Testosterone Therapy for Postmenopausal Women: Efficacy and Safety

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ABSTRACT

The treatment of postmenopausal women with a variety of androgen formulations is increasing, despite the lack of clear guidelines regarding the diagnosis of androgen insufficiency. This review summarizes evidence on the efficacy and safety of adding testosterone to hormone therapy in postmenopausal women. Fair to good evidence exists that the use of testosterone in combination with hormone therapy has both benefits and risks. The benefits are an improvement in sexual function with various regimens of testosterone use (good evidence), an improved sense of well-being with transdermal testosterone (fair evidence), and a reduction in triglyceride levels with methyl testosterone (fair evidence). The most consistent risk is a reduction in high-density lipoprotein (HDL) cholesterol, particularly with methyl testosterone (good evidence). There has been insufficient reporting of other side effects; hence, testosterone therapy should be used with caution. The use of testosterone may be justified in specific clinical circumstances and should be limited to short-term use; long-term studies are not available. Close surveillance for HDL cholesterol and other side effects is necessary.

KEYWORDS: Hormone therapy, postmenopausal women, testosterone

Testosterone is one of three hormones secreted by the ovaries, and research has documented the physiological effects of testosterone in women such that any imbalance in androgen biosynthesis or metabolism will affect any or all of these systems.[1,2] Clinically, the concept of female androgen insufficiency is supported by surrogate evidence from therapeutic trials and expert opinion. The frequently described symptoms of female androgen insufficiency syndrome are fatigue, low energy, decreased or absent sexual motivation and desire, and a generalized decrease in the sense of well-being.[3]

It is well established that testosterone levels decline after oophorectomy.[4–7] Several cross-sectional and prospective studies have reported that serum total testosterone levels decrease across the menopausal transition,[8–12] but a prospective study does not support this.[13] Testosterone levels are known to vary during the menstrual cycle[14,15] with levels peaking at the middle third of the cycle, and remaining moderately elevated through to the mid-luteal phase.[15] In the late reproductive years there is failure of the midcycle increase in free testosterone, which characterizes the menstrual cycle in young ovulating women.[16] Therefore, to establish whether levels decline during the menopause transition, it is necessary to measure levels at times other than during the early follicular phase nadir in premenopausal women. Of note, the two prospective studies that reported a decrease in testosterone across the menopausal transition did not specify the particular day of the menstrual cycle that blood samples were taken.[10,11]

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Current Perspectives on the Use of Androgens in Women; Guest Editor, Susan R. Davis, M.B.B.S., FRACP, Ph.D.

Semin Reprod Med 2006;24:115–124.
DOI 10.1055/s-2006-939570. ISSN 1526-8004.

In contrast, Burger et al[13] measured total testosterone levels using an insensitive assay during day 4 to 8 of the menstrual cycle, when it is known to be low, and compared these levels to those of postmenopausal women. Thus, the interpretation of these findings is limited.

Recently, the U.S. Preventive Services Task Force found good evidence that the use of combined estrogen and progestin results in both benefits and harm, and they have recommended against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.[17] The treatment of postmenopausal women with a variety of androgen formulations is increasing, despite the lack of clear guidelines regarding the diagnosis of androgen insufficiency.[18] We therefore reviewed the evidence on the efficacy and safety of combining testosterone with hormone therapy (T + HT) on the health of postmenopausal women.

GRADING OF EVIDENCE

The level of epidemiological evidence for each outcome was graded for its strength (Table 1). A conclusion about the strength of evidence and the magnitude of the net benefit (i.e., benefits minus risks) of adding testosterone to hormone therapy was graded according to one of five classifications (Table 2).

TESTOSTERONE REGIMENS

Various testosterone preparations currently are used for testosterone therapy (Table 3). Availability depends on regulatory approval, which varies among states and nations.

Table 1 Classification of Evidence Levels

Grade	Definition
Good	Evidence includes consistent results from well-designed and conducted studies in representative populations that directly assess effects on health outcome
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcome
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number, power, quality of study design; important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

(From Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med 2005;142:855–860.)

Table 2 Classification of Recommendation

Category	Definition
A	There is good evidence to support the recommendation that the intervention improves health outcomes and concludes that benefits substantially outweigh risks
B	There is fair evidence to support the recommendation that the intervention health outcomes and concludes that benefits substantially outweigh risks
C	There is poor evidence to recommend for or against the use of the intervention, but recommendations may be made on other grounds. The balance of benefits and risks is too indistinguishable to justify a general recommendation
D	There is fair evidence against the use of the intervention; the intervention is ineffective or that risks outweigh benefits
E	There is a good evidence against the use of the intervention; evidence that the intervention is effective is lacking, poor quality, or conflicting, and the balance of benefits and harm cannot be determined

(From Canadian Task Force for Periodic Health Care. Evidence-based clinical prevention. Available at: http://www.ctfphc.org. Accessed June 27, 2005; and Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. Ann Intern Med 2005;142:855–860.)[72]

In the early 1990s, the testosterone implant was approved for postmenopausal women in the United Kingdom. Alternatively, testosterone and its esters are available as an intramuscular injection. A dose of between 50 and 100 mg of either may be administered if testosterone levels are within the low normal range for young women; the latter may be administered every 4 to 6 weeks.[19]

Oral estrogen/methyl testosterone (MT) therapy is available in the United States in two strengths: 0.625 or 1.25 mg of esterified estrogen and 1.25 or 2.5 mg of MT, respectively. Notwithstanding, no indication has been approved by the Food and Drug Administration for androgen insufficiency syndrome.[20] Testosterone undecanoate, an oral form, is available in Europe and Canada. It is widely used for treatment of partial androgen insufficiency in men. It is believed to be efficacious in that it is absorbed via the lymphatics, particularly if ingested with a fat load.[21]

The transdermal matrix patch has been developed specifically for use in women. It has been studied to phase III, and although optimal dosing remains undetermined, it is designed to deliver 150 to 300 μg/d with a twice-a-week application.

Testosterone creams are available in Australia and have been used in clinical trials.

Table 3 Testosterone Formula in Postmenopausal Women*

Route	Type	Dosage Range	Frequency
Subcutaneous	Testosterone implant	50– 5 mg	Once every 3–6 months
Intramuscular	Mixed testosterone esters	50–100 mg	Once every 4–6 weeks
Oral	Methyl testosterone	1.25–2.5 mg	Daily
	Testosterone undecanoate	40 mg	Daily
Transdermal	Testosterone patch	150–300 μg	Twice a week
	Testosterone cream 1%	5–10 mg	Daily

The articles from the same trials were (1) Davis 1995 and Davis 2000 (2) Basaria 2002, Dobs 2002, Nguyen 1999, and Wisniewski 2002 (3) Miller 2000, Luciano 1998a, and Luciano 1999 (4) Barrett-Connor 1999 and Barrett-Connor 1996 (5) Sherwin 1988, Sherwin 1984, Sherwin 1985a; Sherwin 1985b; Sherwin 1985c. *Population is classified into three groups: surgically menopausal women, naturally menopausal women and surgically/naturally menopausal women.

EFFICACY OF TESTOSTERONE

Sense of Well-Being

Diminished well-being is one of the proposed key symptoms of female androgen insufficiency. Androgen administration may affect brain function directly through androgen receptors and indirectly through conversion to estrogen and dihydrotestosterone, both of which are important neuromodulators capable of stimulating 5-hydroxytryptamine receptors and serotonin transporter protein metabolism.[22,23] Dysfunctions of serotonin neurotransmission have been associated with the occurrence of major depressive disorder.[24]

The benefit to the sense of well-being with the addition of testosterone to HT in postmenopausal women was reported from testosterone patch studies; one was a crossover study with no washout period,[25] and another was a parallel study.[26] Both studies were conducted in surgically menopausal women. However, there has been no evidence to indicate clinically significant effects on sense of well-being for any other forms of testosterone, including implant,[27] injection,[28] or oral.[29,30] The discrepancy of the results may be because of a difference in the pharmacokinetics of each testosterone formula, type of menopause (natural/surgical), and/or the type of questionnaire used.

Thus, fair evidence exists for the benefits of the testosterone patch on well-being in surgically menopausal women, but evidence for the other regimens is poor.

Sexual Function

Female sexual dysfunction is a complex problem with multiple overlapping etiologies. Androgenic activation of sexual behavior is documented for men, but less clear for women (reviewed by Bancroft[31]). A correlation of endogenous testosterone levels and sexual function is also inconclusive (reviewed by Cameron et al[32]). The variables that are most problematic in attempts to correlate androgen levels to sexual function include insufficiently sensitive testosterone assays, insufficient study power, and the lack of validated measures to assess sexual function.[32] The most recent study measured testosterone by a highly sensitive direct manual radioimmunoassay, and measured sexual health by a validated questionnaire in 1021 women. This study has reported that no single androgen level is predictive of low female sexual function.[33] This supports the important role of the intracrine physiology. Sex steroids influence female sexual dysfunction, but there is no serum androgen level that defines female androgen insufficiency.

For exogenous testosterone, the benefits for sexual function have been confirmed in all studies that used validated questionnaires for monitoring sexual function.[25,26,29,34–41] Other studies that measured sexual function using other scores/scales or an unspecified questionnaire reported inconsistent results.[30,42–46]

In our Cochrane Review, a meta-analysis of two to three fair-quality, randomized, controlled trials (Fig. 1) comparing HT alone and T + HT indicated the latter improved libido by 0.42 points (95% confidence interval [CI], 0.18 to 0.66), the mean composite score for sexual function by 0.41 points (95% CI, 0.15 to 0.67), and the mean score for sexual activity by 1.00 point (95% CI, 0.4 to 1.58).[47] Thus, there is evidence to support a beneficial effect of testosterone therapy on sexual health among postmenopausal women.

Unexplained Fatigue

Unexplained fatigue is another proposed symptom of female androgen insufficiency. However, the pharmacological evidence is insufficient to support the benefit of testosterone on unexplained fatigue. This is because of the limited number and power of studies.

A crossover study on testosterone injections with a washout period found that surgically menopausal women treated with estrogen alone reported significantly lower energy levels than those receiving either of the androgen-containing preparations ($p < 0.01$).[28] For the methyl testosterone and the testosterone patch, crossover studies without any washout period yielded no significant difference in vitality between surgically menopausal women treated with T + HT and HT alone.[25,29] It is

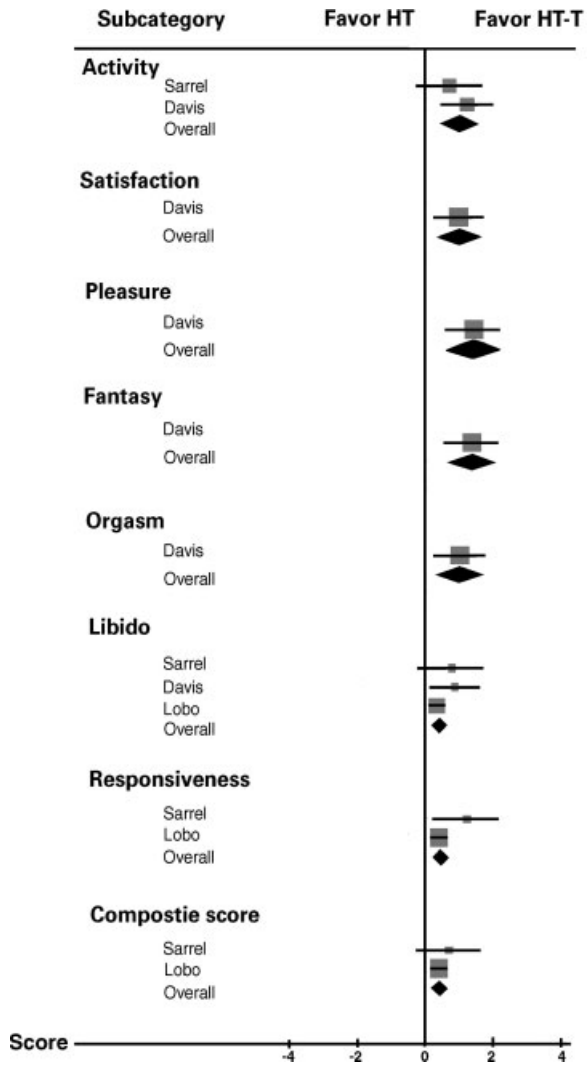

Figure 1 Meta-analysis of sexual function. The size of the point estimates is defined by the study weight. A fixed-effects model was used to combine the trials. HT, hormone therapy; T, testosterone. (From Somboonporn et al.[47])

possible that the lack of a washout period in the latter two studies contributed to an underestimation of the treatment effect, or perhaps differences in the testosterone formulation had an influence.

Bone Health

Androgens appear to play a critical role in the development and maintenance of the skeleton; however, there is great uncertainty about the mechanisms of their effects.[48] Androgens, as well as estrogens, maintain cancellous bone mass and integrity, regardless of age or sex.[49] Although androgen, via the androgen receptor, and estrogens, via the estrogen receptors, can exert these effects, their relative contribution remains uncertain.[49]

For an interventional study, the clinically important outcome with respect to bone health is the incidence of osteoporotic fractures; however, the outcome used has been bone mineral density (BMD). Several studies of the effects of testosterone on BMD have been undertaken, but the results are conflicting. For testosterone implants, a significant effect of adding 50 mg of testosterone to 50 mg of estrogen on spinal and femoral BMD was reported in a single-blinded study.[36] Garnett et al[50] studied the testosterone implant and reported no significant differences in BMD at any site measured between women receiving estrogen (75 mg) alone versus those receiving estrogen (75 mg) plus testosterone implants (100 mg). These two studies recruited both naturally and surgically menopausal women.[36]

For oral MT, Watts et al[51] reported that the difference between spinal and femoral BMD between HT and T + HT were not significant at 12 or 24 months, whereas Barrett-Connor et al[45] demonstrated a significantly greater improvement in both lumbar and femoral BMD at 24 months in the MT + HT group compared with the HT group. Only surgically menopausal women were enrolled into these studies.

When sublingual testosterone was used in both surgically and naturally menopausal women, no differences in lumbar BMD were found between HT alone and T + HT vis-à-vis percent change ($p = 0.58$); however, the improvement in hip BMD was significant for the T + HT versus HT group ($p < 0.05$).[52]

To date, no investigations of the effect of testosterone injection or testosterone patches on BMD have been published.

One open, randomized study reported no significant effect on bone resorption markers after the addition of MT to an HT regimen; however, a significant increase in all bone formation markers was recorded after estrogen (E) + T therapy versus E alone.[53] Miller et al[52] reported that levels of deoxypyridinoline and cross-linked N-telopeptide of type I collagen decreased significantly in all treatments, but no comparative results of biochemical markers of bone metabolism were provided.

The lack of information on fractures and inconsistent findings on BMD obscure any putative benefits to bone health by the addition of testosterone.

Body Composition

In a small study of postmenopausal women, E + T therapy for 2 years resulted in an increase in fat-free mass in the E + T group but not in the E-only group during the study period (24.8 + 5.9 kg to 27.9 + 5.9 kg), whereas the fat mass to fat-free mass ratio declined.[54] Further analysis of body variables indicated a significant treatment effect.[54]

Similarly, a study of MT + HT showed significantly increased lean body mass in the arms, legs, and trunk with the inclusion of MT compared with HT alone.[39] When the changes in arms, legs, and trunk in each patient were analyzed simultaneously, the

difference between treatments was significant for lean body mass ($p < 0.05$) and percentage of fat tissue ($p < 0.05$), but not for fat tissue ($p < 0.05$).[39] Although the two studies cited were of good quality and the results were consistent, the limited number of participants limits the validity of population-wide generalizations.

Cognition

Testosterone may moderate cognitive function by influencing cholinergic neurotransmission via an increase in acetylcholine release and by modulating nicotinic acid receptors (reviewed in Bates et al[55]) The interaction of neurosteroids, including androgens, with neurotransmission and neuronal excitability has several implications not only for cognitive disorders but also for epilepsy, depression, alcoholism, and anxiety disorders (reviewed in Rupprecht et al[56]).

The effects of exogenous testosterone on cognition were reported in four randomized, controlled trials,[30,40,57,58] one in surgically menopausal women[30,40,57,58] and three in both surgically and naturally menopausal women.[30,40,57,58] The investigations focused on specific outcomes related to an androgenic effect. For hormone administration by injection, the cognitive function scores for women treated with all hormone preparations (E alone, T alone, and E + T therapy) were higher during both treatment phases compared with scores of women who received placebo ($p < 0.01$).[58] This crossover study did not report a comparative effect on cognitive function of E treatment alone versus E + T treatment.[58]

Three studies have evaluated the effects of oral testosterone on cognition.[30,40,57] Women receiving E + MT maintained a steady level of performance on memory-building tasks, whereas those receiving E alone had a significant decrease in performance.[57] This effect was significantly different between the two groups.[57] In the Switching Attention Test, the mean reaction time in the switching condition was faster in the T than in the E group ($t = 3.25$; $df = 37$; $p < 0.002$; effect size = 0.53 standard deviations).[30] Results from another double-blind study showed no significant advantage in adding T to E alone on tasks involving spatial transformation or orientation, mathematics, or nonverbal reasoning.[40]

Overall, the results suggest that testosterone may exert beneficial effects on memory-building tasks and the Switching Attention Test. However, because of the small number of studies and limitation of study design, findings to date remain inconclusive.

MENOPAUSAL SYMPTOMS

In the 1960s, MT was added to esterified estrogens and received class approval from the U.S. Food and Drug Administration only for the improvement in menopausal symptoms such as hot flushes (reviewed by Lobo[20]). However, a majority of studies of MT have not shown a benefit over E alone.[30,38,51,53,59] In contrast, Simon et al[60] reported that E + MT therapy provided greater relief from menopausal symptoms than E alone.

For testosterone injection, Sherwin et al[28] reported a significantly greater improvement in somatic and psychological symptoms in the combined T + E treated group compared with the E-alone group. In another report of the same trial, the comparative effects vis-à-vis hot flushes were not provided.[61] For other testosterone regimens (i.e., implant[46] and sublingual administration[43]), no data exist to support the beneficial effects of adding T to HT on menopausal symptoms.

In conclusion, evidence is inadequate to support the effects of T + HT in either surgically or naturally menopausal women on menopausal symptoms.

SAFETY

Hirsutism and Acne

Evidence from randomized, controlled studies has shown that adding exogenous T to HT may be associated to a higher incidence of hirsutism and acne when compared with HT alone. In a majority of studies, the incidence of hirsutism and acne was noticeably higher in the T + HT group than for those in HT group, although no statistical significance was achieved.[26,34,37,43,45,51,59] Adding T to HT tends to be related to hirsutism and acne, although there is poor evidential support. In fact, most studies lacked any formal plan to report on hirsutism and acne. In addition, the focus of testosterone research is on its efficacy rather than its safety; therefore, its side effects are likely underreported.

Mood Alteration, Specifically Relating to Aggression

Aggressive behavior in men and women has been related to endogenous testosterone levels; however, a cause-effect relationship has not been demonstrated (reviewed by Christiansen[62]). Exogenous testosterone has not been shown to relate to hostility.[63] However, the effect of testosterone on mood is unclear because of the limited clinical data.

Lipid Profile

Hyperandrogenemia in women is not only associated with increased risk of coronary artery disease, but also with visceral obesity, insulin resistance, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, low-density lipoprotein (LDL) cholesterol, and

plasminogen activator inhibitor type 1 (reviewed by Wu and von Eckardstein[64]). In postmenopausal women, the effects of exogenous testosterone therapy on lipid profiles are described in the following sections.

NONORAL TESTOSTERONE

The evidence in support of the safety of nonoral testosterone on lipid profile is weak. The testosterone patch studies consistently demonstrated no significant change in the lipid profile[25,26,34,35]; however, the studies were designed to test efficacy rather than side effects, and the data on the lipid profile were not shown. For the testosterone implant and sublingual testosterone, there has been no comparative analysis between HT + T versus HT alone.[36,42,65,66]

ORAL TESTOSTERONE

Meta-analyses were conducted to summarize the effects of oral testosterone on lipid profiles as shown in Figs. 2 to 4. Evidence for oral methyl testosterone is good for support of the adverse effects of the combined treatment on HDL cholesterol at all study durations (Fig. 2). In addition, the increase in LDL cholesterol was observed at 12 and 24 months of treatment (Fig. 3). Despite these side effects, fair evidence exists for a reduction of triglyceride levels (Fig. 4). The decrease in triglyceride levels was evident between 3 to 12 months, 12 months, and 24 months.

For testosterone undecanoate, the HDL cholesterol level was significantly lower in the E + T group than those in the E-alone group. In contrast, LDL cholesterol was significantly higher.

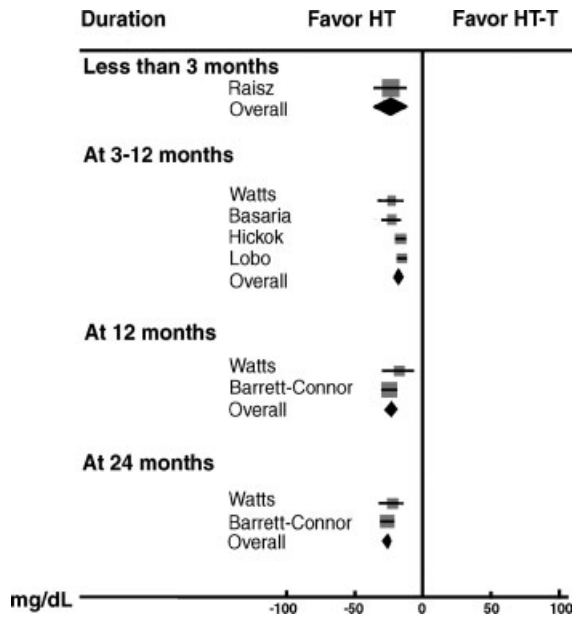

Figure 2 Meta-analysis of high-density lipoprotein cholesterol. The size of the point estimates was defined by the study weight. A random-effects model was used to combine the trials. HT, hormone therapy; T, testosterone.

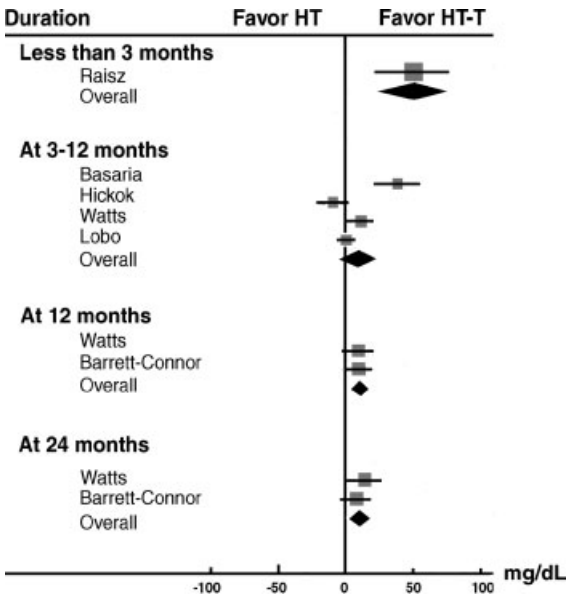

Figure 3 Meta-analysis of low-density lipoprotein cholesterol. The size of the point estimates was defined by the study weight. A random-effects model was used to combine the trials. HT, hormone therapy; T, testosterone.

Breast Cancer

In experimental studies, testosterone action is antiproliferative and proapoptotic, and mediated via the androgen receptor, despite the potential for testosterone to be aromatized to estrogen.[67] Animal studies suggest that testosterone may serve as a natural, endogenous protector of the breast, and limit mitogenic and cancer-promoting effects of estrogen on mammary epithelium.[67] However, in postmenopausal women, who are estrogen

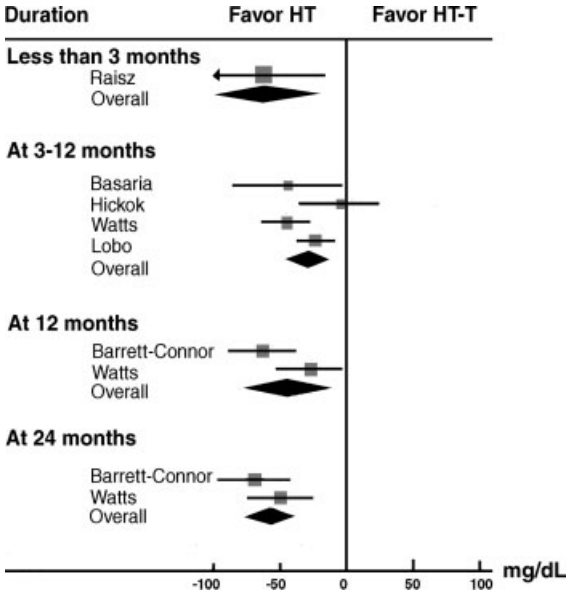

Figure 4 Meta-analysis of triglyceride levels. The size of the point estimates was defined by study weight. A random effects model was used to combine the trials. HT, hormone therapy; T, testosterone.

depleted and have increased adipose aromatase activity, higher endogenous testosterone has been associated with greater breast cancer risk.[67] The assessment of the effects of adding T to HT on the risk of breast cancer is inconclusive because of significant methodological limitations on study design.[68–70]

Cardiovascular Disease

Sex hormones can influence a multitude of factors implicated in the pathogenesis of atherosclerosis and coronary artery disease (reviewed by Wu and von Eckardstein[64]). There has been no study on the effects of adding T to HT on cardiovascular disease in postmenopausal women. In a 20-year retrospective survey of 293 female-to-male transsexuals between 17 and 70 years of age (mean age, 34), treated with oral testosterone undecanoate (160 mg/d) or testosterone (250 mg every 2 weeks) for between 2 months and 41 years (i.e., for a total exposure of 2418 patient-years), there was no excess of cardiovascular mortality or morbidity compared with the general female population.[71]

Discontinuation Rate

A recent meta-analysis of 15 fair-quality, randomized, controlled trials indicated no statistically significant difference between treatments.[47] The Peto odds ratio for the overall discontinuation rate and the discontinuation rate due to adverse events was 1.01 (95% CI, 0.76 to 1.33) and 1.28 (95% CI, 0.85 to 1.92), respectively.[47] The sensitivity analysis (according to very large studies, length of treatment follow-up period, different dosages) and subgroup analysis (according to surgical/natural menopause, oral/nonoral HT, MT + T, and adequacy of symptom control) did not affect the results.[47] According to this meta-analysis, there is fair evidential support that T + HT is not associated with a higher discontinuation rate.

CONCLUSIONS

We found fair to good evidence that the use of testosterone in combination with hormone therapy results in both benefits and risks. The benefit is improved sexual function in postmenopausal women (good evidence) in various regimens of testosterone use. The sense of well-being improves with testosterone patch (fair evidence). Adding testosterone to hormone therapy is associated with a reduction in HDL cholesterol (good evidence) and triglyceride levels, particularly methyl testosterone (fair evidence). Because of insufficient evidence, we could not assess the impact of testosterone therapy on other health outcomes. In addition, we cannot determine the effects of menopausal type (surgically induced versus natural menopause) on benefits and risks of adding testosterone to hormone therapy because there are insufficient data. Although the benefit of testosterone therapy on sexual function has been established, the ideal duration of treatment is still unclear.

Based on the evidence, we cannot recommend for or against routine use of testosterone in postmenopausal women. The use of testosterone may be justified in specific clinical circumstances and should be limited to short-term use, given that long-term studies are not available. In this application, close surveillance for changes in HDL cholesterol and other side effects is necessary.

ADDITIONAL RESEARCH

To provide concrete evidence regarding the use of testosterone in postmenopausal women, research addressing safety issues of testosterone therapy in postmenopausal women is needed. The important adverse effects include short-term effects, such as hirsutism, acne, and deepening of the voice, and long-term effects, such as cardiovascular disease, cancers (breast, endometrial, and ovarian) and others. Studied populations should be more specific regarding menopausal type; stratification of menopausal type (surgically induced and natural) before enrollment is essential. In addition to safety, potential benefits should be directly investigated, including sense of well-being, unexplained fatigue, bone health (BMD and fracture rate), and cognition.

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