] Lower androgen levels were associated with reduced BMD at the hip, increase in hip fractures and loss of height. Height loss is a surrogate marker for vertebral compression and osteoporotic fractures.[71]

In 1995, Davis et al.[72] concluded that in postmenopausal women, treatment with both testosterone and estradiol pellet implants was more effective in increasing bone mineral density (BMD) in the hip and lumbar spine than estradiol implants alone. In fact, the largest annual increases in BMD using HRT have been seen with testosterone in post-menopausal females.[73]

RESOLUTION 9. Testosterone Therapy in Women Has No Adverse Effects on Lipids and/or CV Risk.

S.R. Davis et al.[74] conducted a double blind, placebo controlled 52 week trial of 814 women from 65 centers around the world. There were no adverse effects on lipid or lipoprotein profiles, liver function, or blood clotting factors among 147 subjects receiving 150 µg testosterone per day and 166 receiving 300 µg testosterone per day, out of 814 women randomly assigned to a study group with approximately 71% completing 24 weeks and 57% completing 52 weeks. Within each group, there were no clinically relevant changes from baseline in any of the variables.

S.R. Davis et al.[75] also reported on a 2-year single-blind randomized study of 34 volunteers, in which either 50 mg estradiol or 50 mg estradiol plus testosterone were administered monthly. Of the 32 women who completed the study, improvement in lipid profile and in body composition parameters

were observed in women treated with testosterone. Total cholesterol and LDL decreased in both groups, while total body fat-free mass increased in the testosterone group only.

Elizabeth Barrett-Connor[76] followed premenopausal women through the menopausal transition, reviewed CHD risk factors and outcomes based on and prospective cohort studies of younger and older women with CHD risk markers or disease outcomes in the context of menopausal history. Those studies suggest that oophorectomized women are at greater risk for CHD than intact women. These findings demonstrated increasing importance of low testosterone and the harmful effect of oophorectomy on cardiovascular risk.

In a 3-year study of 61 oophorectomized patients treated with estradiol pellets or estradiol plus testosterone, lipoprotein levels associated with each of the two treatment regimens were compared. Levels were also measured in 67 untreated age-matched bilaterally oophorectomized women. LDL cholesterol in the estrogen/testosterone treated group were lower than in the untreated group.[77]

In a study of 8,412 women—2,103 testosterone users and 6,309 controls—van Staa and Sprafka[78] found no significant increase in the risk of cardiovascular disease or breast cancer in women using testosterone (implants, tablets, or injections), There were no statistically significant differences between the cohorts in the rates of cerebrovascular disease, ischemic heart disease, breast cancer, deep vein thrombosis/pulmonary embolism, diabetes mellitus or acute hepatitis.

S. Worboys et al.[79] investigated the effects of testosterone implant therapy on arterial reactivity encompassing endothelial-dependent and -independent vasodilation in women using hormone replacement therapy (HRT). Results showed parenteral testosterone therapy improved both endothelial-dependent (flow-mediated) and endothelium-independent (GTN-mediated) brachial artery vasodilation in postmenopausal women on long-term estrogen therapy.

An in vivo study of human umbilical vein endothelial cells placed into mice found that "estradiol and testosterone have a synergistic effect on early stage atherosclerosis" and they suppress development of atherosclerosis by reducing lipid lesions, formation of foam cells, endothelial injury, modulating the coagulation system function and inhibiting inflammation.[80]

K. Maclaran and N. Panay[81] found no association between testosterone and increased risk of cardiovascular events. Current data indicate that testosterone supplementation isn't associated with cardiovascular, breast or endometrial side-effects.

RESOLUTION 10. Studies of Testosterone supplementation show benefits exceed the risk and Consistent Purity and Potency can be Achieved

The use of testosterone in women dates back to 1939 becoming popularized in hysterectomized women as per Greenblatt et al.[82] The use of testosterone pellets antedated use of transdermal preparations. Sub-cutaneous testosterone pellet therapy has been used on five continents for nearly 80 years.

Jockenhovel et al.[83] and Kelleher et al.[84] published pharmacokinetic studies on sub-cutaneous testosterone pellet absorption which was predictable enough to allow calculation of proper dosing in men and women.

Cardoza et al.[85] in 1984, reported 60% of women with TI in the study treated with sub-cutaneous testosterone implants experienced successful relief in vasomotor, insomnia, fatigue symptoms, decreased libido, and cognitive decline.

Cameron and Braunstein concluded in 2004[88] that "symptoms of androgen insufficiency in women may include a diminished sense of well-being, low mood, fatigue, and hypoactive sexual desire disorder with decreased libido, or decreased sexual receptivity and pleasure that cause a great deal of personal distress. The evidence from clinical trials supports the correlation between decreased endogenous androgen levels and the presence of these symptoms and their alleviation with the administration of Testosterone.

There are no Food and Drug Administration- approved androgen preparations on the market for treating androgen insufficiency in women. There are however multiple sources for human identical testosterone. Compounding pharmacies were the original source but problems with consistent purity, potency, and sterility called their products into question. Treatment with exogenous testosterone from 503b FDA approved and supervised outsourced pharmacies conforms to the highest level of safety and sterility standards in the industry today.

In 2012, Maclaran and Panay[89] reviewed the data on postmenopausal testosterone therapy, focusing specifically on the effects of testosterone on breast, endometrium and cardiovascular health. They found testosterone safe and recommended more pre and postmenopausal research be conducted to further demonstrate cardiovascular and breast safety and possibly influence regulatory agencies to give better consideration to the broader use of testosterone in women.

Discussion

In the face of considerable public and scientific confusion regarding testosterone insufficiency and its treatment in women, an expert consensus conference was held to define fundamental tenets based on the best available evidence and to provide an accurate scientific framework for practitioners to identify and treat testosterone insufficiency as it may present in the female patient. These resolutions address key areas representing areas of concern with the goal of removing barriers to improving quality of life and care in women's health in wellness.

This review presents a broader use for testosterone in women. The timing is critical to women's health. In 2002, post WHI, 79% of women discontinued usage of HRT. The impact on quality of life alone was a set-back for post-menopausal women everywhere. Fifteen years of insecurity and indecision about the safety of HRT followed. In September 12, 2017 an article in J.A.M.A. by the principal investigators of WHI reported that all the women followed in the WHI study for 18 years were found to have similar all-cause mortality, cardiovascular mortality, and cancer mortality whether they were in the treatment group or not.[90] The impact of this report is far reaching and brings new perspective on HRT in general. Endorsement by the medical societies is necessary to change HRT prescribing habits and testosterone treatment is unfortunately not even in the conversation.

Many professionals in multiple primary care specialties have been hesitant to recommend testosterone to female patients because of the lack of an FDA approved product. The Consensus group presented a plethora of data and studies that cannot be ignored when the health and wellbeing of women are at stake. The FDA is responsible for determining pharmacotherapeutics

of new medications. They are not tasked to tell practitioners how to practice medicine. The use of human identical testosterone in women to treat the clinical problems associated with testosterone deficiency requires individualization of both dose and route of delivery, precisely tailored to each woman's unique metabolism, genetics, and clinical make-up.

General health issues such as obesity, low bone density, cognitive decline and cardiovascular disease highlight the need for preventive healthcare for women around the world. Testosterone insufficiency and other hormonal imbalances in women may be the underlying cause for many of these women's health issues. This paper raises awareness to the clinical experience and scientific literature worldwide so that both will become available to patients and practitioners.

The Consensus group reviewed available data. No increased risk of breast cancer or cardiovascular disease with supplemental testosterone was found. Support for physiological replacement was noted (need reference- it's in Panay's article #82).

To address health issues like obesity, low bone density, cognitive decline and cardiovascular disease preventive health must be considered. Testosterone insufficiency in women may be the underlying cause for many of these women's health issues and may easily fall in the domain of prevention.

Studies have shown that testosterone insufficiency can occur at any decade of life after the mid-twenties and may be exacerbated by OCPs. The literature does not define an age specific normal serum value for testosterone. There are multifactorial determinants of response to testosterone therapy including but not limited to S.H.B.G., receptor pleomorphism, and genetic variation in the (AR) gene. There is no specific testosterone threshold that defines testosterone insufficiency or that guarantees symptom relief in all women.

Conclusion

Many symptoms consistent with possible testosterone insufficiency result in physicians prescribing anti-depressants, diet and sleeping pills and neurotropics to millions of women leaving the possibility of testosterone deficiency as a root cause unaddressed.

The importance of testosterone during women's lifespan must be identified and understood by clinicians. The Consensus recommends societies who champion women's health consider our findings on the benefits of testosterone supplementation in their recommendations. Medical schools and residency programs in primary care must also incorporate education on testosterone insufficiency and testosterone optimization in their training.

More studies on both pre and postmenopausal women and on those using estrogen therapy are needed. The more reassuring data on the efficacy and safety of testosterone for general wellbeing as well as cardiovascular, breast cancer and Alzheimer's prevention, the more comfortable physicians and patients will become with its use.

Acknowledgements:

The committee wishes to thank Derrick Desilva M.D. and Neal Rouzier M.D. for their contributions to this manuscript.

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Testosterone in Men: A Review

Gary S. Donovitz, MD, FACOG

INTRODUCTION

You wake up one morning after another sleepless night. Who is that person in the mirror? He has less hair, wrinkles that you never noticed, and an enlarging mid-section. He does not feel like going to work or going to work out at the gym. His wife complains he is irritable all the time. Sex has become a chore with less of the great outcomes he remembered ten years ago. How old am I? Forty but I feel 50. Am I just getting old or could it be something else? My wife is on hormones. Do I need those? Could it be male menopause or andropause? My friends prefer to call it low T.

As men age, their blood levels of testosterone decrease. This decline after the age of 35 is gradual in most but can be accelerated in some men. The decline in testosterone is a cause of the clinical syndrome of testosterone insufficiency and is associated with many of the symptoms previously associated with aging. This clinical syndrome also can affect your general health and wellbeing, and without treatment you are at an increased risk for Alzheimer's disease, cardiovascular disease, prostate cancer, diabetes, osteoporosis, and sarcopenia.

Epidemiology of Testosterone Insufficiency

Testosterone levels decline 1-3 percent per year after age thirty.[i] This data reported from the Massachusetts Male Aging Study. The prevalence of low testosterone (total testosterone less than 300 ng/dl) is as high as 38.7 percent in males over 45 in out-patient primary care populations. This study obviously was based on a theoretical biochemical cut off value.[ii] The actual prevalence is much higher if one subscribes to the 2016 Consensus Paper by Abraham Morgentaler et al. whereupon testosterone insufficiency is defined as a clinical syndrome with a foundation based on symptoms and supported by a range of testosterone values not tied to single value threshold.[iii] Total serum testosterone is the most commonly used measurement of androgen activity, though it is a poor indicator of tissue activity.[iv] Based on this research, the fact that symptoms do not correlate with total testosterone, and the need to identify men at risk, health assessment questionnaires should be utilized for screening.

History

The history of testosterone is fascinating and unique.

In Greek mythology, castration was practiced early even within the first generation of gods. Gaea, mother earth, produced Uranos by parthenogenesis with whom she then generated the titan Chronos. When Uranos prevented Gaea from creating children with their son Chronos, she induced Chronos to castrate his father. Uranos' testes, thrown into the sea, caused the water to foam and out of these bubbles was born the goddess of love Aphrodite (Venus). Quite extraordinary events in terms of reproductive physiology! If you are ever in Florence, Italy, the painting by Giorgio Vasari (1511–1574) is in the Palazzo Vecchio.

Castration before puberty maintains the high voice of boys so that they remain soprano and alto voices even as adults. Such high-pitched voices were considered desirable especially at times when women were not allowed to sing in operas or in church. These castrated males performed in operas in the seventeenth and eighteenth centuries; in the Vatican choirs these voices could be heard until the early twentieth century. Strangely enough, while castration was forbidden in the Vatican state, which extended over most of middle Italy, it was not forbidden to employ castrated singers.

Prepubertal castration was thought to offer insight into the influence of testosterone on longevity. A retrospective comparison of the life expectancy of singers born between 1580 and 1858 and castrated before puberty, in order to preserve their high voices, to intact singers born at the same time did not reveal a significant difference between the lifespan of castrated intact singers (65.5 ± 13.8 vs. 64.4 ± 14.1, mean ± SD). This would imply that the presencevi or absence of normal male testosterone levels at the age of puberty, and beyond the age of puberty, has no influence on life expectancy. That's a rather huge misstatement and conclusion because it neglects the fact that 50 percent of males were dying by age 50 before they would have seen the long-term benefits.

If the history of castration transcends centuries, it should not be a surprise that the opposite of castration — using testes for medicinal support — also has its place in the annals of history. Roman Gaius Plinius Secundus (Pliny the Elder) recommended the consumption of animal testes to treat symptoms of testosterone deficiency. Slightly more refined was the prescription of testicular extracts for the same purpose in Arabic medicine, for example, by Mensue the Elder (777–837) in Baghdad. Albertus Magnus (1193–1280) in Cologne, better known as a philosopher, recommended powdered hog testes, but refined his recipe by offering the powder in wine.[vii]

However, the use of testicles grew exponentially towards the end of the nineteenth century when Charles E. Brown-Séquard (1817–1894) [viii], published his scientific paper on the results of his self-experiment in the Lancet. He gave himself 1-ml injections of a mixture of one-part testicular vein blood, one-part semen and one-part juice extracted from dog or guinea-pig testes, daily. Three weeks later he was astonished and purported that, 'A radical change took place in me. I had regained at least all the strength I possessed a good many years ago. I was able to make

experiments for several hours. My limbs, tested with a dynamometer, gained 6 to 7 kg in strength. The jet of urine and the power of defecation became stronger.' Oh, the power of suggestion and observation!

Nearly a half century later, two scientists, Leopold Ruzicka[ix] and Adolf Butenandt synthesized the hormone that would be the most important hormone for men and, as it turns out, also for women. Both scientists received The Nobel Prize for their findings. Initially testosterone was available for clinical use starting in the 1940s, but practitioners limited the therapy to those patients with the most severe cases of testosterone deficiency (TD) such as men with pituitary tumors or anorchia. It wasn't until the 1990s when physicians recognized a more expanded subset of patients who were symptomatic from low testosterone and would benefit from their symptoms being treated with testosterone replacement therapy (TRT).

Controversy

Testosterone has been controversial for many years, even before the hockey stick growth over the past 10 years. Journal articles claim no clinical consequences of the decline in serum testosterone with age are known with certainty, but several parallels between the effects of aging and those of hypogonadism due to pituitary or testicular disease suggest that the decline in serum testosterone might be a cause of several effects of aging. The data presented later in this chapter clearly dispels that myth.

Initially, there were concerns about testosterone and illicit performance enhancement in athletes and body builders[x] — the anabolic steroid craze.

Even before that physicians were convinced that testosterone "fueled the fire" of prostate cancer causing progression of, and increasing the severity of, the disease. A concern that does not have one shred of supporting evidence in the world literature.

In 2013, Vigen et al.[xi] reported an increase in heart attacks, strokes, and all-cause mortality in males taking testosterone. Just a few months later the Food and Drug Administration (FDA) announced an investigation into cardiovascular (CV) risk in males on testosterone products. Then came the black box warning on all testosterone products. Unfortunately, the Vigen study was flawed and the data actually showed testosterone was protective to the heart and there was less all-cause mortality in testosterone users. We are still awaiting a retraction of this misstated flawed study. The scientific research since has shown that CV risk is reduced on testosterone therapy.

Mechanisms of Testosterone Action

Testosterone has many different biologic effects, some occurring in its current molecule, which is testosterone. It can act directly by binding to the androgen receptor. It is here that many of the symptoms of testosterone deficiency (TD) are relieved. It can also be converted in tissues that express the enzyme 5-alpha-reductase, to dihydrotestosterone, which has a greater binding affinity for the androgen receptor than testosterone itself. This is necessary for secondary sex characteristics and sexual hair growth. Finally, it can act as an estrogen following conversion by aromatase to estradiol, which binds to the estrogen receptor. Without this important conversion men develop osteoporosis and have difficulty losing body fat.[xii]

Biologic Effects of Low Testosterone and the Benefits of TRT

In the introduction, I touched on some of the symptoms of low testosterone. These can include low energy level, insomnia, weight gain (especially around the midsection), brain fog, loss of muscle mass, decreased libido, decreased sexual performance (erectile dysfunction), joint pains, and mood disturbances including irritability and anxiety. Unfortunately, only 5 percent of males that suffer from testosterone insufficiency receive testosterone replacement therapy (TRT). Even fewer are receiving testosterone optimization therapy.

Why is this?

I believe it's because of inadequate screening and/or screening with biologic tests like serum or saliva rather than health assessment questionnaires which have a higher sensitivity in evaluating this clinical syndrome. Normal ranges vary widely between laboratories and bear little correlation to clinical findings.[xiii] Free testosterone measurements are equally inaccurate in the clinical setting.[xiv] Quality of life improvements were noted by the Aging Males' Syndrome questionnaire in somatic and sexual functioning in a study reported by Basaria.[xv] Similar results were seen using the St. Louis University ADAM questionnaire. Rather than medicate men with sleeping pills, diet pills, memory pills, and anxiolytics, hormone optimization guided by health questionnaires would widen our scope of males who would benefit from TRT.

We have looked at the short-term biologic effects of low testosterone, and now let us add in the long term effects which can affect the heart, brain, bones, and prostate.

Low testosterone is associated with:

- excess abdominal fat
- loss of insulin sensitivity,
- higher C-reactive protein, and
- atherosclerosis.[xvi]

Evidence from clinical studies[xvii] suggests that patients with low testosterone levels are at increased cardiovascular disease risk. Even though the exact mechanisms remain poorly understood, low plasma testosterone is associated with a pro-atherogenic lipid profile, insulin resistance, increased levels of pro-inflammatory mediators, and vascular dysfunction which is typically observed in patients with hypogonadism. Furthermore, recent evidence suggests that testosterone deficiency also has direct adverse effects on endothelium and nitric oxide bioavailability. Observations from studies in patients with hypogonadotropic hypogonadism (HH) imply that the mechanisms of endothelial dysfunction related with testosterone-deficiency may involve changes in asymmetric dimethylarginine (ADMA) levels, a known endogenous inhibitor of nitric oxide synthase. Evidence suggests that testosterone replacement therapy is not only a safe, but also an effective, means to reduce atherosclerotic risk and reverse endothelial dysfunction in patients with hypogonadotropic hypogonadism.

The damage to the endothelium can be repaired. There are endothelial progenitor cells that can repair the damage. These cells are activated by testosterone.[xviii] Without testosterone, there is accumulation of damage to the endothelium exacerbated by the pro-inflammatory cytokines and an increased risk of cardiovascular disease. In a study at The University of Texas at Galveston 6335 Men > 66 years of age, from 1997-2005, were followed retrospectively using injectable synthetic testosterone. The Highest Risk

Patients had reduction in myocardial infarctions (MI) HR .69 CI .53-.92.

With testosterone optimization:[xix]

- Testosterone reduces insulin resistance
- Testosterone reduces cholesterol
- Testosterone reduces visceral fat
- Testosterone reduces coronary artery disease (CAD)

Men given aromatize-able testosterone:[xx]

- Increase blood flow to the coronary arteries (even in patients with CAD)
- Decrease plaque in the coronary arteries
- Decrease inflammation in the coronary arteries

Multiple studies show low T is associated with high-grade prostate cancer (PCa) and a higher stage at presentation of their PCa.[xxi] If the age-old myth that testosterone "fueled the fire" of prostate cancer is not true, that begs the question: is the corollary true that optimal levels of testosterone are indeed protective to the prostate? A pooled prospective study of 3000 men in Finland, Norway, and Sweden had testosterone blood levels evaluated. 25 percent were diagnosed with PCa afterwards. There was a decreased risk of PCa in men with HIGHER testosterone levels.[xxii] For every 10ng/dL increment in annual reduction of testosterone, the risk of PCa increased by 14 percent. If more than 30 ng/dL reduction à 5X increase in PCa risk.

Osteoporosis is often thought of as a women's disease, as it is particularly common after menopause. The reality is, osteoporosis also affects men. In fact, twenty percent of those affected by osteoporosis are males. Overall, 1 in 5 men over the age of 50 will have an osteoporosis related fracture.[xxiii] This is greater than the likelihood of developing prostate cancer. Fractures from osteoporosis in males can be associated with higher rates of disability and death than in women. With the age of hypogonadism decreasing currently we need to be aware that one of the biologic effects of low T is the loss of bone mass. Testosterone increases bone density in men with low levels of this male hormone. In fact, studies have shown an 8.3 percent increase in bone mineral density (BMD) annually using TRT.

The number of Alzheimer's cases will triple by 2050 at a cost that will increase 500 percent, to $1.1 trillion per year. One of the biologic effects of low testosterone is an increase in cognitive decline, beginning in a man's mid-thirties, co-incidentally with his decline in testosterone. This can progress to a decrease in verbal memory and possibly dementia and Alzheimer's disease. Physiologically as T decreases, there is an increase in inflammatory cytokines in the brain, and this leads to more free radicals and oxidative stress. This causes damage to the endothelium, brain cells, and mitochondria. Both estrogen and testosterone have neuroprotective roles:[xxiv]

- Reducing apoptosis
- Increasing blood flow to the brain
- Decreasing Beta amyloid deposition in the brain
- Decreasing inflammatory cytokines

Evaluation for Possible Hypogonadism in Men

The clinical symptoms of male hypogonadism are well recognized and delineated earlier in this chapter. The causes both central and peripheral are sufficiently well known. Aging is one of the most common, and causes two important changes. One, the testosterone levels both total and free decrease. In addition, Sex Hormone Binding Globulin also increases, diminishing a male's free testosterone further. Health assessment questionnaires and test of the hypothalamic-pituitary-testicular axis are sufficiently accurate to permit the diagnosis in most patients. The patient has primary hypogonadism if the serum testosterone concentration is below normal and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal. The patient has secondary hypogonadism if the serum testosterone concentration is below normal and the serum LH and/or FSH concentrations are normal or low.[xxv]

Aside from aging, which the Endocrine Society and others have not recommended for screening, although the benefits are life changing as outlined above, Endocrine Society guidelines:[xxvi]

- Diseases of the Sella region
- Medications that affect testosterone production, such as high-dose glucocorticoids for a prolonged period and sustained-release opioids
- Human immunodeficiency virus (HIV)-associated weight loss
- End-stage kidney disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Osteoporosis or low-trauma fracture, especially in a young man
- Infertlity
- Type 2 diabetes

The initial test should be a serum total and free testosterone measurement early in the morning. If the result is low, the test should be repeated at least once, preferably twice. Testosterone should be measured in a laboratory that performs the assay by liquid chromatography or chemical luminescence.

If the hypogonadism is secondary and of moderate severity (e.g. <200 ng/dL) and/or associated with other hormonal deficiencies, a serum prolactin should be obtained and if elevated, a magnetic resonance imaging (MRI) of the Sella turcica area should be ordered.

A semen analysis is also part of the evaluation of testosterone insufficiency if the patient is pursuing fertility or has been diagnosed with infertility.

Once the diagnosis of hypogonadism is made, the patient should have his estradiol, thyroid profile, CBC, Vitamin D, CMP, and his HgA1C evaluated.

OPTIONS FOR TESTOSTERONE THERAPY

In Abraham Morgentaler MD's consensus report[xxvii] titled, "Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions," it was unanimously decided that "TD is a well-established, clinically significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life." It was also unanimously decided that, "...symptoms and signs of TD occur as a result of low levels of T and may benefit from treatment regardless of whether there is an identified underlying etiology," and, that "there is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not."

As reported, the starting concentration of testosterone predicts the magnitude and rapidity of response to treatment. The less hypogonadal the

subject, the larger the increase in circulating testosterone values must be for the effect to be 'perceived' by the subject, and the longer the duration of treatment to achieve an instrumentally.

The time-course of the spectrum of effects of testosterone shows considerable variation in the measurable difference in the desired outcome. The following are variables to be considered:

- Pharmacodynamics of the testosterone preparation
- Genomic and non-genomic effects
- Androgen receptor polymorphism
- Intracellular steroid metabolism

Many factors affect choice of regimen, including patient preference, cost, convenience, and insurance coverage. Let me try to break down some of the more common options.

There are many options for treating TD. First there are bio-identical options vs synthetic options. Bio-identical testosterone has the exact molecular structure of testosterone that the body produces. It tends to work synergistically with your hormone receptors. Bio-identical testosterone is usually made from soy or yams. Synthetic testosterone has a different molecular structure than what the body produces. Synthetic testosterone can cause many more side effects and interfere with proper hormone function. It is not plant based. It is usually administered as Testosterone cypionate, enanthate, undecanoate.

Route of delivery also has many variables that contribute to the benefits and side effects of TRT. Understanding the pharmacokinetics is important. There are no bio-identical testosterone preparations that are approved for oral administration. This is because absorption is variable and often poor. In addition, testosterone absorbed from the GI tract is rapidly metabolized in the liver and will give you sustainable levels. In the past, methyl testosterone was administered orally, however its absorption was poor and erratic and there were reports of liver toxicity.

There are bio-identical options for transdermal administration. This route of administration started in 1994 with the introduction of the scrotal patch (now no longer available). These would include Androgel®, Testim®, Axiron®, Fortesta®, and compounded testosterone cream. Most of these need to be administered twice a day and absorption is not predictable. In addition, it is often difficult to achieve optimal hormone levels in a majority of patients.

Injectable testosterone is usually synthetic (e.g. Testosterone cypionate, enanthate, undecanoate). The esterified molecule of testosterone and their oil base extend their period of efficacy. These products are in an oil base and time released. They are administered twice weekly to every 3 months depending on the product. Using testosterone undecanoate there have been reports of pulmonary oil micro embolism. The disadvantages are the need for deep Intra Muscular (IM) administration of an oily solution 50-100 times per year and fluctuations in the serum testosterone concentration, which result in fluctuations in symptom relief in many patients. Many patients have reported a "roller coaster" like feeling with hormone levels varying significantly between injections. On a positive note many insurance carriers will reimburse for these medications.

Finally, testosterone may be administered as a sub-cutaneous pellet (Testopel® or compounded) which is administered under the skin, usually in the gluteal region, and usually using bio-identical testosterone. The benefit of this method is more consistent testosterone hormone levels. This method, however, does require an insertion procedure with local anesthesia. The literature reports more consistent serum levels of testosterone with this method. Adverse events include pellet extrusion, infection, and fibrosis.

SIDE EFFECTS

There are some side effects to testosterone administration for the clinical syndrome of TD. These include:[xxviii]

- **Suppression of spermatogenesis** — This has been especially prevalent in men receiving parenteral testosterone or sub-cutaneous pellets because of the extreme suppression of FSH as part of the normal feedback loop. This side effect is usually reversible in men who want to resume fertility. It is a good idea to get a semen analysis in younger males with TD who may desire fertility in the future.
- **Erythrocytosis (an elevation of RBC mass)** — Testosterone stimulates erythropoiesis, so the hematocrit should be measured before initiating testosterone treatment for a baseline. Occasionally, you will need to have phlebotomy to correct this if symptomatic.
- **Obstructive sleep apnea (OSA)** — The estimated prevalence in North America is approximately 15 to 30 percent in males.xxix Testosterone therapy can worsen the symptoms of sleep apnea in approximately 1/3 of patients. Be alert if patient is African American, older male, obese, hypertensive, diabetic, hypothyroid, and/or a smoker.
- **Reduction in testicular size** — Occasionally there is a 10-15 percent reduction in the size of the testicle. This is thought to be due to a reduction in spermatogenesis in males on TRT. This side effect is reversible once therapy is stopped.
- **Liver Damage** — Non-oral testosterone preparations have not been shown to cause liver damage. Oral testosterone, particularly synthetic oral testosterone, has had reported cases. In the spirit of consistency, the FDA requires all testosterone preparations to carry this warning.
- **Fluid Retention** — A small percent of patients will experience fluid retention on TRT. This is secondary to the early increase in muscle mass which tends to hold onto water. This extracellular water weight usually resolves spontaneously.
- **Acne** — TRT can increase oil production in the glands of the skin. As such, some men will experience an increase in acne that usually responds well to systemic therapy.
- **Skin Rash** — Skin irritation can occur with any of the topical testosterone preparations.
- **Allergic Reaction** — There have been reported cases of allergic reactions to the cottonseed oil in parenteral preparations.
- **Breast Enlargement** — Many men will have breast enlargement (gynecomastia) with low testosterone levels. After TRT some men will develop gynecomastia from the aromatization of testosterone to estradiol causing proliferation of the breast tissue. This side effect and its predecessor, nipple sensitivity, are fortunately rare. Treatment usually involves a reduction in testosterone.

TAKEAWAYS

This chapter has focused on helping men who might have low testosterone recognize what symptoms make up the clinical syndrome of testosterone deficiency/insufficiency.

The short-term benefits including symptom relief were discussed. Clearly most men feel better with TRT. They have more energy, better sexual performance, improved cognition, sleep better, and have less anxiety/irritability. Testosterone optimization can be of paramount importance in avoiding the side effects of using multiple medications to treat the symptoms of TD.

In addition, the longterm benefits on the heart, brain, bones, and prostate were elucidated and expanded upon. TRT can reduce cardiovascular disease, diabetes, Alzheimer's disease, osteoporosis, and prostate cancer.

The type of hormone (synthetic vs bio-identical) MATTERS! The route of administration MATTERS! Physiologic HRT/TRT should mirror your hormone production when you felt your best in your 20's and 30's. It should be hassle free and be utilized with minimal side effects.

Longevity with your testosterone optimized as a male = Healthy Aging! Feeling your best as you age = A Pristine Quality of Life!

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Correspondence: Hormone Therapy for Postmenopausal Women

TO THE EDITOR:

In an assessment of therapies to treat the symptoms of menopause, Pinkerton (Jan. 30 issue)[1] dismisses compounded therapies (except for those used in patients with allergies or when there is a medical need for unusual dosing regimens), and she notes safety concerns. This blanket generalization overlooks the substantial Food and Drug Administration (FDA) oversight established by the 2013 Drug Quality and Security Act (DQSA).

Contrary to Pinkerton's assertion of "minimal government regulation and monitoring," the drug outsourcing facilities supervised under the DQSA must register with the FDA, be subject to regular unannounced inspections, comply with Current Good Manufacturing Practices, and use FDA regulated ingredients. Patients have depended on compounders and outsourcing facilities for decades to provide the customized formulations that work well for them, along with counseling on use of the compounded medication. I am extremely concerned about the potential consequences for women who use these therapies of disregarding this sector in its entirety owing to unfounded safety concerns.

ERIKA SCHWARTZ, M.D.
EVOLVED SCIENCE
New York, NY
drerika@eshealt.com

No potential conflict of interest relevant to this letter was reported.

1. Pinkerton JV. Hormone therapy for postmenopausal women. N Engl J Med 2020; 382: 446-55.

DOI: 10.1056/NEJMC2005199

TO THE EDITOR:

In her article on hormone therapy, Pinkerton focused on data from the Women's Health Initiative and did not mention the Danish Osteoporosis Prevention Study, which randomly assigned 1006 recently postmenopausal or perimenopausal women to estradiol or no estradiol for 11 years and followed them for 16 years. Women who received estradiol had significantly lower mortality (among 15 women vs. 26 women) and a significantly lower incidence of myocardial infarction (5 vs. 11) than women who did not receive estradiol, without an increase in the incidence of cancer (36 and 39, respectively), venous thromboembolism (2 and 1), or stroke (11 and 14).[1]

The article by Pinkerton also did not address sexual dysfunction[2] or menopause-related cognitive impairment,[3] which has been reported to be present in 60% of perimenopausal and postmenopausal women.[2-4] Subjective reports of symptoms are confirmed by objective evidence of decreases in measures of verbal memory, episodic memory, list learning, verbal fluency, or executive functioning.[2-4] Lack of awareness among physicians of this association between memory loss and menopause may have disastrous consequences for menopausal women, including the misdiagnosis of dementia in women with these symptoms.[3]

GAYATRI DEVI, M.D.
LENOX HILL HOSPITAL–NORTHWELL HEALTH
New York, NY
gd@ybrain.org

CHRIS CREATURA, M.D.
WEILL CORNELL MEDICINE
New York, NY

VIRGINIA R. DEVI-CHOU, M.A.
RUTGERS ROBERT WOOD JOHNSON MEDICAL SCHOOL
New Brunswick, NJ

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMC2005199

THE AUTHOR REPLIES::

Schwartz notes concerns about the recommendation to avoid the use of compounded therapies except in special circumstances. The 2013 DQSA provides national licensure standards and FDA inspections for outsourcing wholesale distributors and third-party logistics providers who ship across state lines.[1] Compounding pharmacies that are not outsourcing providers are monitored by states, with wide variability in oversight.[1] The Pharmacy Compounding Accreditation Board assesses voluntary compliance with sterile and nonsterile pharmacy compounding processes. Major medical societies, including the American Medical Association, the American College of Obstetricians and Gynecologists, and the North American Menopause Society, recommend against compounded

hormone therapies owing to safety concerns regarding overdosing or underdosing, impurities, the lack of sterility, insufficient scientific efficacy and safety data, and the lack of labels providing information on dosing, ingredients, and risks.

FDA-approved bioidentical therapies include systemic and vaginal estrogen and progesterone and vaginal dehydroepiandrosterone. Medical indications for compounded hormone therapies should be documented.[1,2] For example, oral progesterone should not be used in patients with peanut allergy, preservative-free vaginal estrogen may be warranted, pellets with supraphysiologic levels of testosterone for sexual disorders are not recommended, and special dosing or formulations may be required. Federal and state oversight is needed for increased transparency about compounded product ingredients, financial conflicts of interest, and monitoring of adverse events.

With respect to the comments by Devi and colleagues: since the Danish Osteoporosis Prevention Study was open label, did not involve a placebo, and was much smaller than the Women's Health Initiative, the data are less robust. Devi et al. also call attention to the effects of menopause on sexual function and memory. Systemic and vaginal estrogen improve lubrication and blood flow and decrease the symptoms of genitourinary syndrome of menopause and painful sex, without effects on sexual interest, arousal, or orgasm beyond reduced vasomotor symptoms.[2] For women with low libido, transdermal estrogen is recommended because it has less effect on testosterone bioavailability than oral hormone therapy.

Memory problems during menopause (e.g., forgetfulness, losing keys, and difficulty concentrating or retrieving names) are usually not associated with clinically significant impairment. Treatment of depression, anxiety, and sleep disturbances, increased concentration to focus attention, and increased exercise may decrease memory problems.[3] Neuropsychological testing is recommended if cognitive symptoms interfere with daily life.3 Estrogen has been associated with improved cognition after early surgical menopause,[3] has neutral effects if used early in postmenopausal women,[4,5] and may worsen memory if initiated in patients older than 65 years of age.[2] Hormone therapy is not recommended to prevent or treat cognitive dysfunction or decline.

JOANN V. PINKERTON, M.D.
UNIVERSITY OF VIRGINIA HEALTH SYSTEM
Charlottesville, VA
jvp9u@ virginia.edu

Since publication of her article, the author reports no further potential conflict of interest.

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DOI: 10.1056/NEJMC2005199

The effect of hormone therapy on the ocular surface and intraocular pressure for postmenopausal women

A systematic review and meta-analysis of randomized controlled trials

Hao, Yuan MD[1,2]; Xiaodan, Jiang MD[1,2]; Jiarui, Yang MD[1,2]; Xuemin, Li MD[1,2]

[1]Department of Ophthalmology, Peking University Third Hospital, Beijing, China

[2]Beijing Key Laboratory of Restoration of Damaged Ocular Nerve, Beijing, China.

Address correspondence to: Li Xuemin, MD, Department of Ophthalmology, Peking University Third Hospital, No 49 Huayuan North Road, Haidian District, Beijing 100191, People's Republic of China. E-mail: lxmlxm66@sina.com

Received 24 December, 2019

Revised 9 March, 2020

Accepted 9 March, 2020

Y.H. and J.X. contributed equally as first authors.

This abstract was presented in the 24th Congress of Chinese Ophthalmological Society.

Funding/support: This project was supported by National Science and Technology Major Project (numbers 2018ZX10101004) from Ministry of Science and Technology of the People's Republic of China. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Financial disclosure/conflicts of interest: None reported.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website (www.menopause.org).

Menopause: June 08, 2020 - Volume Publish Ahead of Print - Issue - doi: 10.1097/GME.0000000000001559

Abstract

Objective:

The aim of the study was to investigate the impact of hormone therapy (HT) on the ocular surface and intraocular pressure in postmenopausal women.

Methods:

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement. PubMed, EMBASE, Cochrane Library of Systematic Reviews, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Chinese Biomedical Literature Database, and China National Knowledge Infrastructure were searched from inception to November 2019 without language restrictions. Only randomized controlled trials that evaluated the impact of HT on the ocular surface and intraocular pressure in postmenopausal women were eligible. The trials had to report at least one of the following outcomes: break-up time, Schirmer test, corneal staining, ocular surface symptom score, and intraocular pressure. Two investigators independently extracted the information, assessed the risk of bias, and evaluated the publication bias. All data were analyzed by Review Manager V.5.3. Sensitivity analysis and subgroup analysis were performed to find the source of heterogeneity and evaluate the different effects among subgroups.

Results:

Nine randomized controlled trials (N = 612) were included. The HT group showed significant improvements compared with the control group in break-up time (mean difference [MD] = 2.09, 95% confidence interval [CI] 1.00-3.19, P = 0.0002), Schirmer test without anesthesia (MD = 4.17, 95% CI 1.55-6.80, P = 0.002), Schirmer test with anesthesia (MD = 1.44, 95% CI 0.71-2.18, P = 0.0001), and corneal staining scores (standardized mean difference [SMD] = −0.85, 95% CI −1.39 to −0.30, P = 0.002). Moreover, significant beneficial effects were observed on all four symptoms, including dryness (SMD = −1.21, 95% CI −1.99 to −0.44, P = 0.002), foreign body sensation (SMD = −1.02, 95% CI −1.29 to −0.76, P < 0.00001), ocular fatigue (SMD = −1.74, 95% CI −2.12 to −1.36, P < 0.00001), and burning (SMD = −0.53, 95% CI −0.78 to −0.29, P < 0.0001) after HT. Subgroup analysis revealed that, in terms of break-up time, postmenopausal women younger than 55 years achieved more improvements (MD = 0.88, 95% CI 0.16-1.59, P = 0.02) than women older than 55 years old (MD = 2.60, 95% CI −1.34 to 6.55, P = 0.20), and the estrogen subgroup received more benefits (MD = 3.11, 95% CI 0.93-5.30, P = 0.005) than the estrogen plus progestogen subgroup (MD = 0.42, 95% CI −0.02 to 0.85, P = 0.06). Sensitivity analysis and subgroup analysis suggested that the heterogeneity might derive from the methodological quality, the age of participants, and the intervention of the control group. Intraocular pressure (MD = −1.54, 95% CI −3.39 to 0.32, P = 0.10) was not evidently decreased after HT. No more specific adverse events (relative risk = 1.66, 95% CI 0.41-6.77, P = 0.48) were found in the HT group.

Conclusions:

Our study revealed that HT could improve ocular surface function in postmenopausal women effectively and safely, especially for those who were younger than 55 years, and estrogen only showed more improvements than estrogen plus progestogen. The effectiveness of HT in treating dry eye in postmenopausal women is, however, still a controversial topic. In addition, we did not find HT led to a significant reduction of intraocular pressure.