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Effects of DHEA replacement on bone mineral density and body composition in elderly women and men

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Summary

OBJECTIVE Dehydroepiandrosterone (DHEA) is a precursor for both oestrogens and androgens. Its marked decline with ageing may influence age-related changes in tissues influenced by sex hormones. The aim of this study was to determine the effects of DHEA replacement on bone mineral density (BMD) and body composition in elderly women and men with low serum DHEA sulphate (DHEAS) levels.

DESIGN Prospective 6 month trial of oral DHEA replacement, 50 mg/day.

PATIENTS Experimental subjects were 10 women and eight men, aged 73 ± 1 years. Control subjects were 10 women and eight men, aged 74 ± 1 years.

MEASUREMENTS BMD, body composition, serum markers of bone turnover, serum lipids and lipoproteins, oral glucose tolerance, serum IGF-I, total serum oestrogens and testosterone.

RESULTS BMD of the total body and lumbar spine increased (mean ± SEM; 1·6 ± 0·6% and 2·5 ± 0·8%, respectively; both $P \leq 0{\cdot}05$), fat mass decreased (− 1·3 ± 0·4 kg; $P < 0{\cdot}01$) and fat-free mass increased (0·9 ± 0·4 kg; $P \leq 0{\cdot}05$) in response to DHEA replacement. DHEA replacement also resulted in increases in serum IGF-I (from 108 ± 8 to 143 ± 7 μg/l; $P < 0{\cdot}01$) and total serum testosterone concentrations (from 10·7 ± 1·2 to 15·6 ± 1·8 nmol/l in the men and from 2·1 ± 0·2 to 4·5 ± 0·4 nmol/l in the women; both $P \leq 0{\cdot}05$).

CONCLUSIONS The results provide preliminary evidence that DHEA replacement in those elderly women and men who have very low serum DHEAS levels can partially reverse age-related changes in fat mass, fat-free mass, and BMD, and raise the possibility that increases in IGF-I and/or testosterone play a role in mediating these effects of DHEA.

Dehydroepiandrosterone sulphate (DHEAS) is an abundant steroid hormone secreted primarily from the adrenal cortex, in humans and other primates, that is a precursor for both oestrogens and testosterone. It is considered a marker of development and ageing, as serum levels increase markedly during adrenarche, reach peak levels in the third decade and decline steadily and dramatically with advancing age, to 10–20% of peak values by 80 years of age (Orentreich *et al*., 1984; Belanger *et al*., 1994). The biological functions of DHEAS remain largely unknown. Although the decline in DHEAS correlates with a variety of age-related phenomena, including loss of bone and muscle mass, increase in fat mass, and increased risk for atherosclerosis and Type 2 diabetes mellitus (Watson *et al*., 1996), the role that DHEAS deficiency plays in these changes has not been established. DHEA supplementation in rodents has potent hypolipidaemic, antiatherogenic, antiobesity, and antidiabetogenic effects (Gordon *et al*., 1988; Hansen *et al*., 1997; Han *et al*., 1998). However, because rodents produce little DHEAS (Vinson *et al*., 1978), it is uncertain whether DHEA administration has similar effects in humans.

In many of the original studies of the biological effects of DHEAS in humans, pharmacological doses (e.g. 1600 mg/day) were administered to young people for a relatively short duration (e.g. 28 days) (Nestler *et al*., 1988; Mortola & Yen, 1990; Usiskin *et al*., 1990; Welle *et al*., 1990). However, it seems unlikely that responses of people with normal DHEAS levels to excessive doses of DHEA would have relevance to the responses of people with low DHEAS levels to DHEA replacement therapy. In middle-aged and older women and men, the replacement dose necessary to raise serum DHEAS levels to the normal young adult range appears to be only about 50 mg/day (Morales *et al*., 1994; Casson *et al*., 1998; Morales *et al*., 1998). There have been studies of the effects of DHEA replacement on body composition and bone mineral density (BMD), but results are conflicting (Morales *et al*., 1994; Diamond *et al*., 1996; Labrie *et al*., 1997a; Casson *et al*., 1998; Morales *et al*., 1998; Flynn *et al*., 1999). The discordance in the literature may be attributable to a number of factors, such as the

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inclusion of subjects with only moderately reduced serum DHEAS levels, varying treatment duration, and small study samples. Moreover, the effects of DHEA replacement in oestrogen-deficient women are largely unknown, as the majority of the postmenopausal women who have been studied have been on oestrogen replacement therapy (Morales *et al*., 1994; Morales *et al*., 1998). Therefore, the purpose of this study was to determine the effects of DHEA replacement therapy on BMD, body composition, and related metabolic parameters in elderly women and men with low serum DHEAS levels who were not on sex hormone replacement therapy.

Subjects and methods

Subjects

Volunteers were recruited by advertisement. Eighteen subjects, aged 64–82 years, including 10 women and eight men (74 ± 2 years and 72 ± 2 years, respectively) received DHEA replacement therapy (Professional Compounding Centers of America Inc., Houston, TX, USA) at a dose of 50 mg/day for 6 months. Because this was a preliminary study of the biological effects of DHEA replacement in the elderly, rather than a clinical trial, control data were obtained on 18 sex- and age-matched women and men (75 ± 2 years and 71 ± 2 years, respectively) who were participating as control subjects in other ongoing studies in the Washington University Claude Pepper Older Americans Independence Center. All subjects provided informed consent to participate in the study, which was approved by the Washington University School of Medicine Investigational Review Board.

All experimental and control subjects were nonsmokers and were not on hormone replacement therapy. They were healthy, as assessed by medical history, physical examination and serum and urine chemistry profiles. They were on stable medications for at least 6 months and none had taken any drugs known to affect bone metabolism for at least 1 year prior to participation in the study. Body weight had been stable (± 2 kg) in all participants for the past year. They were normally active for their age, but did not participate in regular exercise. Subjects were instructed not to change their physical activity or eating habits over the period of study.

Young (20–30 years) women ($n = 15$) and men ($n = 15$) were also recruited to establish the range of normal DHEAS levels in young adults. All of the volunteers had a stable weight and were not taking any medication, including oral contraceptives. To be eligible for the study, the older volunteers had to have a serum DHEAS concentration that was less than 20% of the mean value for the young subjects. This cut-off was selected because the average DHEAS levels in 70-year-old women and men are approximately 20% of the peak values in young people (Orentreich *et al*., 1984).

Study protocol and procedures

Compliance with DHEA replacement was checked by pill counts at monthly intervals. Potential adverse side-effects were monitored by interview, physical examination and standard laboratory tests including CBC, electrolytes, liver and renal function tests, and in men, serum PSA levels. Assessments of BMD, body composition, oral glucose tolerance, and blood lipid profile were performed at baseline and at the end of the study in all subjects. Fasting blood samples were also obtained from subjects receiving DHEA replacement for measurement of DHEAS, IGF-I, IGF binding protein-3 (IGFBP-3), total testosterone, oestrogens (17β-oestradiol + oestrone), and markers of bone resorption and formation.

Assessment of BMD and body composition. BMD of the total body, lumbar spine (L_2-L_4), and proximal femur, were measured by dual-energy X-ray absorptiometry (DXA) using a QDR-1000/W instrument (Hologic Inc., Waltham, MA, USA). Assessments of test-retest reliability of BMD yielded intraclass correlation coefficients that were greater than 0·98 for all sites of interest. Regarding precision, the coefficients of variation for BMD were 0·6 ± 0·2% for the whole body, 1·1 ± 0·6% for the lumbar spine, and 1·2 ± 0·5%, 1·5 ± 0·9%, 1·1 ± 0·6% and 3·2 ± 2·0% for the total, neck, trochanter, and Ward's triangle regions of the proximal femur, respectively. DXA was also used to estimate body composition using v5·71 of the enhanced whole body analysis software. The precision of measuring total mass, fat mass, bone mineral mass, and nonbone fat-free mass was 0·9 ± 0·4%, 1·6 ± 1·0%, 0·8 ± 0·3%, and 1·8 ± 0·9%, respectively.

Oral glucose tolerance test (OGTT). Subjects were instructed to eat a weight-maintaining diet containing at least 150 g carbohydrate/day for 3 days before each OGTT. The 75 g OGTT was performed in the morning, after an overnight fast. Venous blood samples were obtained in the fasted state and 30, 60, 90, and 120 minutes after glucose beverage ingestion for determination of plasma glucose (glucose oxidase method) and insulin (Morgan & Lazarow, 1963) concentrations. The total and incremental areas for the glucose and insulin responses during the OGTT were calculated using the trapezoid method.

Hormone, lipid and PSA measurements. Serum DHEAS (DSL Inc., Webster, TX, USA), total testosterone (ICN, Costa Mesa, CA, USA) and oestrogens (17β-oestradiol + oestrone; ICN), and IGF-I (Daughaday *et al*., 1980) were measured by radioimmunoassay at the Radioimmunoassay Core Laboratory of the Diabetes Research Training Center at Washington University. The inter- and intra-assay coefficients of variation of these assays were all < 10%. IGFBP-3, which binds more than 95% of the IGF in serum (LeRoith *et al*., 1992), was measured by a two-step sandwich-type ELISA (DSL). Intra- and interassay precision was 7·3–11·5%. In the men, total and

free serum PSA levels were determined using monoclonal antibody assays (Hybritech Inc., San Diego, CA, USA).

Measurement of serum lipid and lipoprotein concentrations was performed in the Core Laboratory for Clinical Studies at Washington University. Cholesterol and glycerol-blanked triglycerides were measured by automated enzymatic commercial kits (Miles/Technicon, Tarrytown, NY, USA). HDL-cholesterol was measured in plasma after precipitation of apolipoprotein B-containing lipoproteins by dextran sulphate (50 000 MW) and magnesium (Warnick *et al*., 1982). These methods were continuously standardized by the Lipid Standardization Program of the Centers for Disease Control. All methods were monitored daily and were controlled for long-term consistency using a variety of internal and external quality control and quality assurance programs. LDL-cholesterol was calculated using the Friedewald equation.

Biochemical markers of bone turnover. Bone-specific alkaline phosphatase (BAP) activity (Metra Biosystems Inc., Mountainview, CA, USA), a marker of bone formation, and serum cross-linked N-telopeptides of type I collagen (NTx) (Ostex International, Seattle, WA, USA), a marker of bone resorption, were measured by ELISA in the Core Laboratory for Clinical Studies at Washington University. The inter- and intra-assay coefficients of variation for both of these measurements were in the range of 4–7%.

Statistical analyses. All data were analysed using SAS statistical software (SAS, Cary, NC, USA). Changes in outcomes over time in the experimental and control groups were examined using two-way analyses of variance for repeated measures. Changes over time within the experimental group were also examined by sex, using two-way analyses of variance for repeated measures, to investigate the sex-specificity of the responses. In the event of significant interaction effects, paired *t*-tests were performed to determine if there were significant changes within a group. Linear regression analyses were performed to determine whether changes in predictor variables of interest (e.g. hormone levels) were related with changes in outcomes (e.g. fat-free mass). Statistical significance was defined as an alpha level at or below 0·05. All data are presented as mean ± SEM.

Results

At baseline, the average serum DHEAS level in the older subjects was less than 15% of the mean level in the young subjects (1·3 ± 0·9 *vs*. 10·3 ± 2·4 nmol/l). Administration of DHEA at a dose of 50 mg/day raised serum DHEAS in the older subjects to the young adult range (Fig. 1), indicating that this was an appropriate replacement dose in this population. The median (9·5 nmol/l) and range of values (3·1–13·4 nmol/l)

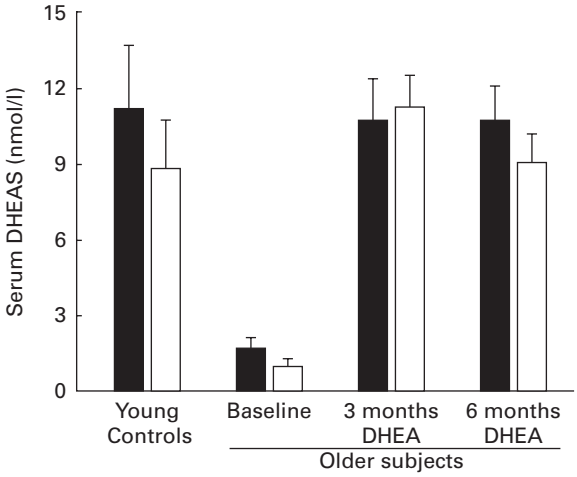

Fig. 1 Serum dehydroepiandrosterone sulphate (DHEAS) levels (mean ± SEM) in young men and women and in older men (■) and women (□) at baseline and 3 and 6 months after DHEA replacement.

achieved in the older women were comparable to values in the young women (median, 8·8 nmol/l; range, 6·7–12·0 nmol/l). Similarly, the median (10·6 nmol/l) and range of values (5·4–14·7 nmol/l) achieved in the older men were comparable to values in the young men (median, 11·4 nmol/l; range, 7·0–15·5 nmol/l).

At baseline, there were no significant differences between the treatment and control groups in BMD. BMD values were relatively high, particularly in the older men, given the age of the participants. When expressed as standard deviation scores normalized to average values in young people, the lumbar spine, femoral neck and trochanter BMD values in the men averaged 0·1 ± 0·8, − 1·3 ± 0·5, and 0·1 ± 0·5 SD, respectively; comparable values in the women were −1·0 ± 0·5, − 2·3 ± 0·4, and −1·5 ± 0·4 SD. There were significant group-by-time interaction effects for total body ($P = 0·049$) and lumbar spine BMD ($P = 0·042$). There were significant increases in total BMD (1·6 ± 0·6%; $P = 0·015$) and lumbar spine BMD (2·5 ± 0·8%; $P = 0·007$), but not the proximal femur in response to DHEA replacement (Table 1). There were no significant changes in BMD at any of the regions in the control group.

There were no significant differences between the treatment and control groups at baseline in body composition, or the glucose and insulin responses to the OGTT. There were significant group-by-time interaction effects for total fat mass ($P < 0·001$), trunk fat mass ($P < 0·001$), and fat-free mass ($P = 0·021$). Specifically, there were significant decreases in total (− 1·3 ± 0·4 kg; $P = 0·004$) and trunk fat mass (− 1·4 ± 0·3 kg; $P < 0·001$) and an increase in fat-free mass (0·9 ± 0·4 kg;

Table 1 Body composition and bone mineral density (BMD) before and after 6 months of DHEA replacement

	Men		Women	
	Before	After	Before	After
Weight (kg)	83·2 ± 4·5	82·3 ± 4·4	75·9 ± 6·5	75·7 ± 6·6
Fat-free mass (kg)	66·1 ± 2·1	66·6 ± 1·9*	42·5 ± 2·2	43·7 ± 2·2*
Fat mass (kg)	17·1 ± 2·7	15·7 ± 2·7†	33·4 ± 4·6	32·0 ± 4·6†
Trunk fat (kg)	9·2 ± 2·0	8·0 ± 2·0†	15·8 ± 2·3	14·3 ± 2·3†
BMD (g/cm^2)				
Total body	1·260 ± 0·056	1·282 ± 0·057*	1·042 ± 0·034	1·056 ± 0·036*
Lumbar spine	1·120 ± 0·088	1·160 ± 0·100*	0·973 ± 0·059	0·992 ± 0·060*
Total hip	1·043 ± 0·069	1·032 ± 0·069	0·788 ± 0·049	0·785 ± 0·049
Femoral neck	0·837 ± 0·057	0·831 ± 0·057	0·666 ± 0·045	0·661 ± 0·045
Trochanter	0·807 ± 0·059	0·802 ± 0·061	0·589 ± 0·033	0·590 ± 0·032

Significant main time effect: *$P \leq 0{\cdot}05$, † $P \leq 0{\cdot}01$.

$P = 0{\cdot}050$) in response to DHEA replacement. There were no significant changes in body composition of the control group.

There was no change in glucose tolerance over the period of study. The incremental insulin response to a glucose challenge was reduced by an average of nearly 25% in response to DHEA replacement (38·2 ± 5·2 *vs*. 29·1 ± 2·8 nmol/l.min), but this was not significant ($P = 0{\cdot}08$) due to the large variability in this parameter. There was a strong tendency for the change in trunk fat mass to be correlated ($r = 0{\cdot}46$, $P = 0{\cdot}055$) with the change in the incremental insulin response during the OGTT.

DHEA replacement resulted in significant increases in serum IGF-I (from 109 ± 8 to 143 ± 7 μg/l; $P < 0{\cdot}001$) and total testosterone (from 5·9 ± 1·2 to 9·4 ± 1·6 nmol/l; $P < 0{\cdot}001$) and a significant decrease in serum NTx (from 13·1 ± 0·7 to 12·2 ± 0·6 nM BCE; $P = 0{\cdot}002$). There were no significant changes in IGFBP-3 (117 ± 5 *vs*. 118 ± 4 nmol/l; $P = 0{\cdot}842$), BAP (22·9 ± 1·8 *vs*. 22·0 ± 1·6 U/l; $P = 0{\cdot}188$), or oestrogens (52·1 ± 9·0 *vs*. 54·3 ± 8·3 pmol/l; $P = 0{\cdot}684$) in response to DHEA. There were no significant effects of DHEA replacement on blood lipids and lipoproteins (Table 2).

Neither the baseline levels nor the changes in serum testosterone, oestrogens, or IGF-I in response to DHEA replacement were predictive of the changes in BMD (all *P*-values > 0·20).

Changes in outcomes in the DHEA replacement group were analysed further to determine whether the responses were sex-specific (Tables 1 and 2). There were decreases in trunk fat mass and total fat mass and an increase in fat-free mass in response to DHEA replacement in both women and men (Fig. 2). The only outcomes for which there were significant sex-by–time interaction effects were serum IGF-I ($P = 0{\cdot}028$), which increased to a greater extent in women than in men, and

Table 2 Hormonal and metabolic parameters before and after 6 months of DHEA replacement

	Men			Women		
	Before	After	Normal range	Before	After	Normal range
IGF-I (μg/l)	119 ± 14	141 ± 12*‡	71–290	101 ± 8	145 ± 10*‡	71–290
IGFBP-3 (ng/ml)	3067 ± 191	3298 ± 214*	2670–5580	3586 ± 101	3433 ± 161*	2670–5580
NTx (nM BCE)	13·3 ± 0·9	12·5 ± 0·8‡	5·4–24·1	12·9 ± 1·1	12·0 ± 1·0‡	6·2–19·0
BAP (U/l)	20·7 ± 0·9	20·6 ± 1·0	15·0–41·3	24·6 ± 3·1	23·2 ± 2·7	14·2–42·7
Oestrogens (pmol/l)	52·7 ± 5·9	53·8 ± 12·5	140–770	52·0 ± 16·0	55·3 ± 11·8	< 140
Testosterone (nmol/l)	10·7 ± 1·2	15·6 ± 1·8‡	10–35	2·1 ± 0·2	4·5 ± 0·4‡	< 3·5
Cholesterol (mmol/l)						
Total	4·42 ± 0·34	4·53 ± 0·32		5·61 ± 0·23	5·59 ± 0·26	
LDL	2·79 ± 0·30	2·97 ± 0·25		3·49 ± 0·17	3·70 ± 0·19	
HDL	1·24 ± 0·06	1·27 ± 0·10		1·40 ± 0·09	1·27 ± 0·07	
Triglycerides (mmol/l)	0·82 ± 0·07	0·91 ± 0·13		1·54 ± 0·30	1·33 ± 0·26	

Significant sex-by-time effect: *$P < 0{\cdot}05$; significant main time effect; †$P \leq 0{\cdot}05$, ‡$P < 0{\cdot}01$.

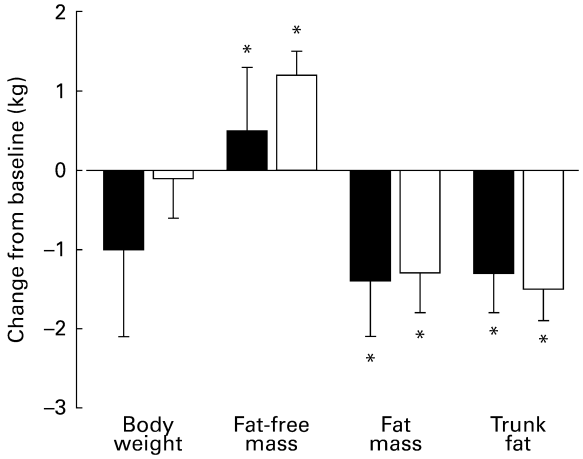

Fig. 2 Changes in body composition (mean ± SEM) in older men (■) and women (□) in response to 6 months of DHEA replacement. *Time effect $P < 0{\cdot}05$.

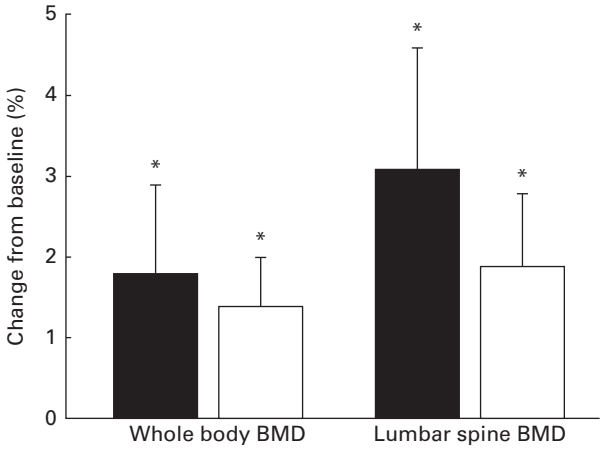

Fig. 4 Changes in whole body and lumbar spine bone mineral density (BMD) (mean ± SEM) in response to 6 months of DHEA replacement in older men (■) and women (□). *Time effect, $P < 0{\cdot}05$.

IGFBP-3 ($P = 0{\cdot}024$), which increased in men and decreased in women (Fig. 3). There were tendencies for larger increases in BMD (Fig. 4) and serum testosterone in the men (4·9 ± 1·2 nmol/l in men *vs.* 2·4 ± 0·3 nmol/l in women; $P = 0{\cdot}08$). However, the relative increase in serum testosterone concentration was significantly less in the men (from 10·7 ± 1·2 to 15·6 ± 0·4 nmol/l; 50 ± 12%) than in the women (2·1 ± 0·2–4·5 ± 0·4 nmol/l; 136 ± 18%).

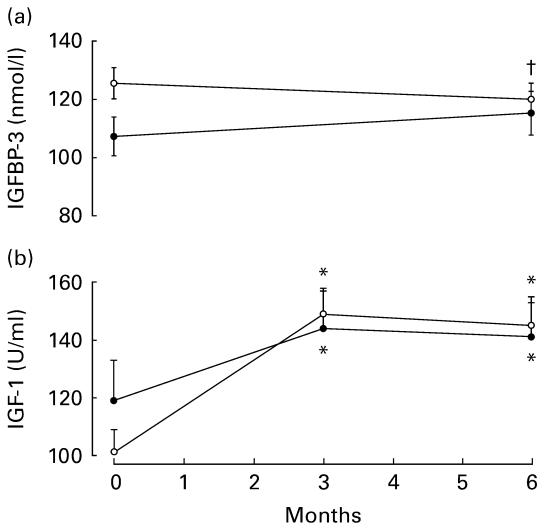

Fig. 3 (a) Serum insulin-like growth factor 1 (IGF-I) and (b) IGF binding protein 3 (IGFBP-3) at baseline and after DHEA replacement (mean ± SEM) in older men (●) and women (○). *Time effect, $P < 0{\cdot}01$; †Sex-by-time interaction effect, $P < 0{\cdot}05$.

There were no serious adverse effects of DHEA replacement. One woman reported mild facial acne that cleared spontaneously despite continued DHEA therapy. There were no changes in serum renal or liver biochemistry. Importantly, in men, there were no significant changes in total (1·3 ± 0·3 *vs.* 1·5 ± 0·2 ng/ml) or free (0·23 ± 0·05 *vs.* 0·27 ± 0·06 ng/ml) PSA levels after 6 months of DHEA replacement therapy.

Discussion

The results of this preliminary study demonstrate that DHEA replacement for 6 months in elderly people with low serum DHEAS levels had beneficial effects on BMD and body composition. Specifically, raising serum DHEAS up to the normal levels found in healthy young people resulted in significant increases in total body and lumbar spine BMD, a decrease in body fat content, and an increase in fat-free mass. Moreover, the DHEA was well tolerated by the subjects and there were no apparent serious adverse effects.

Labrie *et al*. (1997a) found significant increases in BMD and a decrease in bone resorption in 60- to 70-year-old women who used a skin cream containing DHEA for 12 months. The present study is the first to report that DHEA replacement can also improve BMD in men. The increases in lumbar spine (+ 3·1 ± 1·5%) and total body BMD (+ 1·8 ± 1·1%) in response to DHEA therapy in the men were similar in magnitude to the increases we have observed previously in older women after 6 months of oestrogen replacement therapy (Kohrt *et al*., 1995; 1998).

The changes in BMD appeared to be due to a suppression of bone turnover, specifically bone resorption, as evidenced by a

small, but significant decrease in serum NTx concentration, coupled with a maintenance of bone formation rate. However, the absence of a significant reduction in the rate of bone formation should be interpreted cautiously, as the power to detect a change in BAP was low. Although 15 of the 18 subjects had a decrease in serum NTx, the clinical significance of the small magnitude of the decline ($-9 \pm 2\%$) is unknown. Chesnut *et al*. (1997) reported that a 30% decrease in urinary NTx over 6 months increased the odds of gaining BMD in response to oestrogen by a factor of 2·6. This suggests that a 9% decline in serum NTX may have little clinical relevance. On the other hand, differences between HRT-treated and non-HRT-treated women in serum NTx levels (21%) are considerably smaller than differences in urinary NTx levels (46%) (Eastell *et al*. 2000). It will be important to determine whether the decrease in NTx and increase in BMD can be sustained or amplified with long-term DHEA replacement.

The mechanism for the suppressive effect of DHEA replacement on bone resorption is unknown. DHEAS can be converted to oestrogen, which is a potent antiresorptive agent, but circulating oestrogen levels were not significantly increased in this study. Others (Morales *et al*., 1994; 1998) have also failed to find increases in oestrone or oestradiol in response to DHEA replacement. There is evidence for a transient increase in serum oestrogens for a few hours after oral DHEA administration (Arlt *et al*., 1999) and for increases in sulphated metabolites (Labrie *et al*., 1997b), but whether such changes have an effect on bone metabolism is not known.

It is also possible that the effects of DHEA on bone were mediated by the increase in serum testosterone concentration that occurred in response to DHEA, which tended to be larger (in absolute terms) in men than in women. Testosterone replacement has been shown to inhibit bone resorption and stimulate formation in hypogonadal men (Wang *et al*., 1996). It is likely that the observed increase in total testosterone underestimated the increase in free testosterone, as DHEA administration lowers sex hormone-binding globulin (Morales *et al*., 1998). This may explain the finding of nonsignificant relationships between the change in testosterone and the changes in BMD.

DHEA replacement resulted in a marked increase in circulating IGF-I levels, which may exert anabolic effects on bone. In adults with growth hormone deficiency, growth hormone replacement and the consequent increase in serum IGF-I stimulates both bone formation and resorption (Kann *et al*., 1998). Bone formation was not increased in the current study, but this could have been due to the fact that turnover rates (i.e. resorption and formation) were already elevated in this elderly population

The increase in BMD and decrease in bone resorption that we observed was consistent with changes reported by Labrie *et al*. (1997). In contrast, Morales *et al*. (1998) reported no increase in BMD despite a nonsignificant reduction in bone resorption of approximately 28% in eight men and eight women, aged 50–65 years, after 6 months of DHEA treatment at a dose of 100 mg/day. The discordance with our results may be related to the younger age range of the volunteers studied by Morales *et al*. (1998) or to the fact that seven of the eight women in that study were on oestrogen replacement therapy. It seems plausible that the potent antiresorptive effects of oestrogen may have masked potential antiresorptive effects of DHEA and diminished the chances of finding significant changes in bone mass. Clearly, further studies are necessary to understand the mechanisms by which DHEA replacement alters bone metabolism.

An important finding in our study was that DHEA replacement had beneficial effects on both fat mass ($-1{\cdot}4$ kg) and fat-free mass ($+0{\cdot}9$ kg) in elderly women and men. The potent anti-obesity effect of DHEA supplementation in rodents is well documented (Yen *et al*., 1977; Hansen *et al*., 1997; Han *et al*., 1998), but the reported effects of replacement doses in humans have been mixed (Morales *et al*., 1994; Diamond *et al*., 1996; Casson *et al*., 1998; Morales *et al*., 1998). One study (Morales *et al*., 1998) found that fat mass decreased significantly in response to DHEA replacement in men ($-1{\cdot}0$ kg), but not in women ($+0{\cdot}5$ kg). We found no such sex-specificity of this response. Again, the lack of agreement between studies could be related to the fact that seven of the eight women in that study (Morales *et al*., 1998) were on oestrogen replacement, as oestrogens appear to play a regulatory role in regional fat deposition in postmenopausal women (Espeland *et al*., 1997; Kohrt *et al*. 1998).

The increase in fat-free mass that we observed suggests that DHEA replacement may have a role in ameliorating age-related sarcopaenia. Elderly women are at particular risk of becoming physically frail because of the loss of muscle mass and in this regard it is noteworthy that fat-free mass tended to increase more in response to DHEA in women (1·2 kg) than in men (0·5 kg). A similar trend for a sex-specific response was observed (Morales *et al*., 1998) in younger women (0·7 kg) and men (0·1 kg). It is possible that the anabolic effects of DHEA on fat-free mass were mediated by the increases in serum androgens and/or IGF-I that we and others (Morales *et al*., 1994; Casson *et al*., 1998; Morales *et al*., 1998) have observed. However, the identification of DHEAS binding sites in skeletal muscle cells *in vitro* (Tsuji *et al*., 1999) raises the possibility of direct effects of DHEA on muscle.

The replacement dose of DHEA that was used in this study was not associated with any evidence of serious adverse clinical effects. A potential health concern with DHEA replacement is the reduction in serum HDL-cholesterol in women that has been observed by others (Morales *et al*., 1994; Diamond *et al*., 1996; Casson *et al*., 1998) and is presumably related to increased

androgenicity. Both we and others Morales *et al*. (1998) observed nonsignificant decreases in HDL-cholesterol of approximately 0·13 mmol/l in women. In our study, this decrease was observed after 3 months of DHEA therapy, with no further decline after 6 months of DHEA use. Although epidemiological studies suggest that high DHEA levels are protective against cardiovascular disease, at least in men (Barrett-Connor & Goodman-Gruen, 1995), the impact of DHEA replacement on metabolic risk factors should be more thoroughly evaluated in a controlled, prospective fashion.

In summary, the results of this study suggest that 6 months of DHEA replacement therapy can partially reverse age-related changes in BMD, fat mass, and fat-free mass in older women and men with low serum DHEAS levels who are not on sex hormone replacement therapy. However, these results must be considered preliminary because of the relatively small sample size and the nonrandomized, nonblinded study design. It will be necessary to confirm or refute the findings in a larger study population, randomized to receive either DHEA or placebo in a blinded fashion. It will also be important to identify the mechanisms by which DHEA brings about changes in BMD and body composition. Our results suggest that increases in serum IGF-I and testosterone levels that occur in response to DHEA replacement may play a role in mediating these effects.

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