Testosterone Insufficiency and Treatment in Women: International Expert Consensus Resolutions

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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.

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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] Cross-sectional epidemiologic studies[68] have demonstrated a positive correlation between endogenous androgens and BMD in both adolescent females and in premenopausal adult women.

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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.

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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.

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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.

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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.

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