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Oral dehydroepiandrosterone (DHEA) replacement in older adults: effects on central adiposity, glucose metabolism, and blood lipids

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Abstract

Objective—The aim was to determine the effects of dehydroepiandrosterone (DHEA) therapy on changes in central adiposity, insulin action, and blood lipids. Many of the actions of DHEA in humans are thought to be mediated through its conversion to sex hormones, which are modulators of adiposity, muscularity, and insulin sensitivity. The effects of DHEA replacement on regional tissue composition, glucose metabolism, and blood lipid profile in older adults have been inconsistent.

Design—a randomized, double-blinded, placebo-controlled trial. The intervention was oral DHEA 50 mg/d or placebo for 12 months.

Participants—58 women and 61 men, aged 60–88 yr, with low serum DHEA sulfate (DHEAS) levels at study entry.

Measurements—Computed tomography measures of abdominal fat areas, thigh muscle and fat areas, DXA-derived trunk fat mass, serum glucose and insulin responses to an oral glucose challenge, and fasted serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were assessed before and after the intervention.

Results—There were no significant ($P > 0.05$) differences between the DHEA and placebo groups in the changes in regional tissue composition or glucose metabolism. HDL-cholesterol ($P = 0.01$) and fasted triglycerides ($P = 0.02$) decreased in women and men taking DHEA.

Conclusion—Restoring serum DHEAS levels in older adults to young adult levels for 1 year does not appear to reduce central adiposity or improve insulin action. The benefit of DHEA on decreasing serum triglycerides must be weighed against the HDL-lowering effect.

Key terms

dehydroepiandrosterone; regional adiposity; insulin action

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INTRODUCTION

Changes in the systemic hormonal milieu partly explain the increase in central adiposity, loss of muscle mass, and insulin resistance associated with aging. The hormonal profile of aging includes a marked decrease in the adrenal hormone dehydroepiandrosterone (DHEA). By 70 years of age, average serum DHEA sulfate (DHEAS), the predominant circulating form of DHEA, is about 20% of young adult levels.¹ Many of the actions of DHEA in humans are thought to be mediated through its conversion to sex hormones,² which are modulators of adiposity, muscularity, and insulin sensitivity.³ Whether DHEA replacement in older adults results in beneficial changes in body composition is controversial, with decreases in adiposity or increases in fat-free mass observed in some studies,^{4–6} but not others.^{7–11} The effects of DHEA replacement on glucose metabolism are also inconsistent.^{4;5;12–14} A number of factors may contribute to the inconsistent findings across DHEA replacement trials, including variability in the dose and duration of DHEA treatment, small sample sizes in some studies, and lack of control over such factors as use of exogenous sex hormone therapy.

We previously reported that there were no significant changes in fat or fat-free mass in a relatively large randomized, double-blinded, placebo-controlled trial of DHEA replacement therapy in older women and men.¹¹ We now report on secondary outcomes from that trial, including changes in regional tissue composition (abdomen, thigh), insulin action, and fasted lipids and lipoproteins.

SUBJECTS AND METHODS

Study participants

Participant characteristics and intent-to-treat and secondary compliance analyses of the changes in bone mineral density (BMD) and body composition in response to DHEA replacement therapy have been reported.^{11;15} Briefly, participants were 140 women and men aged 60+ years, with low serum DHEAS (< 3.8 $\mu\text{mol/L}$, 140 $\mu\text{g/dL}$), and no use of prescribed or over-the-counter hormone therapies or oral glucocorticoids in the previous six months. Volunteers were excluded for unstable health and contraindications for sex hormone therapy. The cohort was predominantly Caucasian (2 Hispanic, 2 African American, 1 Native American, 11 other or unknown). The study was approved by the Colorado Multiple Institutional Review Board (IRB). Written informed consent was obtained from all volunteers. Intervention

Participants were randomly assigned with stratification by sex to receive oral DHEA 50 mg/d (Belmar Pharmacy, Lakewood, CO) or placebo for one year. The intervention was administered in a double-blinded manner. The dose was selected because it raised serum DHEAS levels of older adults to the normal range for young adults.^{4;16} Drug compliance was assessed by measuring serum DHEAS levels at 3-month intervals, as previously described.¹¹ The original trial was powered to detect a main effect of DHEA therapy on the primary outcomes (i.e., hip and spine bone mineral density and fat-free mass), but was not powered to detect sex differences. The analyses of secondary outcomes reported herein included only participants compliant to the intervention (i.e., 119 of 140). Because the trial was not powered to detect changes in the secondary outcomes, negative findings should be interpreted cautiously. Procedures

Computed tomography (CT) and dual-energy x-ray absorptiometry (DXA)—

Sagittal abdominal and thigh composition was measured by CT at baseline and 12 months using General Electric CT/i (Waukesha, WI) instruments. Two images (120 kVp, 200–300 mAs, 10mm slice thickness) of the abdomen were acquired at the center of the vertebral disc

spaces between the second and third (L₂-L₃), and fourth and fifth (L₄-L₅), lumbar vertebrae. One thigh image was centered on a point 20 cm superior to the lateral inferior aspect of the right femur. Images were analyzed using programs developed by the Department of Radiology CT reading center using IDL (RSI Inc., Boulder, CO) on a Sparc 20 workstation (Sun Microsystems, Sunnyvale, CA). Fat and lean soft-tissue areas were measured using CT intensity thresholds that were determined for each image from histograms of signal intensities, as described previously.¹⁷ The subcutaneous and intra-abdominal fat regions were distinguished by manually outlining the interior border of the subcutaneous fat layer. Bowel fat was subtracted from the total and intra-abdominal fat areas. Subcutaneous fat area was calculated by subtracting the intra-abdominal fat area from the total fat area. For all abdominal composition variables, the averages of the L₂-L₃ and L₄-L₅ slices are reported. Total, fat, and lean areas in the thigh image were determined using similar methods. Total body DXA scans were performed as previously described¹¹ at baseline and 12 months for the measurement of trunk fat mass.

Metabolic parameters—Oral glucose tolerance tests (OGTT; 75 g) were performed in the morning after an overnight fast at baseline and 12 months. Subjects were instructed to consume at least 150 g/day of carbohydrate for three days before the OGTT. Blood samples were obtained before and 30, 60, 90, and 120 min after glucose ingestion for plasma glucose, insulin, and C-peptide determinations. The total areas under the glucose (GLU_{AUC}), insulin (INS_{AUC}), and C-peptide (CPEP_{AUC}) curves were calculated using the trapezoidal rule. Insulin action was the product of the insulin and glucose areas (INS_{AUC} × GLU_{AUC}). Participants were classified at baseline and 12 months as having diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or normal glucose tolerance using American Diabetes Association criteria.¹⁸ Fasted serum total cholesterol, high-density lipoprotein-cholesterol (HDL), and triglycerides (TG) were measured at baseline and 12 months.

Serum analyses: Blood samples were stored at −80°C and serial samples for individuals were analyzed in batch. Serum insulin and C-peptide concentrations were determined by double-antibody RIAs (Diagnostic Systems Laboratories, Inc., Webster, TX and Diagnostic Products Corp., Los Angeles, CA, respectively). Serum glucose was measured using a hexokinase assay on a Cobra Mira Plus instrument (Roche Diagnostic Systems, Indianapolis, IN). Intra- and interassay CVs were: 1) insulin, 5.2 and 9.8%; 2) C-peptide, 8.9 and 12.7%; and 3) glucose, 0.7 and 1.4%. Total cholesterol, HDL, and TG concentrations were measured by automated enzymatic commercial kits on a Cobra Mira Plus instrument (Roche Diagnostic Systems, Indianapolis, IN). Intra- and interassay coefficients of variation were: 1) total cholesterol, 0.8 and 1.5%; 2) HDL, 0.5 and 1.1%; and 3) TG, 0.8 and 2.2%. Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation.¹⁹ Measurement of serum DHEAS was previously described.¹¹

Statistical analyses—Baseline characteristics of the treatment groups were compared using 2-sample *t*-tests in women and men separately. Because the changes in circulating sex hormones in response to DHEA replacement differed in women and men,¹⁵ sex-specific linear regression methods were used to analyze differences in outcomes between treatment groups with adjustment for baseline value of the dependent variable. Pooled analyses of women and men were also conducted. Baseline and 12-month data are presented as mean ± SD unless otherwise indicated. Changes in outcomes from baseline to 12 months are reported as the point estimate for mean change and 95% confidence interval with two-sided *P* values unless otherwise noted. All analyses were performed in SAS (version 9.1; SAS Institute, Inc., Cary, NC).

RESULTS

Baseline characteristics (Tables 1 and 2)

Participants were 69 ± 2 years of age. Average BMI values in the placebo and DHEA groups were 26.2 ± 5.0 and 26.5 ± 4.2 in women and 28.1 ± 4.1 and 26.6 ± 3.4 in men. As previously reported, there were no significant differences between the placebo and DHEA groups in baseline characteristics, including serum DHEAS, fat mass, or fat-free mass.¹¹ There were no significant differences between the treatment groups at baseline in any of the CT-derived abdominal or thigh areas or in trunk fat mass from DXA.

The prevalence of abnormal glucose tolerance, based on medical history and response to the OGTT, was not different between the groups. The placebo group included 7 participants with type 2 diabetes and 15 with IFG or IGT. The DHEA group included 5 participants with type 2 diabetes and 21 with IFG or IGT. One person in each group was using a hypoglycemic medication at study entry **and maintained use throughout the study. None of the participants started a hypoglycemic medication during the study.** Ten participants (1 woman) had a history of cardiovascular disease (2 placebo, 8 DHEA). The placebo and DHEA groups included 11 and 12 participants, respectively, on lipid-lowering medications at baseline, and 13 per group at the end of the study. Women in the DHEA group tended to have a greater baseline INS_{AUC} ($P = 0.05$) and $CPEP_{AUC}$ ($P = 0.08$) and reduced insulin action (i.e., greater $INS_{AUC} \times GLU_{AUC}$; $P = 0.08$) than women in the placebo group (Table 2). There were no significant treatment group differences at baseline in the other glucoregulatory and lipid parameters in women or men.

Changes in regional body composition

After 1 year of DHEA replacement, there were no significant ($P > 0.08$) treatment group differences in the changes in any of the abdominal or thigh areas in women or men (Figure 1). Similarly, the changes in DXA-derived trunk fat mass did not differ significantly ($P > 0.2$) between the placebo and DHEA women (-0.39 ± 0.23 vs. -0.32 ± 0.20 kg, respectively) or men (0.07 ± 0.30 vs. -0.29 ± 0.29 kg, respectively).

Metabolic changes

There were no significant differences between treatment groups in the changes in serum glucose, insulin, or C-peptide measures in the women, men, or when combined (Table 3). HDL-cholesterol tended to decrease in response to DHEA treatment in women (-3.4 ± 2.2 vs. 1.5 ± 1.8 mg/dL; $P = 0.07$) and men (-2.4 ± 6.8 vs. 0.2 ± 5.8 mg/dL; $P = 0.08$) (Figure 2). In men, serum triglycerides decreased significantly (-21.3 ± 44.5 vs. 0.7 ± 43.9 ; $P = 0.02$) in response to DHEA replacement therapy; changes in women were not significant (-22.7 ± 48.9 DHEA vs. -7.0 ± 59.9 placebo; $P = 0.36$). When women and men were combined, there were significant reductions in HDL-cholesterol (-2.8 ± 8.7 mg/dL vs. 0.9 ± 8.0 mg/dL; $P = 0.01$) and triglycerides (-21.9 ± 46.1 mg/dL vs. -3.1 ± 52.2 mg/dL; $P = 0.02$) in the DHEA group when compared with the placebo group. Although changes in total and LDL-cholesterol tended to be more favorable in the DHEA group, they did not reach statistical significance in the combined (data not shown) or sex-specific analyses (Figure 2). We repeated the analyses of serum lipids after excluding participants using lipid-lowering medications. HDL-cholesterol decreased in response to DHEA in women (-4.0 ± 11.0 mg/dL vs. 1.9 ± 10.2 mg/dL; $P = 0.05$) and men (-2.9 ± 5.8 mg/dL vs. 1.1 ± 5.9 mg/dL; $P = 0.03$). The trend for a decrease in serum triglycerides in the men taking DHEA remained but the magnitude of difference between the groups was diminished and was not significant (-12.0 ± 32.7 mg/dL, DHEA vs. 1.71 ± 39.5 mg/dL, placebo; $P = 0.15$). When women and men not using lipid lowering medications were combined, HDL-cholesterol decreased in response to DHEA (-3.5 ± 8.9 mg/dL vs. 1.5 ± 8.4 mg/dL; $P = 0.006$). In the combined

analysis, the serum triglyceride response to DHEA replacement was not significantly different from placebo (-13.4 ± 33.5 mg/dL DHEA vs. -5.8 ± 43.8 mg/dL placebo; $P = 0.30$).

DISCUSSION

The major findings of the study were that raising serum DHEAS of older adults to young adult levels for 12 months with oral DHEA therapy resulted in decreased serum HDL-cholesterol and triglycerides in older women and men. However, DHEA replacement therapy did not result in significant changes in regional body composition, glucose tolerance, or insulin action.

Body composition

DHEA is thought to be an important prohormone in older women and men.²⁰ It can be metabolized to potent androgens and estrogens in a tissue-specific manner through the actions of steroidogenic enzymes. Target tissues include adipose, muscle, liver, and bone, although most of the evidence for this is from animal models.^{21–25} DHEA replacement may also act systemically by increasing circulating levels of testosterone and estrogens. It has been postulated that the marked decline in serum DHEAS with aging contributes to biological changes in outcomes that are known to be influenced by sex hormones, such as the loss of muscle mass and the increase in central adiposity, and that DHEA replacement therapy may prevent or reverse such changes.^{4;6;7}

We previously reported that DHEA replacement resulted in significant increases in serum estradiol of approximately 60% and 35% in women and men, respectively, and an 80% increase in serum testosterone in women.¹⁵ Serum testosterone decreased 5% in men ($P=0.11$) whereas SHBG levels decreased significantly in women and men. Despite these changes in sex hormones, we found no effect of DHEA therapy to increase muscle area or decrease fat area of the thigh or abdomen in the present study. Previously, we found that the increase in bone mineral density in response to DHEA therapy was explained by increases in serum estradiol.¹⁵ However, it is not clear whether the changes in serum sex hormones generated by DHEA would be expected to result in measureable changes in fat mass or fat-free mass over 1 year of therapy. It is possible that restoring youthful DHEA levels slows the age-related changes in body composition, but this may be apparent only after several years of therapy.

Our body composition results corroborate those of Nair et al⁸ and Percheron et al¹⁰ that 1–2 years of DHEA replacement therapy had no effect on muscle or fat areas in older women or men. Nair and colleagues did find a small, but significant, increase in total fat-free mass and decrease in total body adiposity in response to DHEA therapy in women and men.⁸ However, two other relatively large randomized controlled trials of DHEA therapy, including ours, did not find changes in total body composition.^{7;11}

These findings suggest that DHEA replacement therapy does not effectively increase muscle mass in older adults. Because the expected loss of muscle over 1 to 2 years is small, longer duration trials will be necessary to determine whether sustaining youthful serum levels of DHEAS in older adults slows the rate of muscle loss. Further, it is possible that DHEA therapy stimulates skeletal muscle hypertrophy only when combined with an appropriate mechanical stimulus. In one study of 56 older women and men, 6 months of DHEA therapy alone had no effect on thigh muscle area or strength.²⁶ However, an additional 4 months of DHEA or placebo therapy combined with high-intensity progressive resistance training resulted in larger increases in cross-sectional thigh muscle area and several measures of muscle strength in the DHEA group than in the placebo group; changes in total body fat-free

mass were not reported. In contrast, a smaller study of 31 postmenopausal women found that DHEA therapy did not augment adaptations to a 12-week resistance and endurance exercise training program when compared with placebo therapy.²⁷ However, although not significant, the changes in mid-thigh muscle area (placebo 2.2%; DHEA: 8.4%) and total body fat-free mass (placebo: 1.0%; DHEA: 2.3%) in response to exercise tended to be larger in DHEA-treated women, suggesting that significant benefits of DHEA therapy may have emerged if the intervention had been of longer duration or focused only on resistance training. In frail older women engaged in mild chair aerobic and yoga exercise, DHEA therapy was associated with the preservation of total body and appendicular lean mass whereas placebo-treated women lost lean mass over 6 months.²⁸ Further research will be necessary to determine whether DHEA therapy enhances the physiologic adaptations to exercise training in older adults.

Regional fat distribution

The age-related decline in circulating sex hormones and DHEAS has been associated with an increase in abdominal adiposity.^{29;30} Therefore, it was of interest to determine whether replacement of DHEAS to youthful levels for one year would change the regional fat distribution of older women and men. We are aware of only one randomized controlled trial that found significant changes in regional abdominal adiposity in response to DHEA therapy. Villareal and Holloszy⁵ reported a significant decrease in visceral and subcutaneous abdominal fat in women and men in response to a 6-month DHEA intervention. In contrast, we and others⁸ found no significant effects of DHEA therapy on visceral or subcutaneous abdominal adipose tissue areas by computed tomography. We also found no significant effects of DHEA therapy on trunk fat mass measured by DXA, which corroborated the findings from the DAWN trial.⁷ Together, the bulk of evidence from the current study and other trials indicates that 1 to 2 years of DHEA replacement has little, if any, effect on regional adiposity.

Glucose tolerance, insulin action, and lipid profile

We found no benefits of DHEA replacement therapy on glucose tolerance or insulin action, as reflected by the integrated glucose and insulin responses to an oral glucose challenge. DHEA replacement was previously found to result in a significant decrease in the insulin response to an oral glucose challenge in one study⁵ but not in others.^{4;12} The improvement in the insulin AUC in Villareal and Holloszy⁵ may be explained by a significant reduction in abdominal visceral fat. There have also been inconsistent findings regarding the effect of DHEA therapy on insulin action measured by either a meal or an intravenous glucose challenge, with all but one study¹² reporting no benefit.^{8;13;14} In Lasco et al,¹² insulin sensitivity in response to an intravenous glucose challenge improved in women using DHEA therapy but the OGTT responses did not. Therefore, the balance of available evidence weighs against significant glucoregulatory effects of DHEA replacement in healthy, older adults.

In the current study, DHEA therapy resulted in a significant decrease in serum triglycerides. To our knowledge, a triglyceride-lowering effect of DHEA has been reported in only one other randomized controlled study of older adults. Lasco et al¹² found a reduction of approximately 20% in serum triglycerides in 20 postmenopausal women given DHEA 25 mg/d for 12 months, which they attributed to the improvement in insulin sensitivity. In the present study, the 17% reduction in serum triglycerides was of similar magnitude as in that trial, but was not accompanied by changes in insulin action. A double-blinded cross-over study of six obese women treated with a pharmacologic dose of DHEA (1600 mg/day) for 28 days found a trend for serum triglycerides to decrease by 10% to 20%.³¹ Several trials reported no significant triglyceride-lowering effect of DHEA in older adults,^{4;8;13;14} and the

reasons for the discordant findings are not clear. The use of lipid-lowering drugs is a potential source of the disagreement in triglyceride responses to DHEA given that the changes in serum triglycerides we found in men using DHEA were attenuated when individuals using lipid-lowering medications were excluded.

One potential adverse consequence of DHEA replacement is a decrease in serum HDL-cholesterol. We found trends for decreased HDL-cholesterol with DHEA replacement in sex-specific analyses, and the decrease in HDL was significant in the group as a whole. In women, the lowering of HDL-cholesterol may be due to the increase in serum testosterone level that occurs in response to DHEA therapy.^{4;8;11} An HDL-lowering effect of DHEA has been reported for older women using 50 mg/d or less of DHEA^{13;14} and men taking a 1000 mg/d DHEA supplement.³² However, other studies of DHEA replacement found no significant reduction in HDL-cholesterol in women and men after 6 and 24 months of treatment^{4;8} despite increases in serum testosterone. In contrast, Lasco et al,¹² found a significant increase in HDL-cholesterol in postmenopausal women taking DHEA (35 mg/day) for 12 months. However, that study included a relatively small number of participants and was discordant with most other studies of women in that serum testosterone levels did not increase in response to DHEA replacement. It is unclear if DHEA reduces HDL particle size, increases renal clearance, or has other actions on HDL metabolism. In the present study, hypertriglyceridemia was not the stimulus for decreased HDL-cholesterol.

Although the changes in total and LDL-cholesterol in response to DHEA therapy in the current study were in the favorable direction, they were not different from the changes in placebo-treated adults. We are aware of only one study of older women that found an LDL-lowering effect of DHEA replacement.¹²

In summary, restoring serum DHEAS levels in older women and men to the physiological levels of young adults for 1 year does not appear to reduce central adiposity or improve insulin action. The benefit of decreased serum triglycerides must be weighed against the unfavorable HDL-lowering effect of DHEA.

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Figure 1. Changes in abdominal and thigh tissue composition (mean $\pm$ SE). Intra-abd = intra-abdominal; subc = subcutaneous; IM = inter-muscular.

Figure 2.
Changes in plasma lipids (mean $\pm$ SE). HDL = high-density lipoprotein; LDL = low density lipoprotein, * $P = 0.03$.

Table 1

Baseline regional body composition of women and men in the placebo and DHEA treatment arms

	Placebo	DHEA	P value
Women	n=33	n=25	
Abdominal areas, cm ²			
Total	647.0 (187.0)	657.6 (127.4)	0.81
Subcutaneous fat	288.7 (128.6)	294.1 (82.6)	0.85
Visceral fat	111.9 (66.0)	127.8 (45.6)	0.30
Right thigh areas, cm ²			
Total	214.9 (54.6)	217.7 (52.8)	0.85
Subcutaneous fat	105.5 (46.1)	108.9 (42.4)	0.79
Intramuscular fat	8.3 (4.8)	8.7 (3.4)	0.74
Muscle	93.2 (15.3)	92.4 (16.1)	0.86
Right thigh muscle density, HU	41.5 (5.8)	41.7 (4.5)	0.86
Trunk fat mass, kg	13.2 (5.9)	13.9 (4.2)	0.61
Men	n=24*	n=28*	
Abdominal areas, cm ²			
Total	754.1 (160.3)	692.8 (132.8)	0.14
Subcutaneous fat	229.2 (86.9)	209.2 (101.3)	0.45
Visceral fat	206.8 (81.0)	180.8 (63.3)	0.20
Right thigh areas, cm ²			
Total	201.2 (38.8)	200.0 (52.6)	0.93
Subcutaneous fat	53.5 (24.2)	51.3 (45.0)	0.83
Intramuscular fat	8.3 (3.6)	7.4 (4.0)	0.38
Muscle	128.6 (21.1)	131.2 (20.2)	0.67
Right thigh muscle density, HU	43.2 (4.6)	45.8 (5.1)	0.07
Trunk fat mass, kg	14.4 (5.2)	13.0 (4.3)	0.25

Values are mean (SD).

* CT data were available for only 52 of the 61 men.

Table 2

Baseline metabolic measures of women and men in the placebo and DHEA treatment arms

	Placebo	DHEA	P value
Women	n=33	n=25	
Fasted glucose, mmol/L	4.9 (0.6)	5.0 (0.5)	0.50
Fasted insulin, pmol/L	45.4 (27.8)	55.1 (23.0)	0.15
Fasted C-peptide, ng/mL	2.0 (0.7)	2.1 (0.7)	0.48
Glucose _{AUC} , mmol/L × min	932.6 (222.9)	965.8 (161.3)	0.52
Insulin _{AUC} , pmol/L × min × 10 ²	382.1 (186.4)	502.4 (249.2)	0.05
C-peptide _{AUC} , ng/mL × min	831.8 (268.8)	985.0 (333.7)	0.08
Glucose _{AUC} × Insulin _{AUC} × 10 ⁶	37.1 (22.3)	49.6 (27.9)	0.08
Total cholesterol, mg/dL	218.9 (37.1)	232.5 (40.0)	0.19
HDL-cholesterol, mg/dL	59.0 (14.0)	59.1 (13.2)	0.98
LDL-cholesterol, mg/dL	134.1 (35.2)	145.5 (39.8)	0.26
Triglycerides, mg/dL	129.0 (63.0)	139.5 (61.9)	0.53
Men	n=31	n=30	
Fasted glucose, mmol/L	5.1 (0.6)	5.1 (0.6)	0.89
Fasted insulin, pmol/L	53.7 (23.5)	57.2 (27.7)	0.60
Fasted C-peptide, ng/mL	2.1 (0.7)	2.1 (0.8)	0.98
Glucose _{AUC} , mmol/L × min	946.6 (231.3)	986.2 (195.8)	0.47
Insulin _{AUC} , pmol/L × min × 10 ²	437.9 (277.7)	474.6 (251.1)	0.59
C-peptide _{AUC} , ng/mL × min	854.6 (286.4)	882.0 (262.6)	0.70
Glucose _{AUC} × Insulin _{AUC} × 10 ⁶	41.3 (26.0)	47.9 (29.6)	0.36
Total cholesterol, mg/dL	194.8 (51.4)	198.9 (39.4)	0.72
HDL-cholesterol, mg/dL	51.0 (15.6)	49.8 (9.6)	0.72
LDL-cholesterol, mg/dL	116.4 (46.0)	123.4 (32.7)	0.49
Triglycerides, mg/dL	137.1 (64.9)	128.6 (67.2)	0.62

Values are mean (SD). AUC = area under the curve

Conversion factors: glucose mmol/L ÷ 0.05556 = mg/dL; insulin pmol/L ÷ 7.175 = μU/mL

Table 3

Changes in glucose regulation over 12 months

	Placebo	DHEA	Difference ^I 95% CI	P value
Women	n=31	n=24		
Fasted glucose, mmol/L	0.0 (0.4)	-0.2 (0.4)	-0.2 (-0.4, 0.0)	0.11
Fasted insulin, pmol/L	3.9 (21.0)	-2.1 (33.5)	-4.4 (-19.4, 10.6)	0.56
Fasted C-peptide, ng/mL	0.1 (0.5)	0.1 (0.6)	0.1 (-0.2, 0.4)	0.58
Glucose _{AUC} , mmol/L × min	-7.3 (187.8)	-60.7 (210.8)	-44.2 (-149.0, 60.8)	0.40
Insulin _{AUC} , pmol/L × min × 10 ²	2.6 (146.6)	16.7 (150.3)	25.4 (-58.9, 109.6)	0.55
C-peptide _{AUC} , ng/mL × min	39.0 (218.6)	-59.7 (283.6)	-52.1 (-183.0, 78.9)	0.43
Glucose _{AUC} × Insulin _{AUC} × 10 ⁶	-0.9 (19.3)	-0.5 (19.7)	2.6 (-8.1, 13.4)	0.62
Men	n=31	n=30		
Fasted glucose, mmol/L	-0.1 (0.5)	-0.1 (0.4)	0.0 (-0.3, 0.2)	0.70
Fasted insulin, pmol/L	0.2 (39.1)	-1.4 (24.3)	-1.4 (-18.3, 15.5)	0.87
Fasted C-peptide, ng/mL	0 (0.5)	0.1 (0.5)	0.1 (-0.2, 0.3)	0.65
Glucose _{AUC} , mmol/L × min	-15.5 (199.6)	-14.5 (149.9)	13.9 (-70.5, 98.3)	0.74
Insulin _{AUC} , pmol/L × min × 10 ²	-31.1 (283.8)	-11.3 (171.6)	27.3 (-91.4, 146.0)	0.65
C-peptide _{AUC} , ng/mL × min	-17.2 (202.2)	46.9 (222.7)	72.7 (-28.8, 174.2)	0.16
Glucose _{AUC} × Insulin _{AUC} × 10 ⁶	-1.7 (37.3)	-1.6 (21.6)	2.0 (-13.3, 17.4)	0.79
All	n=62	n=54		
Fasted glucose, mmol/L	-0.4 (0.4)	-0.2 (0.4)	-0.1 (-0.3, 0.1)	0.19
Fasted insulin, pmol/L	2.1 (31.2)	-1.7 (28.5)	-0.3 (-14.1, 8.2)	0.60
Fasted C-peptide, ng/mL	0.0 (0.5)	0.1 (0.6)	0.1 (-0.1, 0.3)	0.47
Glucose _{AUC} , mmol/L × min	-11.4 (192.2)	-34.6 (178.5)	-13.1 (-78.5, 35.6)	0.69
Insulin _{AUC} , pmol/L × min × 10 ²	-14.2 (224.6)	0.8 (161.8)	28.9 (-44.4, 102.2)	0.43
C-peptide _{AUC} , ng/mL × min	11.4 (210.8)	0.6 (254.0)	15.0 (-65.5, 95.4)	0.71
Glucose _{AUC} × Insulin _{AUC} × 10 ⁶	-1.3 (29.4)	-1.2 (20.6)	6.2 (-18.0, 0.3)	0.60

^I Adjusted for baseline value and sex.

Values are mean (SD). CI = confidence interval; AUC = area under the curve.

Conversion factors: glucose mmol/L ÷ 0.05551 = mg/dL; insulin pmol/L ÷ 7.175 = μU/mL