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ORIGINAL ARTICLE

The association of androgenic sex steroids with serum lipid levels in postmenopausal women

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Background. The aim of the present study was to examine the correlations between androgenic sex steroids and serum lipid levels in postmenopausal women.
Methods. The study group included 72 postmenopausal women. Correlation analysis between serum hormone [dehydroepiandrosterone sulfate (DHEA-S), androstenedione, free testosterone and sex hormone binding globulin (SHBG)] and lipid {total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), lipoprotein (a) [Lp (a)], apolipoprotein A-1 (apo A-1) and apolipoprotein B (apo B)} levels was performed.
Results. DHEA-S was found to be positively correlated with HDL-C ($r = 0.231$, $p = 0.049$) and negatively correlated with Lp (a) ($r = -0.355$, $p = 0.002$). These correlations were statistically significant even after adjustment for age and body mass index (BMI) ($r = 0.332$, $p = 0.005$ and $r = -0.362$, $p = 0.002$, respectively). SHBG was positively correlated with HDL-C ($r = 0.352$, $p = 0.002$). There was a significant but weaker correlation between SHBG and HDL-C levels after controlling for age and BMI ($r = 0.243$, $p = 0.041$). No other correlations were found between sex hormone and lipid levels.
Conclusion. DHEA-S was found to be associated with a less atherogenic lipid profile in postmenopausal women.

Key words: dehydroepiandrosterone sulfate; high density lipoprotein-cholesterol; lipoprotein (a); postmenopause

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The correlations between androgenic sex steroids and serum lipid levels have been a matter of concern in various studies. Dehydroepiandrosterone sulfate (DHEA-S), the most abundant steroid in the circulation, has been found to be associated with a less atherogenic lipid profile in men but this association is less clear in women (1–4). The sex-dependent difference for the correlations between DHEA-S and lipid levels was thought to occur because DHEA-S would be expected to act in a different manner in androgenic or estrogenic environments (5). Serum lipid levels are well-known predictors of coronary artery disease and an improved lipid profile with higher DHEA-S levels might be associated with reduced cardiovascular diseases. DHEA-S was reported to predict ischemic heart disease in men but such an association is still not clear in women (6).

The hormonal milieu in postmenopausal women resembles that encountered in men due to the decrease in estrogen levels, but studies

Abbreviations:
BMI: body mass index; DHEA-S: dehydroepiandrosterone sulfate; SHBG: sex hormone binding globulin; E2: estradiol; FSH: follicle stimulating hormone; LH: luteinizing hormone; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; Lp (a): lipoprotein (a); apo A-1: apolipoprotein A-1; apo B: apolipoprotein B; TG: triglyceride; HRT: hormone replacement therapy; ELISA: enzyme-linked immunosorbent assay.

concerned with the association of androgenic sex steroids and lipids have produced conflicting results in postmenopausal subjects. The aim of the present study was to examine the correlations between DHEA-S and serum lipid levels in postmenopausal women. We have further analyzed the correlations between free testosterone, androstenedione, sex hormone binding globulin (SHBG) levels and serum lipid concentrations.

Materials and methods

The study population included 72 consecutive postmenopausal women who attended our clinic and fitted the inclusion criteria.

The inclusion criteria for the study were:

1) at least 1 year of amenorrhea, serum estradiol (E2) levels below 40 pg/mL, serum follicle stimulating hormone (FSH) levels more than 30 IU/L and serum luteinizing hormone (LH) levels more than 15 IU/L;
2) having intact ovaries;
3) having no systemic disease that may alter serum sex hormone or lipid levels, e.g. diabetes mellitus;
4) not using hormone replacement therapy (HRT), any hormonal agent or any other lipid-altering medication at least in the preceding 12 months.

All of the postmenopausal women underwent a clinic visit and complete systemic and gynecologic examination. Data were gathered on menstrual history, health history, prior oopherectomy and medication use. Serum FSH, LH and E2 levels were measured at the first visit to confirm menopause. All women were informed about the study and written consent was obtained.

Height and weight were recorded to calculate the body mass index (BMI) [weight (kg)/height $(m)^2$].

Blood samples were obtained between 0800 and 1000 h after an overnight fast.

Serum FSH, LH, E2, DHEA-S and free testosterone levels were measured with chemiluminescence methods using an Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, IN, USA). Androstenedione and SHBG levels were measured by an enzyme-linked immunosorbent assay (ELISA) (Research Diagnostic Inc, Flanders, NJ, USA).

Total cholesterol (TC) and triglyceride (TG) levels were measured with commercial kits (Sigma Cholesterol Procedure and Sigma Triglyceride Procedure, Sigma Chemicals, St Louis, MO, USA) and lipoprotein (a) [Lp (a)], apolipoprotein A-1 (apo A-1) and apolipoprotein B (apo B) levels were measured with immunoturbidimetric methods using the Synchron CX7 system (Beckman Instruments Inc, Brea, CA, USA). High density lipoprotein-cholesterol (HDL-C) levels were measured with an enzymatic direct method (Centronic Ltd, Surrey, UK). Low density lipoprotein-cholesterol (LDL-C) levels were calculated using the Friedewald formula.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Windows 9.0) program. Correlation analysis of sex hormones (free testosterone, DHEA-S, androstenedione, SHBG) and serum lipid levels (TC, HDL-C, LDL-C, TG, Lp (a), apo A-1, apo B) was performed using Pearson's correlation coefficients (r). Partial correlation coefficients were calculated between hormone and lipid levels, using age and BMI as covariates.

Results

Demographic characteristics and mean serum hormone and lipid levels of the women are shown in Table I. Correlation coefficients (r) between serum androgen and lipid levels are presented in Table II.

DHEA-S was found to be positively correlated with HDL-C ($r = 0.231$, $p = 0.049$) (Table II). DHEA-S had an even stronger positive correlation with HDL-C ($r = 0.332$, $p = 0.005$) after controlling for age and BMI.

DHEA-S was negatively correlated with Lp (a) ($r = -0.355$, $p = 0.002$) (Table II). This negative correlation persisted between DHEA-S and Lp (a) after controlling for age and BMI ($r = -0.362$, $p = 0.002$).

SHBG was positively correlated with HDL-C ($r = 0.352$, $p = 0.002$) (Table II). There was a significant but weaker correlation between SHBG and HDL-C after controlling for age and BMI ($r = 0.243$, $p = 0.041$).

No other correlations were found between sex hormone and lipid levels.

Discussion

DHEA-S was found to be positively correlated with HDL-C and negatively correlated with Lp (a) in the present study. Studies concerned with the association of sex hormones, especially DHEA-S with serum lipid levels, have reported conflicting results in postmenopausal women. The secretion of DHEA-S by the adrenals reaches

Table I. Demographic characteristics and mean serum hormone and lipid levels of the women studied

	Mean	SD
Age (years)	50.42	6.68
Time since LMP (years)	4.37	5.22
Gravida	5.26	2.12
Parity	3.59	1.49
BMI (kg/m2)	25.89	4.99
FSH (IU/L)	57.06	18.32
LH (IU/L)	34.96	10.51
E2 (pg/mL)	24.50	11.36
DHEA-S (μg/dL)	291.31	187.33
Free testosterone (pg/mL)	1.78	0.89
Androstenedione (ng/mL)	1.70	0.97
SHBG (nmol/L)	30.16	20.35
Triglyceride (mg/dL)	150.47	77.63
Total cholesterol (mg/dL)	216.12	42.34
HDL-C (mg/dL)	55.17	12.23
LDL-C (mg/dL)	130.06	35.03
Lp (a) (mg/dL)	28.82	20.31
Apolipoprotein A-1 (mg/dL)	158.94	36.85
Apolipoprotein B (mg/dL)	76.46	18.66

SD, standard deviation; LMP, last menstrual period.

Table II. Correlation coefficients (*r*) between serum androgen and lipid levels

	TC	HDL-C	LDL-C	TG	Lp (a)	apoA-1	apo B
DHEA-S	− 0.130	0.231*	− 0.156	− 0.022	− 0.355*	− 0.092	− 0.074
Free testosterone	0.213	0.035	0.191	0.197	0.031	− 0.008	0.118
Androstenedione	− 0.190	0.077	− 0.107	− 0.218	− 0.019	− 0.062	− 0.076
SHBG	− 0.036	0.352*	− 0.024	− 0.214	− 0.210	− 0.072	− 0.167

*$p < 0.05$.

maximal values between ages 20 and 30 years and then decrease substantially, reaching 10–20% of the peak values by the age of 70 (7). The decrease in adrenal secretion of DHEA-S during the lifespan without significant alteration in cortisol secretion might be due to the decrease in 17,20-desmolase activity in the adrenal cortex (8).

There are a number of studies indicating that DHEA-S was not correlated with serum lipid levels in postmenopausal women who were not taking any HRT regimens (1,9).

A study from Japan has demonstrated a direct correlation between DHEA-S and HDL-C in postmenopausal subjects, similar to our findings. Nagata et al. (10) have found that DHEA-S was significantly and positively correlated with HDL-C after controlling for age and BMI in 56 postmenopausal women ($r = 0.28$, $p < 0.05$).

Administration of DHEA to postmenopausal women has also produced conflicting results in terms of changes in serum lipid levels. Mortola and Yen (11) have reported a significant decline in total serum cholesterol and HDL-C in the first and subsequent weeks of DHEA administration.

Diamond et al. (12) have reported an 8% decrease in HDL-C levels after 12 months of treatment with single daily percutaneus application of 10% DHEA cream. The HDL-C/total cholesterol ratio did not change because of a parallel decrease in total cholesterol.

In a randomized, double-blind placebo-controlled trial, the effects of 50 mg/day of oral DHEA supplementation, for 3 months, on 60 perimenopausal women were examined. Women receiving DHEA had a 10.1% [95% confidence interval (95% CI) −15.0, −5.1] decline in HDL-C and an 18.1% (95% CI −32.2, − 3.9) decline in Lp (a) from baseline, but these declines did not differ significantly from those in women who received placebo (13).

Casson et al. (14) reported that 6 months of DHEA replacement resulted in a 12.9% ± 4.6% decrease in HDL-C and 7.8% ± 3.9% decrease in apo A-1 levels in postmenopausal women.

In a recent study, 20 healthy postmenopausal women with serum DHEA-S concentrations <2.5 μmol/L were enrolled and randomly assigned to two different treatment groups: group 1 were treated with micronized DHEA, 25 mg/day for 12 months; group 2 were treated with an identical placebo tablet. After 12 months, the group treated with DHEA showed a considerable improvement in lipid pattern (HDL-C +11.61%, $p = 0.03$; LDL-C −11.07%, $p = 0.04$; triglycerides −19.60%, $p = 0.03$) (15). This study demonstrated an improved, less atherogenic lipid profile with DHEA treatment in postmenopausal women.

DHEA and DHEA-S appear to be associated with improved cardiovascular risk factors in men, but this connection is less clear in women (4,16). A number of studies have shown that DHEA-S levels did not predict ischemic heart disease in postmenopausal women (9,17). Altering serum lipid levels was reported to be a major mechanism involving DHEA-S that might effect cardiovascular risk (6). Serum lipid levels are well-known predictors of cardiovascular diseases in postmenopausal women. HDL-C is a strong predictor of coronary heart disease in women and a decrease in HDL-C of 10 mg/dL is associated with a 40–50% increased risk of coronary heart disease. Women with high HDL-C levels have no increased risk of heart disease even when total cholesterol levels are elevated (18,19). It has been reported that Lp (a) was an independent risk factor for developing atherosclerosis in postmenopausal women (20). Regarding our results, it can be speculated that higher DHEA-S levels might be associated with beneficial effects on atherosclerosis in postmenopausal women due to higher HDL-C and lower Lp (a) concentrations. The inverse correlation between DHEA-S and Lp (a) is an impressive finding of the present study. To the best of our knowledge, no other study exists reporting such an inverse correlation in postmenopausal women.

DHEA-S is expected to act like estrogen in men because of a low estrogenic and high androgenic environment. In women, DHEA-S would act like androgen because of the higher estrogenic environment, leading to an adverse lipid profile (5). Postmenopausal women have a low estrogenic hormonal milieu similar to men, and plasma

levels of DHEA and adrenal C19 steroids remain the primary source of active estrogen in postmenopausal women (6). This could be the reason why we have observed a less atherogenic lipid profile with higher DHEA-S levels in postmenopausal women.

Reduced SHBG levels have been associated with an adverse lipid profile, including reduced HDL-C concentrations (21). We have also found a positive correlation between SHBG and HDL-C levels as reported previously.

In conclusion, DHEA-S was found to be positively correlated with HDL-C and negatively correlated with Lp(a), yielding a less atherogenic lipid profile in postmenopausal women.

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