Journal of Steroid Biochemistry & Molecular Biology 142 (2014) 107–114

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Androgen treatment of postmenopausal women☆

Susan R. Davis*, Roisin Worsley

Women's Health Research Program, School of Public Health and Preventive Medicine, Department of Epidemiology and Preventive Medicine, Monash University, 99 Commercial Road, Melbourne, VIC 3004, Australia

ARTICLE INFO

Article history:
Received 14 November 2012
Received in revised form 12 April 2013
Accepted 18 May 2013
Available online 29 May 2013

Keywords:
Androgens
Postmenopausal women
Sexual dysfunction
Hypoactive sexual desire disorder

ABSTRACT

Testosterone is physiologically important for women. Serum testosterone levels decline with age, with the most precipitous fall being prior to menopause. There is no level of testosterone which defines a woman as being testosterone deficient. However, there is substantial high quality evidence to support the use of testosterone for the treatment of hypoactive sexual desire disorder in postmenopausal women. Although preliminary data suggests testosterone has favorable effects on bone and muscle mass, cognitive function and the cardiovascular system, further research regarding its therapeutic effects in these domains is warranted. As no testosterone product has been approved for women there is extensive off-label prescribing of testosterone products for women as well as the prescription of compounded therapy. This raises serious safety concerns and together with the evidence for the negative impact of FSD on quality of life, highlights the need for an approved testosterone formulation for women.

This article is part of a Special Issue entitled 'Menopause'.

Contents

1. Introduction

Androgen therapies are widely used by menopausal women regardless of the ongoing controversy surrounding their place in the medical armament [1]. High quality randomized controlled

☆ Dr. Davis is an Australian NHMRC Principal Research Fellow (Grant No. 490939).
* Corresponding author. Tel.: +61 399030827; fax: +61 399030828.
E-mail address: susan.davis@monash.edu (S.R. Davis).

0960-0760/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jsbmb.2013.05.006

trials (RCTs) have demonstrated that testosterone therapy that maintains serum testosterone levels close to the physiological range seen in young women is an effective treatment for low sexual desire in postmenopausal women, women approaching the late reproductive years, and women with ovarian or pituitary failure.

The production of testosterone in premenopausal women is in the order of 0.25 mg per day [2]. Serum testosterone is produced in equal measure by the ovaries and the conversion of pre-androgens, such as androstenedione (A) and dehydroepiandrosterone (DHEA), to testosterone. Testosterone can undergo 5α-reduction to form dihydrotestosterone (DHT). Alternatively testosterone can be aromatized to estradiol in a range of tissues including the brain, adipose, vascular endothelium and bone [3]. Most studies indicate that in many women the ovary produces testosterone even after menopause [4,5–9], though other investigators disagree [10,11].

Two-thirds of circulating testosterone is bound to sex hormone-binding globulin (SHBG), with the remainder bound to albumin and only 1–2% circulating as free testosterone [12]. As a consequence plasma SHBG levels directly effect levels of unbound testosterone, with higher SHBG levels resulting in lower free testosterone.

2. Causes of lower testosterone levels in women

Mean testosterone levels halve between the third and the fifth decades of life as shown in Fig. 1 [6,13]. The main testosterone precursors A and DHEA-S also decline with age.

Iatrogenic causes of low testosterone include hysterectomy [6,14], medical oophorectomy, post-chemotherapy or radiotherapy, use of oral or non-oral suppressive doses of estrogen or glucocorticosteroid therapy. Oral estrogen therapies suppress luteinizing hormone production and increase SHBG levels, thereby reducing both the production of testosterone and the unbound component [15,16]. Likewise, oral glucocorticoids suppress ACTH, reducing adrenal androgen production [17]. Women with reduced ovarian and adrenal androgen production, such as women with hypopituitarism, have markedly lower testosterone levels [18,19].

In the reproductive years, low circulating testosterone levels are also seen in hypothalamic amenorrhea, hyperprolactinemia and premature ovarian failure [20,21].

3. Testosterone and female sexual dysfunction

Despite a lack of correlation between total and free testosterone levels and sexual function [22] or overall wellbeing [23] exogenous testosterone improves sexual problems in women. Female sexual dysfunction (FSD) is complex, for example including disorders of sexual desire, arousal, pleasure and overall satisfaction [24,25]. The largest RCTs have focused on women with hypoactive sexual desire disorder (HSDD) defined as 'persistent or recurrent deficiency or absence of sexual thoughts and fantasies and/or desire for, or receptivity for, sexual activity causing personal distress or interpersonal difficulties' [26].

HSDD occurs in 9–14% of postmenopausal women [27].

HSDD is associated with reduced health-related quality of life to a similar extent as that seen in women with diabetes or chronic back pain [28].

4. Testosterone therapy for HSDD

The early studies demonstrating efficacy of testosterone in postmenopausal women with FSD (as opposed to HSDD) were small and involved the use of testosterone implants [29] or injections [30]. A single blind study that compared estradiol implants alone versus estradiol plus testosterone implants in postmenopausal women experiencing lowered libido found sustained benefits of the addition of testosterone when women were assessed by a validated sexual function questionnaire every 6 months over 2 years [31]. Similar benefits of oral methyltestosterone (methylT) therapy were subsequently reported [32–34]. However concerns that oral methyl T lowers HDL-cholesterol and may increase weight and visceral fat accumulation [35,36] has resulted in diminished interest in its use and the development of non-oral testosterone therapies for women. The most extensively investigated therapy has been the transdermal testosterone patch (TTP) which delivers 300 mcg of testosterone per day. Although the TTP as a treatment for HSDD was studied first in surgically menopausal women using oral estrogen, it has been shown to be efficacious in both naturally and surgically menopausal women taking oral and non-oral estrogen or not using concurrent estrogen. A Cochrane Review found that sexual function was improved in postmenopausal women given testosterone therapy in addition to standard hormone therapy [36].

The research into the TTP followed the guidelines set out by the Food and Drug Administration of the USA (FDA). For evidence that testosterone therapy was an effective treatment for HSDD, the FDA required the primary outcome to be the frequency of satisfactory sexual events determined by the treated woman. Study participants kept a daily diary documenting each sexual event and stating whether it was 'satisfactory' or not. Women not in a monogamous ongoing relationship and women found to be depressed or experiencing poor relationship satisfaction were excluded from these large RCTs. Women continue to engage in sexual activity despite low desire, such that the number of sexual events is a poor measure of a woman's sexual satisfaction [37]. Determination of treatment efficacy needs to address aspects of sexual function important to the woman rather than just a count of total sexual events.

In two large studies of the TTP versus placebo in surgically menopausal women on oral estrogen therapy, the increase in the number of satisfying sexual events per month was from 3 times per month to 5 times per month with active therapy [38,39]. In the active arm of these large trials personal distress decreased by 65% and 68% in comparison with 40% and 48% with placebo. Testosterone therapy improved sexual function across all domains. Naturally menopausal women with HSDD on oral estrogen had an increase in their 4-week frequency of satisfying sexual events with TTP 300 mcg/day of 1.92 compared with placebo, 0.5, accompanied by increases in the other domains of sexual function assessed and decreased distress [40]. Similar results are seen in postmenopausal women treated with transdermal estrogen and those not using any concurrent estrogen therapy in randomized controlled trials (RCTs) [41–43].

Whilst the general emphasis has been on the development of testosterone as a treatment for postmenopausal women, testosterone levels do not decline with natural menopause. So, women who have lowered testosterone in their early postmenopausal years would have had lowered testosterone in their late reproductive years. Therefore the argument for treating women with HSDD in their late reproductive years with testosterone is as strong as for treating naturally menopausal women and HSDD with testosterone. Two placebo-controlled RCTs have also shown transdermal testosterone improves the frequency of satisfactory sexual events and other parameters of sexual wellbeing in older premenopausal women presenting with loss of libido [44,45].

Overall, the currently available clinical data suggests that transdermal testosterone therapy has a useful part to play in the management of women with problems of sexual desire or arousal.

Testosterone also has vasodilatory effects [46], enhancing vaginal blood flow and lubrication with sexual arousal [47,48]. Whether the vaginal effects of testosterone are due to direct testosterone action or aromatization in vaginal tissues is not known [49]. In postmenopausal women treated with a stable dose of transdermal estradiol, the effects of testosterone therapy