



Hormonal profile of menopausal women receiving androgen replacement therapy: a meta-analysis

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Abstract

Purpose Ovarian and adrenal aging leads to a progressive decline in androgen levels and deleterious effects on the quality of life. Despite this, specific replacement is not routinely recommended in the management of women with a physiological or pathological decline in their production, mainly due to the lack of long-term follow-up safety data. The purpose of this paper was to meta-analyze and summarize the existing data about hormonal profile changes in menopausal women receiving androgen replacement treatments. Full-text articles published through May 30, 2018 were found via MEDLINE and Embase and selected according to the strict inclusion criteria.

Methods Randomized clinical trials and case–control studies were enrolled. Studies not reporting steroid serum levels or not providing a control group were excluded from the analysis. Studies enrolling women with genetic defects or severe chronic systemic diseases were excluded. 113 papers fulfilled the inclusion criteria and 56 papers were included in the analysis. Desired data were compiled and extracted by independent observers.

Results Androgen administration increases E1, E2, testosterone, DHEA and DHEAS serum levels, and reduces SHBG. However, the E1 and E2 increase is evident only when DHEA is administered.

Conclusions Whatever androgen formulation we choose in postmenopausal women, the end result is a rise in testosterone serum levels. However, DHEA regimen is also associated with an increased estrogenic availability. This might be crucial when choosing the best possible treatment for each patient individually taking into consideration if potential benefits outweigh the risks.

Keywords Menopause · Androgens · DHEAS · Estradiol · Testosterone · Androgen replacement therapy

Introduction

In the last two centuries, an impressive progress in medicine and quality of life has been detected, contributing to a markedly prolonged life span. Considering that the average age of menopause is around 51 years of age, women today will spend more than one-third of their lifetime after menopause [1, 2]. Natural menopause represents a significant milestone in women's life and endocrinologically wise, it means that women will spend this period in a hormone deficiency state.

In the literature, there is a large evidence of the deleterious consequences of the deficiency of the main female hormone, estradiol. Estrogen deficiency impairs quality of life, mainly through vasomotor symptoms (VMS), increases the incidence of major cardiovascular events, dementia and osteoporosis, and, if not treated, overall accelerates aging [3].

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Decline of testosterone levels starts much earlier than menopause and together with adrenal aging and linear fall of dehydroepiandrosterone sulfate (DHEAS) leads to an overall progressive decline in androgens levels. Physiologically, steroidogenesis occurs in both ovaries and adrenals, in which C-19 steroids, DHEA, androstenedione and testosterone are produced [4]. C-19 steroids derive from C-21 precursors and are subsequently converted to C-18 steroids, e.g., the estrogens [5]. DHEA serum levels decrease with increasing age and they are reduced by 60% after menopause [6]. Similarly, a 55% decline in serum testosterone levels is detected at the age of menopause [7]. In menopausal women, about 80% of the serum DHEA is of adrenal origin and approximately 20% originates from the ovaries [1]. On the other side, ovaries are main sources of testosterone production, increasing from 25 to 50% from fertile to postmenopausal woman. However, the final testosterone levels decrease with age due to the inability of ovaries to compensate the decrease of the adrenal production of the testosterone prohormones (DHEA and its sulfate, DHEAS) [8, 9].

As well as estrogen deficiency, androgen insufficiency is also demonstrated to be associated with deleterious effect on the quality of life [10]. In particular, sexual dysfunction, low libido, cognitive decline, low energy, vasomotor instability, bone loss, decreased muscle strength, and changes in cognition or memory are most frequently observed [11]. In the genitourinary system and pelvic floor, androgens are important for the maintenance of the structure and function of the tissues, and the lack of androgenic activity contributes to symptoms of the genitourinary syndrome of menopause (GSM), including dysuria, recurrent urinary tract infections, vaginal dryness, poor arousal and dyspareunia [12].

Despite the crucial role of androgens, specific replacement is not routinely recommended in the management of women with a physiological or pathological (i.e., due to premature ovarian insufficiency, surgical menopause or hypopituitarism) decline in their production, mainly due to the lack of long-term follow-up safety data. In 2014, the Endocrine Society Guidelines recommended against making a clinical diagnosis of “androgen deficiency syndrome” in healthy women, because of the lack of a well-defined syndrome [13]. The primary indication for the prescription of androgens in postmenopausal women remains loss of sexual desire causing significant distress (hypoactive sexual desire disorder, HSDD).

Studies of transdermal testosterone have consistently shown efficacy of HSDD treatment in both naturally and surgically postmenopausal women, either alone or in combination with the estrogen therapy [14]. Conversely, systematic reviews and meta-analyses have found no statistically significant benefit of systemic DHEA on female sexual function; no significant effect of DHEA on serious adverse effects was observed either [15].

Recently, a systematic review and meta-analysis on the safety and efficacy of testosterone treatment in women was published followed by a Global Consensus Position Statement on the use of testosterone therapy for women. The authors showed and agreed that non-oral administration of testosterone to menopausal women with low sexual desire causing distress is effective and safe with no severe side effects noted [16, 17]. Further, they pointed that all registered testosterone formulation are for men and that there was no approved testosterone formulation in any country [16, 17]. Finally, the authors highlighted the need for more research into testosterone treatment for women [17].

Surprisingly, current literature lacks a systematic investigation of hormonal profile changes in women receiving androgen replacement treatments. Thus, the aim of our meta-analysis was to evaluate and summarize the existing data about hormonal profile changes in menopausal women receiving androgen replacement treatments, considering all available androgens formulation and regimens.

Materials and methods

This meta-analysis was performed according to the Cochrane Collaboration and PRISMA statement. To ensure originality and transparency of the review process, the meta-analysis was first registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration ID CRD42018099414).

Literature search was performed considering the following criteria in MEDLINE and Embase databases: (((((((menopause) OR postmenopause) OR post menopause) OR menopausal) AND women) OR woman) OR female) AND testosterone administration) OR androgen administration. All studies published until May 30, 2018 were considered.

Study selection and inclusion criteria

The following inclusion criteria were searched: (1) all androgens formulations, (2) interventional study design, (3) comparison with a control group, and (4) evaluation of steroid serum levels. The randomization of patients was not considered an inclusion criterion, thus both randomized clinical trials (RCT), and case-control studies were enrolled.

Studies not reporting steroid serum levels or not providing a control group were excluded from the analysis. Moreover, studies enrolling women with genetic defects (i.e., Turner syndrome) or severe chronic systemic diseases (i.e., severe heart failure) were excluded.

Data collection process and quality

Two authors (DS and GS) performed separately literature search and extracted the abstracts of studies of interest. All abstracts were evaluated for inclusion criteria and the data were extracted from each study that was considered eligible, with regard to the design of the study, year of publication and number of included/excluded subjects. Moreover, the inclusion criteria of each study were evaluated to highlight the etiology of menopause (natural vs. surgical). Also, the laboratory method used to measure hormonal parameters was extracted for each included study. DS, GS, ASS, LM and SP performed quality control checks on extracted data. Data were extracted using steroid serum levels as primary end points, considering estrone (E1), estradiol (E2), sex hormone-binding globulin (SHBG), testosterone, DHEA, DHEAS, androstenedione, 3 α -diol-3G, 3 α -diol-17G, ADT-G, free androgen index and serum weekly bound estradiol.

Secondary end points were cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), serum albumin, insulin-like growth factor (IGF)-1, IGF-2, IGF-binding protein (IGFBP)-3 and IGFBP-1.

Data synthesis and analysis

Data were extracted only if the measured parameter was assessed in at least three different studies. Using the Review Manager (RevMan) 5.3 Software (Version 5.3.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), continuous variables were comprehensively evaluated as inverse variance of mean variables. Dichotomous variables were comprehensively evaluated using Mantel–Haenszel method. The fixed model was initially chosen, whereas the random effect model was preferred in case of I^2 higher than 60%. The degree of heterogeneity among the results of different studies was examined by inspecting both the scatter in the data points and the overlap in their confidence intervals (CIs) and by performing I^2 statistics. Weighted mean differences and 95% CIs were estimated for the literature search. Standard mean difference was considered when standard deviation showed higher heterogeneity among studies included in the analysis. Values of $p < 0.05$ were considered statistically significant.

All evaluated papers were further analyzed with regard to the studies reported in the manuscript. Thus, different drug dosages, routes and schedules of administration were separately considered. The analysis was performed comparing patients to controls after treatment. Sensitivity analyses were performed considering the androgen used in the trials, distinguishing among DHEA, androstenedione and testosterone administration. Moreover, a second sensitivity analysis was performed, considering the assay

accuracy. In particular, studies using mass spectrometry were considered to be highly accurate, whereas studies using immunoassays were considered to have low accuracy. Finally, a third sensitivity analysis was performed dividing studies according to the nature of menopause: physiological versus surgical.

Results

We identified 24,549 papers by the literature search. Among these, 107 papers fulfilled the inclusion criteria and were evaluated for data extraction. Sixty-five papers were finally analyzed for data extraction (Table 1). Among these, 53 papers were included in the analysis and data were extracted from 83 different trials (Table 1). Figure 1 shows the study flowchart.

Among studies included, seven studies used mass spectrometry to measure hormones; thus, only 12.5% of the studies included were considered highly accurate. Further, 13 studies (23.2%) enrolled postmenopausal women after ovariectomy, thus 76.8% of all studies enrolled women with physiological menopause.

Effect of androgen therapy on estrone (E1) levels in menopausal women

Seventeen papers reported data on E1 levels comprising a total of 3553 patients (1757 treated women vs. 1796 controls). E1 serum levels were significantly higher in treated patients compared to the controls (11.21 pg/mL, 95% CI 7.71, 14.72 pg/mL, $p < 0.001$) (Fig. 2). The level of estrone was only affected by DHEA treatment (11.21 pg/mL, 95% CI 7.67, 14.99 pg/mL, $p < 0.001$), but not when testosterone (11.46 pg/mL, 95% CI – 3.14, 26.06 pg/mL, $p = 0.12$) or androstenedione (8.79 pg/mL, 95% CI – 11.74, 29.33 pg/mL, $p = 0.400$) was administered (Fig. 2).

The second sensitivity analysis was available only for the DHEA administration. E1 serum levels were significantly higher in women treated with DHEA considering both accurate (8.63 pg/mL, 95% CI 7.19, 10.06 pg/mL, $p < 0.001$) and non-accurate studies (19.51 pg/mL, 95% CI 3.39, 35.63 pg/mL, $p = 0.020$).

The third sensitivity analysis was available only for testosterone administration and not for DHEA or androstenedione treatments. Estrone serum levels did not change between treated and untreated women considering both physiological menopause (5.59 pg/mL, 95% CI – 22.44, 33.62 pg/mL, $p = 0.700$) and menopause after ovariectomy (12.00 pg/mL, 95% CI – 2.87, 26.86 pg/mL, $p = 0.110$).

Table 1 Studies analyzed for data extraction after the literature search

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group		Control group					
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Fernandes	2018	RCT	Hormones, metabolism	ELISA	PM	Testosterone propionate	900 mcg 3 times a week	IV	20	56.2±5.3	Placebo	20	57.7±4.7
Golebiewski	2017	RCT	Hormones, ocular symptoms	ELISA	PM	Testosterone	1% testosterone cream	T	10	63.1±4.1	Placebo	11	66.1±4.0
Espinosa De Ycaza	2016	RCT	Hormones, systemic lipolysis	CI	PM	DHEA	50 mg	Oral	30	68 (66–69)	Placebo	30	69 (65–75)
Labrie	2016	RCT	Hormones	MS	PM	DHEA	6.5–13–23.4 mg/day	IV	10	61 (53–69)	Placebo	10	–
Ke	2015	RCT	Hormones	MS	PM	DHEA	6.5–12.5–25 mg/day	IV	325	52±5	Placebo	157	40–80
Davis	2014	RCT	Hormones, psychometric parameters	CI	PM	Testosterone	0.22 gr/day	T	47	61 (57–63)	Placebo	45	60 (58–63)
Huang	2014	RCT	Hormones, sexual function, physical function	MS	Ovariectomized	Testosterone enanthate	3–6.25–12.5–25 mg/week	IM	12	54±5	Placebo	13	53±5
Labrie	2013	RCT	Hormones	MS	PM	DHEA	6.5 mg/day	IV	10	61 (53–69)	Placebo	10	–
Caufriez	2013	RCT crossover	Hormones, sleep analysis	CI	PM	DHEA	50 mg/day	Oral	7	48–74	Placebo	7	48–74
Merritt	2012	RCT crossover	Hormones, psychometric parameters	CI	PM	DHEA	50 mg/day	Oral	48	63.5±6.8	Placebo	48	63.5±6.8
Kocoska-Maras	2011	RCT	Hormones, psychometric parameters	CI	PM	Testosterone undecanoate	40 mg/day	Oral	67	58.3±4.2	Placebo	67	58.1±4.0
Kenny	2010	RCT	Hormones, bone density, physical function	CI	PM	DHEA + aerobics or yoga	50 mg/day	Oral	49	76.4±6.2	Placebo + aerobics or yoga	50	76.9±5.8

Table 1 (continued)

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group			Control group				
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Boxer	2010	RCT	Hormones, metabolism, body composition	CI	PM	DHEA + aerobics or yoga	50 mg/day	Oral	49	76.4 ± 6.2	Placebo + aerobics or yoga	50	76.9 ± 5.8
Ziaei	2010	RCT	Hormones, bone density	CI	PM	Tibolone + calcium/vitD	2.5 mg/day + 500 mg/200 IU	Oral	46	51.4 ± 3.0	Calcium	49	52.3 ± 4.4
Panay	2010	RCT	Hormones, sexual function, physical function	CI	PM	Testosterone	300 mcg/day	T	130	56.2 ± 5.5	Placebo	142	57.0 ± 5.2
Srinivasan	2010	RCT	Hormones, metabolism, body composition	CI	PM	DHEA	50 mg/day	Oral	19	68 (65–69)	Placebo	30	70 (66–75)
Kocoska-Maras	2009	RCT crossover	Hormones, inflammatory markers	RIA	Ovariectomized	Estradiol valerate + testosterone undecanoate	2 mg + 40 mg	Oral	50	45–60	Estradiol valerate + placebo	50	45–60
Chapman	2009	RCT	Hormones, metabolism, body composition	CI	PM	Testosterone undecanoate	40 mg/day	Oral	6	78 ± 3	Placebo	7	74 ± 2
Stanczyk	2009	RCT	Hormones	RIA	PM	DHEA	25 mg/day	Oral	10	55–65	Placebo	10	55–65
Labrie	2008	RCT	Hormones	MS	PM	DHEA	6 gr/day	T	73	60–65	Placebo	74	60–65
Jankowski	2008	RCT	Hormones, bone density	RIA	PM	DHEA	50 mg/day	oral	25	69.3 ± 7.5	Placebo	33	69.1 ± 6.4
Petzel	2008	Case-control	Hormones	ELISA	Ovariectomized	Tibolone	2.5 mg/day	Oral	10	–	No therapies	22	–
Labrie	2008	RCT	Hormones, vaginal epithelial cells	MS	PM	DHEA	6.5–13–23.4 mg/day	IV	10	40–75	Placebo	10	40–75

Table 1 (continued)

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group			Control group				
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
von Mühlen	2008	RCT	Hormones, bone density, body composition	RIA	PM	DHEA	50 mg/day	Oral	57	68.9±8.1	Placebo	58	68.5±6.7
Igwebuike	2008	RCT	Hormones, body composition, physical function	CI	PM	DHEA+exercise training	50 mg/day	Oral	17	54–72	Placebo+exercise training	14	54–72
De Paula	2007	RCT	Hormones, metabolism, cardiovascular risk factors	CI	PM	Conjugated equine estrogen + medroxyprogesterone acetate + methyltestosterone	2.5 mg/day	Oral	85	55.4±4.7	Estrogens + medroxyprogesterone acetate + placebo	85	56.6±4.9
El-Hage	2007	RCT crossover	Hormones, sexual function	CI	Ovariectomized	Testosterone	10 mg/day	T	18	54	Placebo	18	54
Barton	2007	RCT crossover	Hormones, sexual function	CI	PM	Testosterone	10 mg/day	T	75	52.2±7.9	Placebo	75	52.3±7.9
Hofling	2007	RCT	Hormones	CI	PM	17β-estradiol + norethisterone + testosterone	2 mg + 1 mg + 30 mcg/day	T + oral	50	55.2	17β-estradiol + norethisterone + placebo	49	54.7
Basu	2007	RCT	Hormones, metabolism	CI	PM	DHEA	50 mg/day	Oral	27	68.4±0.6	Placebo	29	70.4±0.8
Heard-Davison	2007	RCT crossover	Hormones, sexual function	CI	PM	Methyltestosterone	5 mg in single dose	Oral	5	50–62	Placebo	5	50–62
Labrie	2007	RCT	Hormones	MS	PM	DHEA	3 g	T	15	60–65	Placebo	15	60–65
Nair	2006	RCT	Hormones, metabolism, bone density, body composition	CI	PM	DHEA	50 mg/day	Oral	27	68.4 (65.6–71.3)	Placebo	30	70.4 (65.6–74.5)

Table 1 (continued)

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group		Control group					
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Shifren	2006	RCT	Hormones, sexual function	RIA	PM	Testosterone	300 mcg/day	T	276	53.9±4.8	Placebo	273	54±4.9
Davis	2006	RCT	Hormones, sexual function	RIA	Ovariectomized	Testosterone	300 mcg/day	T	37	51 (38–66)	Placebo	40	49.3 (30–63)
Jankowski	2006	RCT	Hormones, bone density, body composition	RIA	PM	DHEA	50 mg/day	Oral	34	68.3±7.3	Placebo	36	68.4±6.5
Leau	2006	RCT	Hormones, metabolism, bone density	RIA	Ovariectomized	Estradiol + methyltestosterone	1 mg + 1.25 mg/day	T + oral	16	54.1±4.8	Estradiol + placebo	21	52.6±6.3
Nathorst-Böös	2006	RCT crossover	Hormones, metabolic parameters, sexual function	RIA	PM	Testosterone	10 mg/day	T	30	55.4±3.5	Placebo	30	55.4±3.5
Simon	2006	RCT	Hormones, sexual function	RIA	Ovariectomized	Testosterone	300 mcg/day	T	283	49.2±7.7	Placebo	279	48.9±7.4
Braunstein	2005	RCT	Hormones, sexual function	RIA	Ovariectomized	Testosterone	150–300–450 mcg/day	T	106	50.4±8	Placebo	119	48.5±7.4
Dayal	2005	RCT	Hormones, metabolism, body composition	RIA	PM	DHEA	50 mg/day	Oral	12	44–70	Placebo	6	44–70
Frisoli	2005	RCT	Hormones, metabolism, bone density, body composition	CI	PM	Nandrolone decanoate	50 mg/3 weeks	IM	32	74.0±3.8	Placebo	33	76.8±4.0

Table 1 (continued)

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group		Control group					
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Buster	2005	RCT	Hormones, sexual function	CI	Ovariectomized	Testosterone	300 mcg/day	T	266	48.3±7.4	Placebo	266	49.5±7.5
Tidemark	2004	RCT	Hormones, metabolism, bone density, body composition	CI	PM	Nandrolone	200 ml/day	Oral	20	83.5±6.1	Calcium	20	84.1±4.3
Floter	2004	RCT	Hormones, metabolism	CI	Ovariectomized	Estradiol valerate + Testosterone Undecanoate	40 mg/day	Oral	44	54.0±2.9	Estradiol + placebo	44	54.0±2.9
Chiuve	2004	RCT	Hormones, metabolism	RIA	Ovariectomized	Methyltestosterone + esterified estrogens		Oral	40	48 + -8	Esterified estrogens	39	50±7
Gambacciani	2004	Open label	Hormones, bone density	CI	PM	Tibolone	2.5 mg/day	Oral	30	52.3±1.5	Placebo	30	52.9±2.3
Leder	2002	RCT	Hormones	RIA	PM	Androstendione	50–100 mg	Oral	10	57.6±2.7	No drug	10	58.3±4.2
Wisniewski	2002	RCT	Hormones, psychometric parameters	CI	PM	Esterified estrogen + methyltestosterone for 4 months	1.25 + 2.5 mg	Oral	14	59.8±8.3	Esterified estrogen + placebo	13	56.4±5.9
Meeuwssen	2002	RCT	Hormones, psychometric parameters	CI	PM	Tibolone	2.5 mg	Oral	42	54.2±4.7	Placebo	43	54.1±4.1
Penotti	2001	Open label	Hormones, psychometric parameters	CI	PM	Testosterone undecanoate + T E2 + medroxyprogesterone acetate	40 mg/day	Oral	20	57,4	T E2	20	55.3
Legrain	2000	RCT crossover	Hormones	RIA	PM	DHEA	50 or 25 mg/day	Oral	12	67,9±4,3	Placebo	16	67,9±4,3

Table 1 (continued)

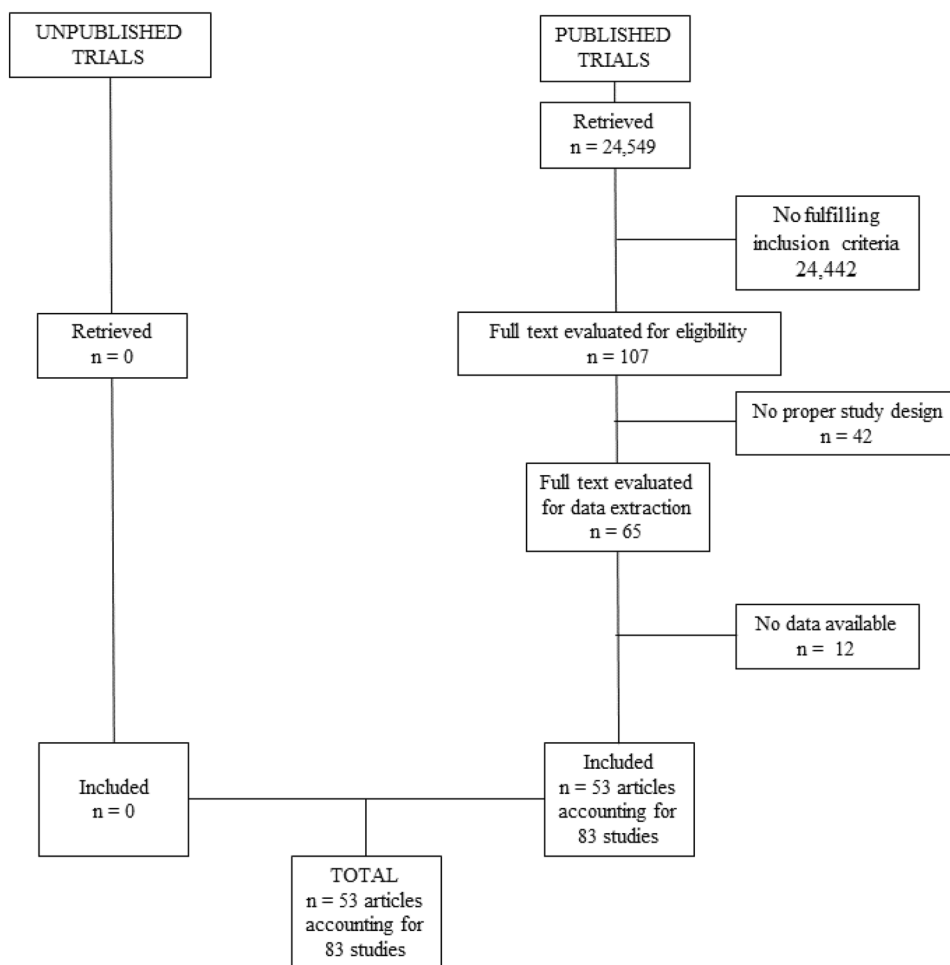
Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group			Control group				
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Shifren	2000	RCT	Hormones, psychometric parameters	CI	ovariectomized	Testosterone + conjugated equine estrogens daily	150 µg/day	T	65	47 ± 2	Placebo	57	47 ± 3
Baulieu	2000	RCT	Hormones, sexual function	CI	PM	DHEA	50 mg/day	oral	35	60–69	Placebo	35	
Castelbranco	2000	Open label	Hormones, metabolism	CI	PM	Estradiol valerate + enanthate of dihydroandrosterone	4 mg + 200 mg	IM	23	53.1	Treatment free	24	53.1
Gruber	1998	RCT crossover	Hormones, psychometric parameters	RIA	PM	Testosterone gel	10 mg	T	27	55.4 ± 3.5	Placebo	26	55.4 ± 3.5
Flicker	1997	RCT	Hormones, metabolism, bone density	CI	PM	Nandrolone	50 mg	Intranasal	32	70.7 ± 7.0	Placebo	30	70.1 ± 6.0
Casson	1995	RCT crossover	Hormones, metabolism, bone density	RIA	PM	Micronized DHEA	50 mg/day	Oral	11	56.1(45–66)	Placebo	11	56.1(45–66)
Savvas	1992	Open label	Hormones, metabolism, bone density	CI	PM	Estradiol, testosterone, norethisterone	75 mg, 100 mg, 150 µg	Oral	10	60	Estradiol, norgestrel	10	60
Paslin	1991	RCT crossover	Hormones, sexual function	CI	PM	Dihydrotestosterone	2%	Topical	5	60	Placebo	5	66.8
Garnett	1991	RCT crossover	Hormones, bone density	CI	PM	E2, testosterone	100 mg	Implant	110	54.7 ± 20	No treatment	254	55 ± 22
Mortola	1990	RCT crossover	Hormones, metabolism	CI	ovariectomized	DHEA	400 mg	Oral	6	46–61	Placebo	6	46–61

Table 1 (continued)

Author	Year	Study design	Outcomes	Laboratory method	Menopause definition	Study group		Control group					
						Drug	Dosages	Route	n	Age (years)	Drug	n	Age (years)
Savvas	1988	Open label	Hormones, bone density	CI	PM	Estradiol, testosterone	50 mg, 100 mg	Oral	37	57.5±6.6	No treatment	36	51.8±4.1
Sherwin	1988	RCT crossover	Hormones, psychometric parameters	RIA	PM	Testosterone, estradiol diethylanthate, estradiol benzoate	150, 7.5, 1 mg	IM	22	47.2±2.7	Placebo	11	47.4±4.8
Sherwin	1988	RCT crossover	Hormones, psychometric parameters	RIA	PM	Testosterone	200 mg	IM	10	45.4	Placebo	10	45.4
Montgomery	1987	RCT	Hormones	CI	PM	Estradiol, testosterone	50, 100 mg	Implant	25	46	Placebo	21	48
Sherwin	1984	RCT crossover	Hormones	RIA	PM	Estradiol, testosterone	4, 8, 69 mg	IM	11	45.3±3.6	Placebo	9	45.3±3.6
Dow	1983	RCT	Hormones, sexual function	CI	PM	Estradiol, testosterone	50, 100 mg	T	20	46.9	Estradiol	20	46.9

DHEA dehydroepiandrosterone, *E2* estradiol, *CI* chemiluminescent immunoassay, *IM* intramuscular, *IV* intravaginal, *MS* mass spectrometry, *PM* physiological menopause, *RCT* randomized controlled trial, *RIA* radio-immuno assay, *T* transdermal

Fig. 1 Study flowchart



Effect of androgen therapy on estradiol (E2) levels in menopausal women

Thirty-three studies comprising 4011 subjects evaluated the effect of androgen therapy on E2 levels in postmenopausal women (1905 treated women vs 2106 controls). E2 serum levels were significantly higher in the treated patients compared to the controls (standard mean difference 1.85 pg/mL, 95% CI 1.36, 2.34 pg/mL, $p < 0.001$) (Fig. 3). Higher E2 serum levels were observed only when subjects were treated with DHEA (standard mean difference 3.73 pg/mL, 95% CI 2.43, 5.04 pg/mL, $p < 0.001$), but not with testosterone (standard mean difference 0.03 pg/mL, 95% CI -0.10 , 0.16 pg/mL, $p = 0.69$) or androstenedione (standard mean difference -0.20 pg/mL, 95% CI -0.82 , 0.43 pg/mL, $p = 0.540$) (Fig. 3). Estradiol mean serum levels (35.09 ± 49.22 pg/ml) remained in a physiological range after androgen treatment.

The second sensitivity analysis was available only for DHEA administration. E2 serum levels were significantly higher in women treated with DHEA considering both studies with high accuracy (5.36 pg/mL, 95% CI 4.19, 6.53 pg/

mL, $p < 0.001$) and low accuracy (1.95 pg/mL, 95% CI 1.05, 2.85 pg/mL, $p = 0.001$).

The third sensitivity analysis was available only for testosterone administration and not for DHEA or androstenedione treatments. Estradiol serum levels did not change between treated and untreated women considering both physiological menopause (0.75 pg/mL, 95% CI -0.30 , 1.79 pg/mL, $p = 0.160$) and menopause after ovariectomy (-0.04 pg/mL, 95% CI -0.13 , 0.06 pg/mL, $p = 0.450$).

Effect of androgen therapy on sex hormone-binding globulin (SHBG) levels in menopausal women

SHBG values were reported in 26 studies. A total of 3349 subjects were included (1652 patients in study group vs 1697 controls). SHBG serum levels were significantly lower in treated patients compared to the controls (-15.35 nmol/L, 95% CI -24.96 , -5.75 nmol/L, $p = 0.00001$) (Fig. 4). The effect of androgen administration on SHBG serum levels was observed with testosterone (-23.07 nmol/L, 95% CI -30.75 , -15.39 nmol/L, $p < 0.001$), but not with DHEA

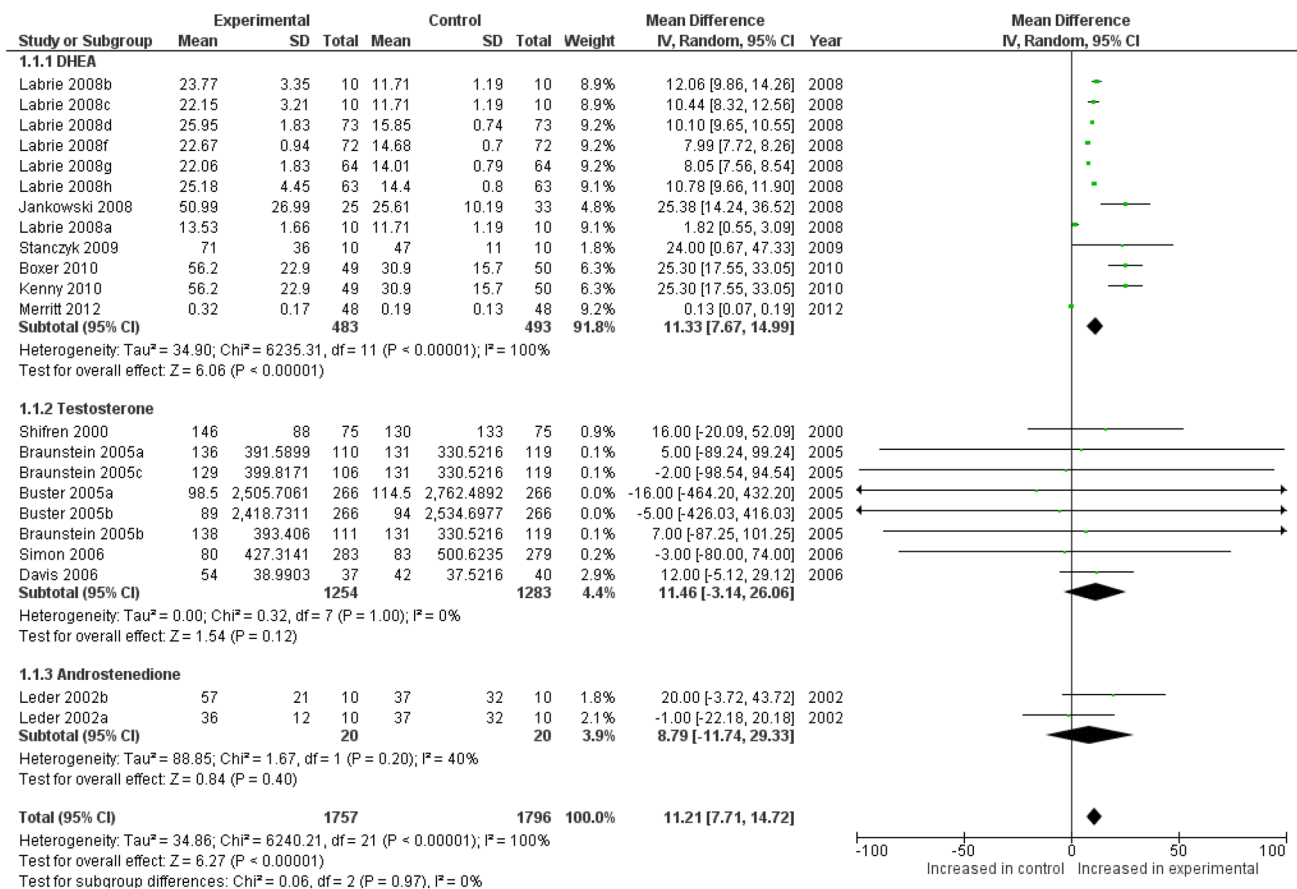


Fig. 2 Forest plot comparing estrone (E1) serum levels between experimental and control groups

(-4.21 nmol/L, 95% CI $-9.98, 1.55$ nmol/L, $p = 0.150$) administration/treatment (Fig. 4).

The second sensitivity analysis was not available for this end point, since all included studies used non-accurate laboratory assays.

The third sensitivity analysis was available only for testosterone administration and not for DHEA or androstenedione treatments. SHBG serum levels were significantly lower in treated than untreated women considering ovariectomized patients (-22.14 pg/mL, 95% CI $-28.90, -15.38$ pg/mL, $p < 0.001$), but not in physiological menopause (-19.01 pg/mL, 95% CI $-41.3, 3.25$ pg/mL, $p = 0.090$).

Effect of androgen therapy on testosterone levels in menopausal women

Testosterone values were reported in 57 studies. A total of 4151 subjects were included (2054 patients in study group vs 2097 controls). Testosterone serum levels were significantly higher in treated patients compared to the controls (131.79 pg/mL, 95% CI 115.36, 148.22 pg/mL, $p < 0.001$) (Fig. 5). This difference remained after we performed the subanalysis of different androgen formulations (Fig. 5).

Testosterone (580.09 ± 457.69 pg/mL) mean serum levels remained in a physiological range after androgen treatment.

The second sensitivity analysis was available only for DHEA administration. Testosterone serum levels were significantly higher in women treated with DHEA considering both accurate (62.10 pg/mL, 95% CI 46.53, 74.67 pg/mL, $p < 0.001$) and non-accurate studies (173.76 pg/mL, 95% CI 114.10, 233.43 pg/mL, $p < 0.001$).

The third sensitivity analysis was available only for testosterone administration and not for DHEA or androstenedione treatments. Testosterone serum levels were significantly higher in treated than untreated women considering both physiological menopause (314.9 pg/mL, 95% CI 133.3, 496.6 pg/mL, $p < 0.001$) and menopause after ovariectomy (477.0 pg/mL, 95% CI 266.1, 688.0 pg/mL, $p < 0.001$).

Effect of androgen therapy on DHEA levels in menopausal women

DHEA was evaluated in 13 studies (511 patients vs 511 controls), all using DHEA as androgen formulation. DHEA was significantly higher in treated patients compared to the controls (1.87 ng/mL, 95% CI 1.28, 2.46 ng/mL, $p < 0.001$).

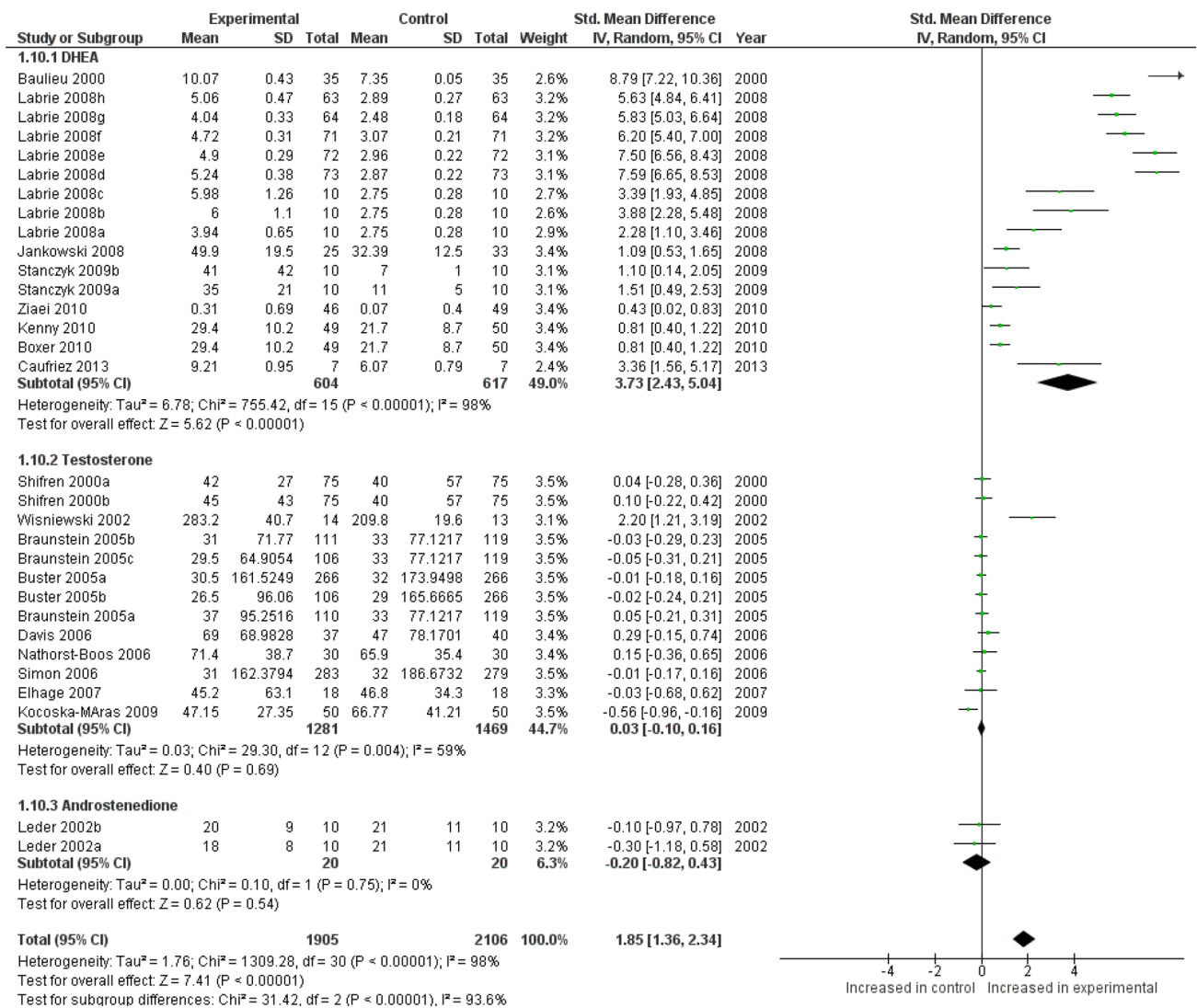


Fig. 3 Forest plot comparing estradiol (E2) serum levels between experimental and control groups

The second sensitivity analysis showed higher DHEA levels in treated patients when hormones were measured with highly accurate assays (2.30 ng/mL, 95% CI 1.61, 2.98 ng/mL, $p < 0.001$), and not when methodologies with low accuracy were used (0.82 ng/mL, 95% CI -0.26, 1.89 ng/mL, $p = 0.140$).

The third sensitivity analysis was not available for this end point, since all included studies evaluated women with physiological menopause.

Effect of androgen therapy on DHEAS levels in menopausal women

DHEAS levels were evaluated in 16 studies (570 patients vs 579 controls), all using DHEA as androgen formulation. DHEA was significantly higher in cases compared to controls

(standard mean difference 1.50 ng/mL, 95% CI 1.36, 1.64 ng/mL, $p < 0.001$).

The second sensitivity analysis showed higher DHEAS levels in treated patients, both when hormones were measured with highly accurate assays (1.42 ng/mL, 95% CI 1.26, 1.59 ng/mL, $p < 0.001$) and methodologies with low accuracy were used (1.67 ng/mL, 95% CI 1.42, 1.92 ng/mL, $p < 0.001$).

The third sensitivity analysis was not available for this end point, since all included studies evaluated women with physiological menopause.

Effect of androgen therapy on androstenedione levels in menopausal women

Androstenedione was evaluated in 15 studies (612 patients vs 608 controls). Androstenedione was significantly higher

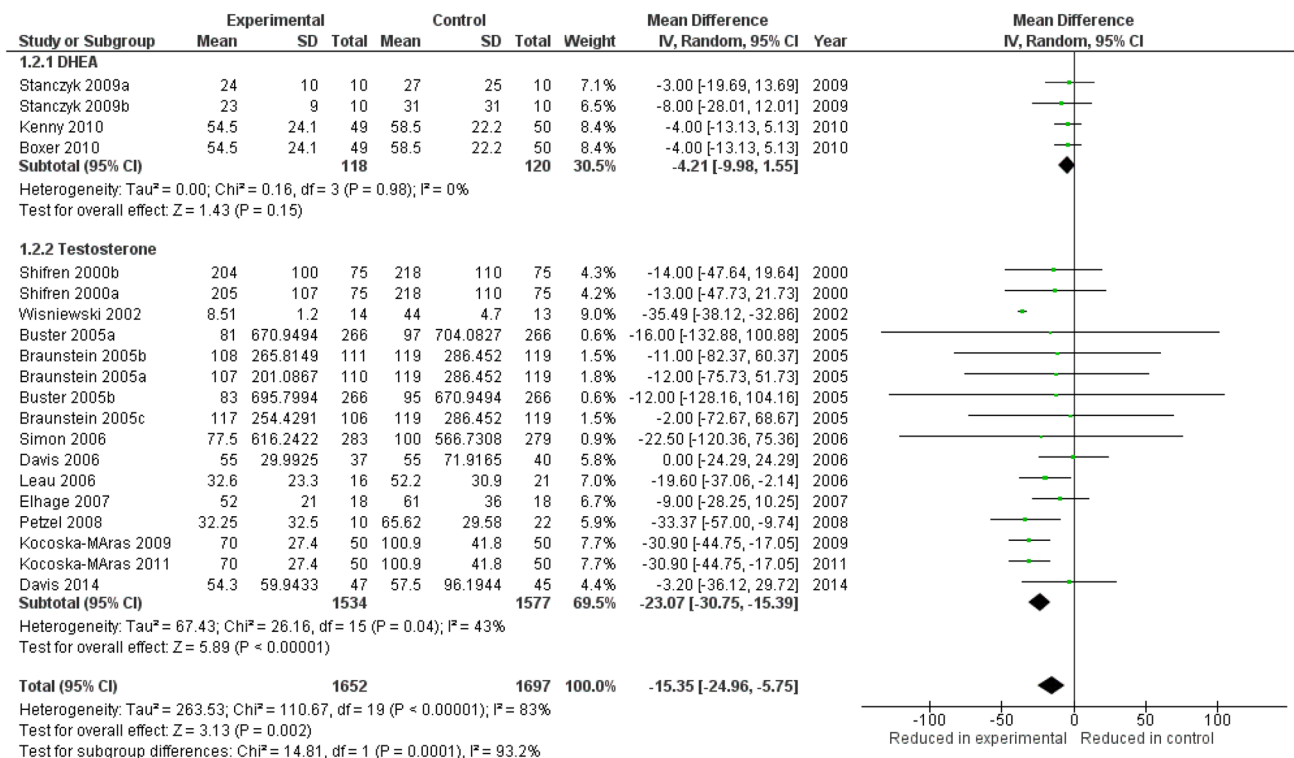


Fig. 4 Forest plot comparing sex hormone-binding globulin (SHBG) serum levels between experimental and control groups

in treated patients compared to the controls (standard mean difference 3.53 pg/mL, 95% CI 1.96, 5.1 pg/mL, $p < 0.001$) (Fig. 6). This comparison remained significant when DHEA ($p < 0.001$) or androstenedione was administered ($p = 0.002$), while testosterone did not significantly change androstenedione levels ($p = 0.330$) (Fig. 6).

The second sensitivity analysis was available only for DHEA administration. Androstenedione serum levels were significantly higher in women treated with DHEA considering both studies with high accuracy (5.80 pg/mL, 95% CI 4.12, 7.49 pg/mL, $p < 0.001$) and low accuracy (1.25 pg/mL, 95% CI 0.56, 1.94 pg/mL, $p = 0.020$).

The third sensitivity analysis was not available for this end point, since all included studies evaluated women with physiological menopause.

Secondary end points extracted were not analysed, since less than three studies evaluated each parameter.

Discussion

This meta-analysis demonstrates that androgen administration is able to modulate serum levels of sexual hormones in postmenopausal women, depending on the type of androgen formulation. Androgen administration increases serum levels of E1, E2, testosterone, DHEA and DHEAS, while it reduces the SHBG levels. However, this effect depends on

the androgen formulation which was used: testosterone or its precursors—DHEA and androstenedione. In particular, the E1 and E2 levels increase was evident only in patients treated with DHEA. This effect is in line with physiological steroidogenesis. In fact, DHEA shows the highest affinity for 3β HSD, which catalyzes the conversion of DHEA to androstenedione that, through the action of gonadal aromatase enzyme (P450aro), is rapidly converted to E1 and E2 [4]. Thus, when DHEA is exogenously administered, it is rapidly metabolized to the final circulating products [18, 19]. On the other hand, androstenedione administration did not affect estrogen levels, although this finding is probably limited by the low number of studies included in this subgroup. Finally, testosterone shows similar affinity to both P450aro and 5α -reductase, therefore a portion of the hormone serves as a precursor for synthesis of estrogens, while the remaining portion is used for dihydrotestosterone (DHT) production [4]. This might be why the final effect of testosterone treatment in postmenopausal women was not an overall increase in estrogen levels. Interestingly, independently of androgen formulation administered to postmenopausal women, the net effect was a rise in total testosterone serum levels.

These findings are of fundamental significance when deciding the type of androgen substitution for menopausal women. Basically, the two compounds differ in that serum DHEA—but not serum testosterone—is the source of intracellular testosterone in women; accordingly, there

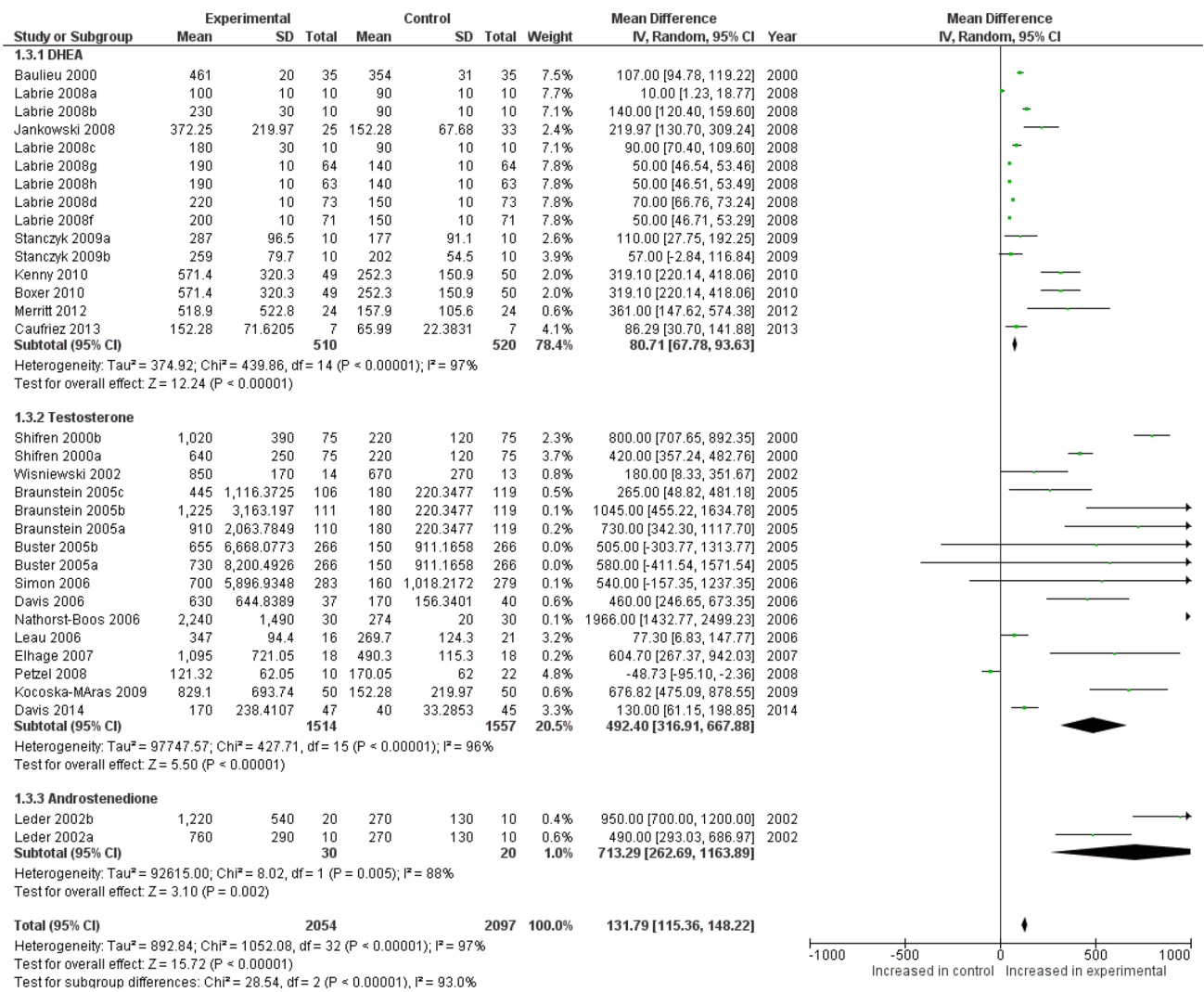


Fig. 5 Forest plot comparing testosterone serum levels between experimental and control groups

is a lack of correlation between circulating testosterone and its effects on androgen-sensitive tissues [2]. The choice between prescribing DHEA or testosterone must be based also on potential benefits as well as adverse effects. Both DHEA and testosterone lead to an increased androgen action, raising total testosterone serum levels and decreasing SHBG. However, DHEA administration is also associated with an increased estrogenic activity. This “side effect” should be considered especially in women with a high baseline risk due to a family history of breast cancer or a biopsy-confirmed high-risk benign breast condition and those with previous breast cancer [20]. Furthermore, it should be considered that, along with the risk of breast cancer, aromatase gene expression increases with age [21]. With regard to androgen signaling, preclinical studies have shown that testosterone has anti-proliferative and pro-apoptotic effects in some breast cancer cell lines

[22]. However, the action of the androgen receptor in different subtypes of breast cancer in humans has not been clarified so far [23]. A recent systematic review on this key safety concern identified only three relevant RCTs on testosterone treatment [24]. Despite their heterogeneity, which prevented a meta-analytic approach, and also several flaws, the main being the incidence of breast cancer not representing the primary end point, these studies suggest that the use of transdermal testosterone to treat HSDD in postmenopausal women does not increase the risk of breast cancer. However, no reported trial has been of sufficient duration to provide definitive conclusions. Similarly, even though DHEA administration results in increased circulating levels of estrogens, there is insufficient long-term evidence to determine the effects of DHEA on the breast [25]. Data on ovarian and endometrial safety with exogenous androgens are also very scarce.

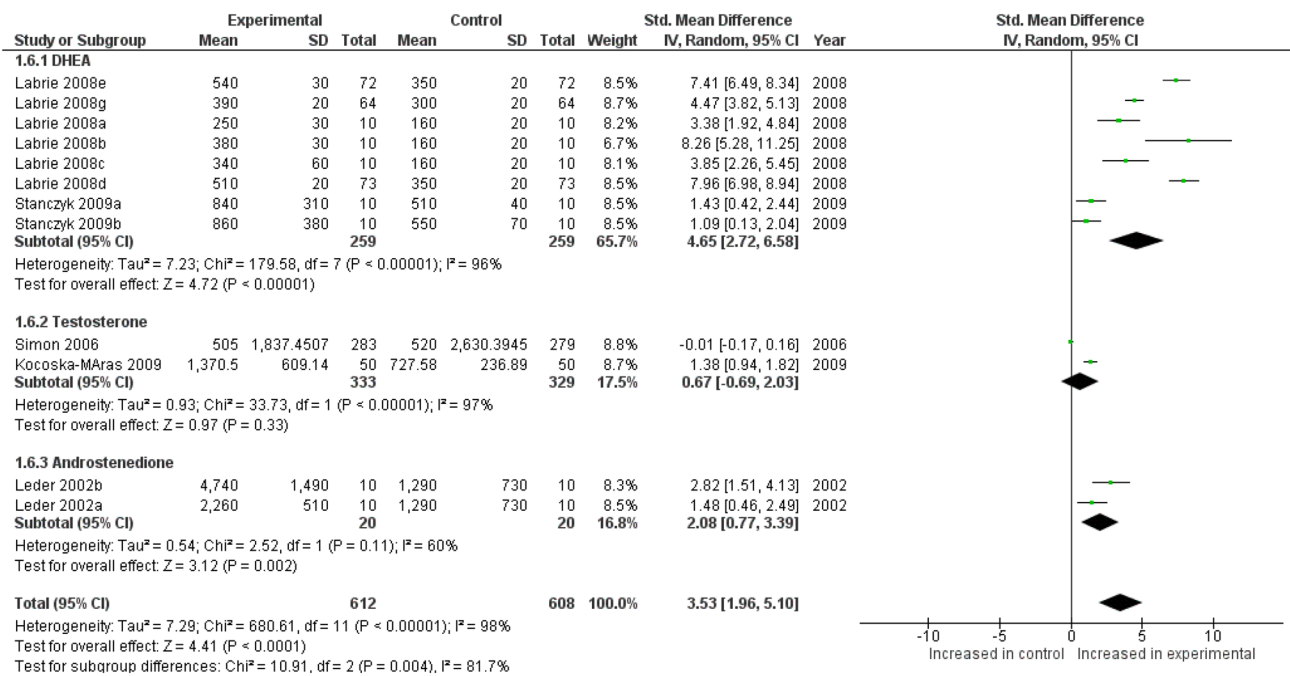


Fig. 6 Forest plot comparing androstenedione serum levels between experimental and control groups

Considering the differences in the accuracy of testosterone measurement between different laboratory techniques (high accuracy techniques—liquid/gas chromatography and tandem mass spectrometry assays vs. low accuracy—direct assays) [17], we performed sensitivity analysis which did not change the overall results of our meta-analysis. Furthermore, another sensitivity analysis was performed which showed that the nature of menopause (surgical vs physiological) did not influence the meta-analyzed levels of sex hormones.

The SHBG levels were significantly lower in patients with physiological menopause receiving testosterone, whereas they did not change in patients receiving DHEA. However, it is important to note that in most of the meta-analyzed studies, the mean baseline levels of SHBG were higher than normal at baseline due to concomitant E2 treatment and remained so at follow-up [26, 27]. Consequently, the SHBG reduction is of uncertain clinical significance. Still, we could speculate that the treatment with testosterone, as opposed to DHEA, is able to modify circulating concentrations of free sex steroids, facilitating their biological activity in target tissues. From a metabolic perspective, low SHBG has recently emerged as an independent marker of insulin resistance and risk of type 2 diabetes, although the causal direction of this association has not been clarified [28]. In postmenopausal women, low concentrations of SHBG, but not high concentrations of total testosterone, are significantly associated with a more adverse lipid and glucose profile [29, 30].

When considering the potential beneficial effects of sex steroids on the peripheral tissues, treatment of

postmenopausal genitourinary symptoms in the last decades involved mainly estrogen-based therapies. Androgens have recently come back in the spotlight as pivotal regulators of genitourinary health in women. In placebo-controlled trials, intravaginal DHEA improved vaginal cytological indexes, dyspareunia and all domains of sexual function and is currently approved in several countries for the management of moderate to severe dyspareunia due to menopause [31]. On the other hand, data for the direct effects of systemic testosterone therapy on urogenital health in women are scant and outdated, whereas data for systemic DHEA therapy on the same outcome are not available [32]. The fact that circulating levels do not reflect the peripheral tissue exposure and sensitivity to androgens, which are thought to be dramatically variable between individuals, according to the genetic differences in receptors and activity of the 5 α -reductase and aromatase enzymes, adds to difficulty in selecting candidates for testosterone treatment. For all these reasons, both the Endocrine Society guidelines [13] and the Findings from the Fourth International Consultation of Sexual Medicine [33] suggest a trial of physiological doses of transdermal T therapy only in case of HSDD.

Overall, like other androgens, DHEA levels decline steeply in the early reproductive years as a consequence of aging [7]. Conversely, during the menopausal transition a rise of DHEAS can be observed, attributed to the action of high levels of LH on the adrenal cortex [34]. However, this phenomenon is not completely understood. Here, we have confirmed the previous evidences that DHEA administration

increases both estrogens and testosterone in postmenopausal women. This is quite different from that in men, in whom after DHEA administration, only an estrogen increase is generally observed [35, 36]. The increased DHEAS serum levels detected after DHEA replacement therapy are further useful considering the suggested neuroprotective effect of this weak androgen. Indeed, circulating DHEAS levels are positively associated with concentration and working memory in women aged 21–77 years [37]. However, a recent meta-analysis did not confirm the beneficial effect of DHEA administration on improving cognitive performance in people older than 50 years with dementia [38], leaving doubts on the real effectiveness of this clinical application. As for the effects of DHEA on sexuality, in 2015 a meta-analysis which compared any dose and form by any route of administration versus any other kind of intervention including placebo in peri- and postmenopausal women found an improvement in sexual function compared to placebo; there were not enough data to undertake meaningful sub-analyses of the various domains of sexual function [25]. It is worth mentioning that several uncontrolled trials showed beneficial endocrine and neuroendocrine effects of oral DHEA/DHEAS supplementation, thereby suggesting a positive pleiotropic role of androgens in women. These effects include increased central and peripheral levels of β -endorphins and neurosteroids (in particular, allopregnanolone) [39, 40] and have been proposed to substantiate the central positive action of postmenopausal DHEA therapy [41].

Noteworthy, our meta-analysis highlighted that both estradiol and testosterone mean serum levels remained in a physiological range after androgen treatment. This could have important implications for safety. Specifically, testosterone levels resulted in the high physiological range for reproductive age (≈ 400 pg/ml) [42], whereas estradiol levels were approximately double of those normally found in menopause (< 20 pg/ml) and similar to levels found after oral hormone replacement therapy (HRT) [43]. This gap also highlights that testosterone circulates at much higher concentrations than estradiol during pre- and postmenopausal years in women, further suggesting its biological significance.

Although there is a body of literature [26, 44] addressing the safety profile of androgen treatment in menopausal women, there is still lack of understanding how the treatment affects sex hormone levels. Resolving this issue will help make final and reliable conclusions on the safety of androgen treatment in menopausal women.

In summary, our meta-analysis is not designed to drive conclusions in favor or against androgen replacement therapy in menopause, but to point out to the hormonal changes, which follow the hormonal administration. Whatever androgen formulation we choose in postmenopausal women; the end result is a rise in testosterone serum levels. However,

DHEA administration is also associated with an increase in estradiol levels. This might be crucial when choosing the best possible treatment for each individual patient taking into consideration if potential benefits outweigh the risks.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals.

Informed consent For this type of study formal consent is not required.

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