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Review

DHEA for postmenopausal women: A review of the evidence

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ABSTRACT

Background: Dehydroepiandrosterone (DHEA) and its sulphate DHEAS are the most abundant sex steroids in women and provide a large reservoir of precursors for the intracellular production of androgens and estrogens in non-reproductive tissues. Levels of DHEA and DHEAS decline with age. It has been proposed that restoring the circulating levels of these steroids to those found in young women may have anti-aging effects and improve sexual function and wellbeing in postmenopausal women.
Aim: To review the published literature for the efficacy of DHEA therapy data regarding safety.
Methods: A systematic literature search of MEDLINE (Ovid) and Pub-Med (1966 to November 2009) for original studies that included any of the terms dehydroepiandrosterone, DHEA or DHEAS, sexual function, wellbeing, women and metabolic parameters of interest.
Results: Overall the interpretation of the data was limited by inadequate sample size and short treatment duration of available studies with inconsistent results. The more recent randomized controlled trials however do not support a benefit of oral DHEA therapy for women. A possible benefit that emerged is that vaginally administered DHEA may improve vaginal atrophy with concomitant improvements in sexual function in women who are estrogen deficient due to menopause. The potential value of oral DHEA therapy for postmenopausal women is called into question.

Contents

1. Introduction

DHEA and its sulphate DHEAS are the most abundant steroids in the human body, however their mechanism of action and physiological implications are not well understood. There is much interest in the possible benefits of administering oral DHEA to postmenopausal women in order to restore serum levels to those of young women. In the USA where the sale of DHEA without prescription has not been restricted by the Food and Drug Administration (FDA), there is considerable off-label or 'over-the-counter' use of DHEA for the purposes of maintaining sexual function, youthfulness, wellbeing and cognition. DHEA is seen as the 'elixir of youth', despite lack of efficacy or safety evidence.

This review will focus on the literature regarding exogenous DHEA therapy for postmenopausal women and the effect on sex-

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ual function, wellbeing and the metabolic parameters lipid and carbohydrate metabolism.

2. Methods

The existing literature was searched using Medline (Ovid) and Pub-Med for original studies. Search terms used included DHEA, DHEAS, dehydroepiandrosterone, dehydroepiandrosterone sulphate, randomized trial, androgen replacement, menopause, libido, wellbeing and lipids, cholesterol, insulin and glucose. We included RCTs that compared DHEA with placebo therapy in women, published as full manuscripts in the English language. The primary outcomes of interest were sexual function, wellbeing, lipids and carbohydrate metabolic effects.

3. The physiology of DHEA/DHEAS

Dehydroepiandrosterone (DHEA) is an important precursor sex steroid secreted in large amounts by the adrenals in humans and other primates but not in lower species. It is not a hormone but is a prohormone or pre-androgen [1]. In women during the reproductive years in addition to the sex steroids testosterone and estrogen, the adrenal glands and ovaries produce DHEA. Its sulphated form dehydroepiandrosterone sulphate (DHEAS) is primarily synthesized by the adrenals, has a longer half-life and provides a stable pool of DHEA. DHEA is converted to estrogen and testosterone in peripheral tissues such as brain, bone, breast and ovaries [2,3]. Most testosterone is made from this pool of precursor DHEA/DHEAS with some synthesized by the ovary [2]. It is controversial as to whether the adrenals directly synthesize testosterone [4]. After menopause the cyclical peaks of androgen production no longer occur [5] although the postmenopausal ovary continues to produce testosterone [6,7]. With increasing age the adrenals are the primary source of both DHEA and DHEAS and therefore indirectly the main source of estrogen and testosterone.

DHEA is synthesized in the adrenals from cholesterol and is converted into 4-dione (androstenedione) and then into potent androgens and/or estrogens in the peripheral cells of tissues (Fig. 1) [8]. The transformation of DHEA into active androgens/estrogens depends upon the level of expression of the various steroidogenic and metabolizing enzymes in each cell type which allows all androgen-sensitive and estrogen-sensitive tissues to control the levels of sex steroids according to local needs. [2] Active androgens and estrogens thus synthesized exert their activity in the cells of origin with little diffusion of the active sex steroids resulting in low levels in the general circulation. This mechanism serves to eliminate the exposure of other tissues to androgens or estrogens, minimizing unwanted side effects [8–10]. The enzyme DHEA-sulphotransferase, found in high levels in adrenal glands but not ovaries, converts DHEA to DHEAS. The further metabolism of DHEA to androstenedione requires another key enzyme 3b-hydroxysteroid dehydrogenase (3b-HSD) [11,12]. Androstenedione is converted to testosterone by 17b-HSD and further to DHT by 5a-reductase. There is subsequent aromatization to estrone and estradiol [8,13]. The active steroids are further metabolized mostly to inactive, conjugated, reduced steroids for excretion. As a result, much of the activity of DHEA via androgens and estrogens occurs intracellularly. This synthesis of active steroids in peripheral target tissues where the action is exerted in the same cells in which synthesis takes place without release to the extracellular space and general circulation is termed intracrinology [14].

Serum levels of DHEA and DHEAS progressively decline with advancing age [3,15] such that by menopause the DHEA level has decreased by 60% [16]. Since DHEA is the main source of androgens in women its decline leads to a corresponding decrease in the total androgen pool. As a result postmenopausal women are "deficient" in both estrogens and androgens [16]. It is thought that the decline in sex steroids is associated with age-related conditions such as loss of libido, low wellbeing and menopausal symptoms [17] as well as conditions such as insulin resistance, obesity and cardiovascular disease [18]. This association between low androgen levels and reductions in mood, general wellbeing and motivation, has been coined "female androgen insufficiency syndrome" [19], however this term remains contentious as there is no defined level of androgen below which women can be said to be deficient exists.

To date a specific DHEA receptor has not been characterized and it is thought that DHEA exerts its action via conversion to androgens and/or estrogens thus interacting with their individual receptors. It remains uncertain whether DHEA exerts any action independently of these mechanisms. Although a specific DHEA receptor has not yet been found there is some evidence for a specific DHEA plasma membrane receptor on bovine aortic endothelial cells [20,21].

Since DHEA is metabolised to both androgens and estrogens, it exerts its action via their receptors. It is proposed that treatment of postmenopausal women with DHEA will mainly result in androgenic effects such as increase in libido and wellbeing via its conversion to testosterone and possibly some estrogenic effects resulting in improvements in menopausal vasomotor symptoms. Previous studies have shown that DHEA administered to postmenopausal women is mainly transformed to androgens rather than estrogens and that there is very little estrogen formation as reflected by estrone sulphate (E1-S) levels [22].

4. Sexual function

It should be noted that problems with sexual function are not limited to women of a particular age group however this review is restricted to postmenopausal women. Population based studies indicate the prevalence of sexual problems among women ranges from 9% to 43% [23]. More specifically Hypoactive Sexual Desire Disorder (HSDD) which is characterized by persistent lack of sexual desire causing personal distress affects 7–26% of community dwelling women [24]. A recent survey of postmenopausal women found that women with HSDD report poorer health status and health related quality of life [25]. Despite evidence suggesting that HSDD is a clinically relevant problem, there is currently no approved treatment for this other than the testosterone patch which is only available in parts of Europe and not available in the USA or Australia.

5. The role of hormones in female sexual function

Knowledge of the role of the sex steroid hormones, estrogens and androgens, in normal female sexual function is limited and is currently the subject of further investigation. In the majority of women, estrogen deficiency associated with menopause results in vasomotor symptoms and vaginal atrophy. During the menopause transition, women can experience cognitive changes and mood volatility possibly as a consequence of night sweats and associated sleep disturbance [26]. The resultant impaired quality of life would likely have a negative impact on sexual function. Vaginal atrophy can result in dyspareunia which can adversely affect sexual function [27]. Taken together it follows that estrogen plays an important role in healthy sexual functioning and that estrogen therapy may improve sexual function by addressing the menopausal problems of vaginal atrophy and vasomotor symptoms [28–31].

Androgens play a role in female sexual functioning. Serum androgen levels have been shown to decrease with age [6] so it is biologically possible that a decrease in sexual functioning may result. Natural menopause is not associated with an abrupt decline

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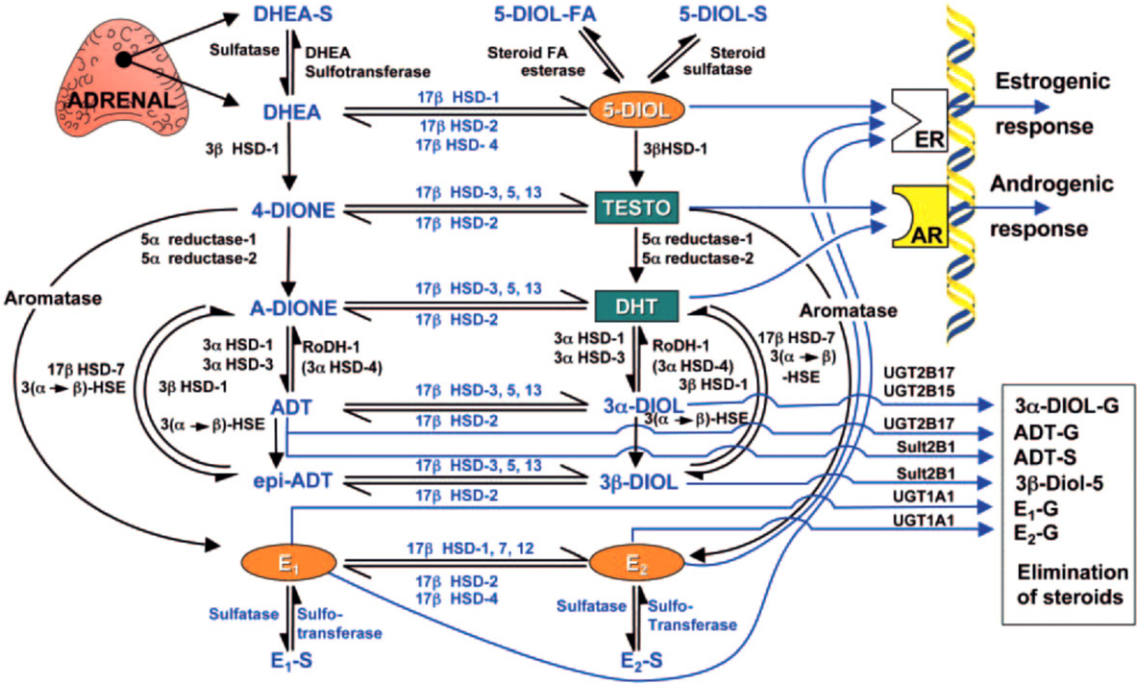

Fig. 1. DHEA metabolism [1].

in serum androgen concentrations, however menopausal women have lower androgens than younger women [32]. Observational studies have demonstrated that sexual function problems increase with age [33,34]. The relationship between androgens and self-reported sexual function in a community based cross-sectional study of 1423 Australian women found that there was no significant association between low serum testosterone (free or total) or androstenedione, and sexual function [35]. An association between serum DHEAS levels and low sexual function was found but the majority of women with low DHEAS did not have low sexual function. However there is much clinical evidence for the efficacy of testosterone treatment for low sexual function [36–41]. The failure to demonstrate that serum levels of DHEAS (or testosterone) were predictive of low sexual function, taken together with the inability to identify a serum androgen level that defines female androgen insufficiency, do not provide support for the use of DHEA therapy to improve sexual function. This can only be substantiated by large, well-designed clinical trials.

To date there are 9 published randomized trials of oral DHEA treatment for low sexual function in healthy, postmenopausal women [18,42–48]. These are summarized in Table 1. Some of the studies demonstrated a positive effect of DHEA treatment on sexual function [18,45,46] while others did not show any benefit [42–44,47,48]. Of the 3 trials where a benefit was shown, two administered supraphysiological DHEA doses and were of short duration [45,46]. The third study was of older aged women and employed a non-validated measure of sexual function which was understood by only 25% of the participants [18]. The early studies in which DHEA was ineffective were also marred by similar issues such as small sample size [42,43], short therapeutic periods [42,44], use of non-validated instruments [42,44], and supraphysiological doses [42].

Recent trials are of superior design to the early trials as they use validated measures of sexual function, have larger sample sizes and are of longer duration. In a recent trial of 50 mg DHEA daily for 52 weeks in 115 older, postmenopausal women, sexual function was assessed by a validated instrument the Female Sexual Function Index (FSFI). No improvements in sexual function were seen [47]. In another trial of 50 mg DHEA daily, sexual function was assessed by 2 methods, a validated questionnaire and a 28-day diary of satisfactory sexual events, no changes in sexual function were observed [48].

It has been hypothesized that the efficacy of DHEA to improve sexual function may be dependent on the route of its administration. Vaginal atrophy and dryness are common symptoms of estrogen deficiency during menopause causing dyspareunia and sexual dysfunction [27]. In a randomized trial of postmenopausal women with vaginal atrophy, DHEA was administered intravaginally for 12 weeks [49,50]. Vaginal atrophy was reversed with minimal changes in serum steroids, which remained within the normal postmenopausal range [49,51]. Beneficial effects on four aspects of sexual dysfunction, desire/interest, arousal, orgasm, and pain at sexual activity were reported for this study [50]. Unfortunately the number of women allocated to each treatment group in this study was small and the study report did not provide any information regarding the number of women in each arm that completed the study. Hence the study findings need to be reproduced in other trials before DHEA can be considered a therapeutic option for the management of vaginal atrophy. Such data suggest that local combined androgenic/estrogenic stimulation in the vagina may exert favorable effects on sexual function in women suffering from vaginal atrophy, without potentially detrimental systemic action on the brain and other tissues. Whether these effects hold for women without vaginal atrophy remains to be investigated.

6. DHEA and wellbeing

As well as loss of libido, women commonly report experiencing fatigue and reduced wellbeing at menopause [52,53]. Some [36,37,54] but not all [38] studies show improvements in wellbeing with testosterone treatment. Given that DHEA is converted to estrogen and testosterone it follows that treatment with DHEA may have a similar beneficial effect on wellbeing. However the data to support the efficacy of exogenous DHEA therapy on wellbeing dur-

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Table 1
DHEA and sexual function.

Authors	Study Design	Duration (weeks)	Dose (mg/day)	Participants—women	Sexual function	Instrument to measure sexual function
Baulieu et al. [18]	RCT double blind placebo parallel	52	50	140 PM (>60y)	Improvement	VAS
Hackbert and Heiman [45]	RCT double blind placebo cross-over	1	300	16 PM (51–68y)	Improvement	FES, DSFI, OFQ, self-report, vaginal photoplethysmograph
Schmidt et al. [46]	RCT double blind placebo cross-over	6	90–450	6 PM	Improvement	DISF
Labrie and Archer [50]	RCT double blind placebo parallel	12	0.25% vaginal 0.5% 1.0%	218 PM	Improvement	ASF, MENQOL,
Panjari et al. [48]	RCT double blind placebo parallel	26	50	93 PM (40–65y)	No change	SSS, SSE diary
Kritz-Silverstein [47]	RCT double blind placebo parallel	52	50	115 PM (55–85y)	No change	FSFI
Mortola and Yen [42]	RCT placebo open label cross-over	4	1600	6 PM (46–61y)	No change	Self-report
Morales et al. [43]	RCT double blind placebo cross-over	24	50	$N = 17$ 2 preM 15 PM (8 on HT) 40–70y	No change	VAS
Wolf et al. [44]	RCT double blind placebo cross-over	2	50	15 PM (69 ± 1.7)	No change	Self report

VAS, Visual Analog Scale; FES, Film Evaluation Scale; DSFI, Derogatis Sexual Functioning Inventory; OFQ, Orgasmic Functioning Questionnaire; FSFI, Female Sexual Function Index; SSS, Sabbattsberg Sexual Self-Rating Scale; SSE, satisfactory sexual events; ASF, Abbreviated Sexual Function; MENQOL, Meonopause-specific Quality of Life

ing menopause is inconsistent. The existing data is summarized in Table 2. The early trials suffered from methodological issues such as small sample size, supraphysiological doses and short treatment duration. Two trials that demonstrated an improvement in mood both used supraphysiological doses of DHEA [46,55]. Of the recent trials none were able to demonstrate a benefit of DHEA on wellbeing [47,48,50,56]. A randomized trial of 57 elderly women (age >60 years) given 50 mg daily DHEA for 24 months showed no improvements in quality of life [56]. In a recently published randomized trial there were no beneficial effects of 50 mg DHEA on mood, quality of life, perceptions of physical and emotional health and life satisfaction [47], likewise another trial of 50 mg DHEA failed to demonstrate improved wellbeing [48]. Despite showing promising, beneficial effects on sexual function, intravaginally administered DHEA failed to show associated improved wellbeing [50].

7. Effects of DHEA on lipids

It has been proposed that exogenous DHEA may influence cardiovascular disease risk primarily by effects on lipoprotein lipids. Research using animal models has shown that DHEA has anti-atherogenic effects [57–59]. There is also a suggestion that DHEA may play a cardio-protective role in men but not women [60,61] which suggests that DHEA exerts its action via conversion to estrogens and androgens. However recently Cheng et al. [59] have provided in vitro data to suggest the possible anti-atherogenic effects of DHEA are not mediated by its conversion to estrogenic or androgenic metabolites but rather via its own bioactivity.

In women, exogenous oral methyl testosterone exerts an adverse effect on the lipid profile such that HDL-cholesterol is lowered [62]. This differs from the effect of exogenous oral estrogen

Table 2
DHEA and wellbeing/quality of life.

Authors	Study Design	Duration (weeks)	Dose (mg/day)	Participants—women	Wellbeing	Instrument to measure wellbeing
Labrie and Archer [50]	RCT double blind placebo parallel	12	0.25% vaginal 0.5% 1.0%	218 PM	No change	PGWB, MENQOL
Panjari et al. [48]	RCT double blind placebo parallel	26	50 mg oral	93 PM (40–65y)	No change	PGWB
Kritz-Silverstein [47]	RCT double blind placebo parallel	52	50 mg oral	115 PM (55–85y)	No change	BDI, SF-36, LSI-Z, SWLS
Nair et al. [56]	RCT double blind placebo parallel	104		57 PM >60y	No change	HSQ, SF-36
Schmidt et al. [46]	RCT double blind placebo cross-over	6	90–450 mg oral	6 PM	Sig. improvement in mood	HDRS, BDI, CDS
Bloch et al. [55]	RCT double blind placebo cross-over	6	90 mg oral (3 weeks) 450 mg oral (3 weeks)	3 PM (45–63y)	Sig. improvement in mood	BDI, HDRS, CDS
Wolf et al [44]	RCT double blind placebo cross-over	2	50 mg oral	15 PM (69 ± 1.7) (4 HT)	NS improvement in mood and wakefulness	QOL Mood questionnaire CESDS

BDI, Beck Depression Inventory; HDRS, Hamilton Depression Scale; CDS, Cornell Dysthymia Scale; PGWB, Psychological General Wellbeing Index; SF-36, The Medical Outcomes Study 36-item Short Form Survey; LSI-Z, Life Satisfaction Index-Z; SWLS, Satisfaction with Life Scale; HSQ, Health Status Questionnaire.

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Table 3
The effect of DHEA on blood lipids and insulin sensitivity.

Authors	Study Design	Duration (weeks)	Dose (mg/day)	Participants	Effects on blood lipids	Effects on insulin sensitivity
Mortola and Yen [42]	RCT placebo open label cross-over	4	1600 oral	6 Postmenopausal 46–61y	Sig ↓HDL-C 20%, total cholesterol 11.3% ns ↓TG, LDL-C	Sig ↑ Insulin resistance 20%
Morales et al. [43]	RCT double blind placebo cross-over	24	50 oral	*N* = 17 2 premenopausal 15 menopausal (8 on HT) 40–70y	Sig ↓HDL-C no ΔLDL-C, total cholesterol, TG	No Δ insulin sensitivity
Diamond et al. [95]	DHEA only	52	300–500 transder-mal cream	15 postmenopausal 60–70y	ns ↓ HDL-C 8–9%, ↓Cholesterol	Inhibitory effect on fasting glucose and insulin
Morales et al. [74]	RCT double blind placebo cross-over	24	100 oral	8 postmenopausal women 50–65y (7 using HT) (include 8 men)	ns ↓ HDL-C −0.15 ± 0.08 (mean diff ± SEM)	No Δ insulin sensitivity
Casson et al. [68]	RCT double blind	24	25 oral	13 postmenopausal women	Sig ↓ HDL-C 12.9 ± 4.6%	No Δ insulin sensitivity
Barnhart et al. [70]	RCT parallel group double blind placebo	12	50 oral	66 Symptomatic Perimenopausal 45–55y	ns ↓ HDL-C −3.1 ± 8.3 mg/dL, ↓total cholesterol	nr
Arlt [75]	RCT placebo controlled Double blind x-over	16	50 oral	24 adrenal insufficiency (primary and secondary) 23–59y	Sig ↓ HDL-C, total cholesterol	nr
Gebre-Medhin et al. [86]	RCT No placebo control group	12	50 versus 200 oral	9 with Addison's 27–51y	Sig ↓ LDL-C	No sig Δ insulin sensitivity
Villareal et al. [78]	Prospective case-control trial	24	50 oral	10 women/8 men, 10 matched controls 64–82y	Ns effect on blood lipids	ns ↓ 25% insulin sensitivity
Callies et al. [87]	RCT double blind placebo controlled cross-over	16	50 oral	24 women with adrenal insufficiency 23–59y	nr	No effect on fasting glucose, insulin, or the glucose/insulin ratio.
Lasco et al. [84]	RCT parallel group double blind	52	25 oral	20 postmenopausal women 57 ± 4.5y	Sig ↑ HDL-C + 11.61%, *P* = 0.03; Sig ↓LDL-C-11.07%, *P* = 0.04, Sig ↓TG-19.60%, P = 0.03	Sig ↑ Insulin sensitivity (M index +29.55%, *P* = 0.01)
Johannsson et al. [71]	RCT double blind placebo controlled then 6 months open label	52	10 or 15 mg twice daily	38 women with hypopituitarism, severe androgen deficiency 25–60y	Sig ↓ 0.04 mmol/l HDL-C at 24 weeks only	No sig Δ
Lovas et al. [77]	RCT parallel group double blind	36	25	39 women with adrenal failure 18–70y	ns	nr
Villareal and Holloszy [85]	RCT parallel group double blind	24	50 oral	28 postmenopausal women 65–78y	nr	↑ insulin sensitivity
van Thiel et al. [80]	RCT double blind placebo controlled cross-over	16	50 oral	15 Postmenopausal 20 adrenal insufficiency on rhGH, 61 ± 2y	No Δ serum lipids	No Δ insulin sensitivity
Dhatariya et al. [72]	RCT double blind placebo-controlled cross-over	12	50 oral	28 hypoadrenal women 50.25 ± 5.93y	Sig ↓ HDL-C, LDL-C, TG, cholesterol	Sig ↑ insulin sensitivity
Dayal et al. [73]	RCT parallel group double blind	12	50 oral	32 postmenopausal 44–70y	Sig ↓ 4% HDL-C, ↓ 8% total cholesterol, ↓ 6% LDL-C ↓ 12% TG	nr
Nair et al. [56]	RCT parallel group double blind	104	50 oral	57 elderly postmenopausal (87 elderly men) > 60y	Sig ↓ HDL-C med diff 95%CI: −5 (−10, 0) mg/ml ns LDL, TG (no Δ)	No Δ insulin sensitivity,
Igwebuike et al. [79]	RCT parallel group double blind	12	50 oral	31 postmenopausal women 54–72y	ns mean % Δ 95% CI) mg/ml HDL-C −1.7 (14.8, 13.3, *P* = 0.98) LDL-C −1.5 (−17.2, 17.2, *P* = 0.9 TG 8.2 (−3.8, 21.6, *P* = 0.28)	Sig ↑ glucose infusion rate

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Table 3 (*Continued*)

Authors	Study Design	Duration (weeks)	Dose (mg/day)	Participants	Effects on blood lipids	Effects on insulin sensitivity
Srinivasan et al. [69]	RCT parallel group double blind	12	50 oral	33 hypoadrenal women 50.25 ± 5.93	Sig ↓ cholesterol (20 mg/dL PL group vs −22 mg/dL DHEA group, $P = 0.02$), HDL-C (2.0 vs −6.0, $P = 0.006$) ns ↓ LDL (6.0 vs −4.0, $P = 0.08$), TG (2.0 vs −5.0, $P = 0.08$)	Nr
Panjari et al. [81]	RCT double blind placebo parallel	52	50	93 PM (40–65y)	ns ↓ HDL-C	No Δ insulin sensitivity,

Nr, not reported; RCT, randomized controlled trial; HDL-C, high density cholesterol; LDL-C, low density cholesterol; TG, triglyceride; HT, hormone therapy; ns, non-significant, sig, significant; Δ, change.

which lowers LDL-cholesterol and total cholesterol and increases HDL-cholesterol and triglycerides [63]. In studies of estrogen treatment, the addition of methyl testosterone resulted in a lowering of HDL-cholesterol [64,65]. In contrast transdermal estradiol and transdermal testosterone have little effect on lipids [62,66]. Whether the effect of DHEA on lipid metabolism is estrogenic or androgenic in nature and whether it follows the effects of oral versus non-oral therapy is not clear. As DHEA can be converted to estrogens and androgens the effect on the lipid profile could be mixed and may vary between individuals. Alternatively no significant effect as seen with transdermal therapy may be manifest.

Table 3 summarizes the studies examining the effects of exogenous DHEA treatment on the plasma lipid profile. These studies were performed in women (and in some cases men), in various health conditions (for example postmenopausal women or women with adrenal insufficiency), using doses of oral or transdermal DHEA ranging from 25 mg to 1600 mg daily. Treatment periods lasted from 4 to 52 weeks. Most studies had a small number of participants however the majority of studies used a randomized, double-blind design. A number of studies reported an effect of DHEA on plasma lipids such that there was a small decrease in HDL-cholesterol [42,43,56,67–75] with concomitant decrease in total cholesterol [42,67,69,75,76]. However not all the studies reported significant changes in the lipid profile [77–81].

The clinical significance of this alteration to the lipid profile is not fully understood. The recent finding that the anti-atherogenicity of HDLs may be better explained by their functionality (particle size, numbers) rather than by plasma concentrations [57,69], calls into question the negative impact of DHEA-induced decreases in HDL-cholesterol levels.

Taken together the existing data demonstrate that the effects of DHEA on the plasma lipid-lipoprotein profile are modest or non significant.

8. Effects of DHEA on carbohydrate metabolism

The lower levels of DHEA seen with aging have been associated with impaired glucose tolerance, insulin resistance and diabetes [1,82,83]. Table 3 summarizes the studies examining the effects of exogenous DHEA on carbohydrate metabolism in postmenopausal women. Studies have shown increased insulin sensitivity after treatment with DHEA, [72,84,85] decreased insulin sensitivity [42] or no modification [43,56,68,79–81,86,87]. The results are inconsistent and the relationship between DHEA and carbohydrate metabolism is uncertain and warrants further investigation.

Oral DHEA therapy may still have a clinical application. Women with adrenal insufficiency, which is characterized by abnormally low serum concentrations of DHEA, are a special case and there is evidence from clinical trials suggesting this group may derive health benefits from DHEA supplementation [88], such as improved wellbeing and sexual function, [75,89] although other studies report no benefit [71,80,90]. A recent review of the available data concluded that the evidence did not support the routine use of DHEA in women with adrenal insufficiency [91].

9. Conclusions

There is little convincing data to support the use of oral DHEA therapy in healthy aging individuals to improve conditions synonymous with normal aging such as reduced sexual function or diminished wellbeing. No well-designed clinical trial has confirmed the benefit of DHEA supplementation in postmenopausal women on sexual function or wellbeing, calling into question the clinical use of oral DHEA therapy for this group.

Findings regarding the safety of DHEA use are contradictory. Although no serious adverse effects have been reported in short-term studies, 50 mg daily oral dose of DHEA has been associated with androgenic side effects [48]. There is a paucity of data regarding androgenic side effects and insufficient documentation on the effect of DHEA on the breast and the endometrium. Labrie [3] and others have investigated the effects of DHEA on mammary tissue extensively in vitro and rodent model and consistently report an inhibitory effect on mammary carcinoma development. This warrants further investigation. DHEA administered percutaneously for 12 months to postmenopausal women was shown to have an estrogenic effect on the vagina without affecting the endometrium which remained atrophic [67]. Endometrial thickness did not increase in postmenopausal women during a 6-month study of 25 mg oral DHEA daily [92] or in a 12-month study of 50 mg oral DHEA daily [93].

DHEA is generally accessed as an over-the-counter therapy and used as a sole treatment. Whether DHEA has a more substantial effect when used in combination with estrogen remains uncertain. In a recent 12-month study 10 mg DHEA in combination with 50 μg transdermal estrogen was shown to restore androgen levels to those of young women and have a positive impact on estrogenic tone however there was no evaluation of sexual function or wellbeing [94]. This requires additional investigation.

To date there remains no compelling evidence for metabolic effects of oral DHEA therapy that could be considered 'anti-aging', and the use of DHEA therapy for this purpose cannot be recommended.

Competing interest

The authors have no competing interest.

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