Effects of estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol responses to exercise in postmenopausal women

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Objective: To determine the effects of hormone replacement therapy (HRT) on dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and cortisol (F) responses to treadmill exercise.

Design: Controlled clinical study.

Setting: Female volunteers in an academic research environment.

Patient(s): Sixteen healthy, postmenopausal women (7 were receiving HRT, 9 were not).

Intervention(s): Blood samples were taken from an intravenous catheter before, during, and after 30 minutes of treadmill exercise following an overnight fast. A second session was conducted one month later for the same subjects using the same blood sampling protocol without exercise.

Main Outcome Measure(s): Serum DHEA, DHEAS, and F concentrations.

Result(s): The HRT and untreated DHEA area under the curve (AUC) for the exercise trials was significantly greater than that for the control trials. The untreated, but not the HRT, DHEAS AUC for the exercise trials was significantly greater than that for the control trials. The HRT and untreated F AUC for the exercise trials was significantly greater than that for the control trials. The AUC for the HRT exercise trials was significantly higher than the untreated exercise trials for DHEA and F, but not DHEAS.

Conclusion(s): Data suggest that treadmill exercise elevates DHEA, DHEAS, and F levels in postmenopausal women and that HRT enhances the DHEA and F responses. (Fertil Steril® 1997;68:836-43. © 1997 by American Society for Reproductive Medicine.)

Key Words: Postmenopausal, dehydroepiandrosterone-sulfate, cortisol, hormone replacement, exercise, DHEA, adrenal androgens

Aging in humans is associated with progressive declines in the secretion of the adrenal androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS), unlike another adrenal steroid, cortisol (F), whose normal serum levels are maintained with aging. Blood concentrations of DHEAS tend to peak at approximately 20 years of age, with levels declining rapidly to concentrations one-third or less that in young adults by the age of 60 years (1). DHEAS concentrations could have an effect on age-related illnesses, such as insulin resistance (2), osteoporosis (3), and immunosenescence (4).

The effects of exogenous estrogen (E) on F, DHEA, and DHEAS levels have been studied. It appears that women who have E deficiencies, ovarian failure, or who have undergone an oophorectomy have lower than normal serum concentrations of DHEAS (5). An earlier study documented significant increases in DHEA and DHEAS serum levels in postmenopausal women who were receiving E therapy compared with
a control group (6). There are dose-related increases in serum levels of DHEA, DHEAS, and F in response to conjugated Es (5).

Previous studies generally have shown that DHEA and DHEAS levels increase in response to exercise in younger populations. Significant elevations in DHEA concentrations have been found in women who have completed a 10-mile run (7), and significant elevations in DHEAS concentrations have been noted in women during treadmill running (8). However, to our knowledge, no studies of these responses in untreated postmenopausal women or in women who are receiving hormone replacement therapy (HRT) have been performed.

Estrogen therapy increases cortisol-binding globulin (CBG) synthesis by the liver. Typically, elevated F levels are seen in women who are receiving HRT because of the increased number of binding sites provided by the greater number of CBG (9).

Cortisol responses differ within various exercise modes and intensities. No change (10, 11) or small decreases in blood F levels may be seen with light or moderate exercise, whereas high-intensity exercise may elicit increases (12). Cortisol responses to exercise in younger persons are stimulated by an increased release of ACTH, as seen after 20 minutes of running at 80% maximal oxygen consumption (VO$_{2\text{max}}$) (12). We also investigated whether F responses to exercise are enhanced by HRT in postmenopausal women. We hypothesized that HRT and exercise may produce a synergistic effect on serum levels of DHEA, DHEAS, and F.

**MATERIALS AND METHODS**

**Human Subjects**

After institutional review board (Southeastern Louisiana University Committee for the Use of Humans and Animals as Research Subjects) approval was obtained, 16 postmenopausal women were recruited from newspaper advertisements as volunteers for the study. Seven of the women had been receiving HRT (conjugated E tablets or estropipate tablets) for a mean $\pm$ SD of 7.64 $\pm$ 3.56 years before entering the study; two of these women also were taking progestin. Six of the patients who were receiving HRT took E daily; one patient took E on days 1–25 of the month (this subject had been receiving E for a minimum of 14 days when tested). Both subjects on progestin were taking it at the time of testing.

Nine women were not taking any hormone replacement because of either personal choices ($n$ = 8) or a physician's advice ($n$ = 1). Menopause was surgically induced (removal of the uterus and both ovaries) in two of the women on HRT and in two of the untreated women. All other subjects experienced menopause naturally (cessation of menses for at least 1 year). Mean values for VO$_{2\text{max}}$ and other descriptive parameters, such as maximum heart rate (HR$_{\text{max}}$), age, weight, height, and percent body fat for subjects were not significantly different between groups (Table 1), indicating that the fitness level of the two groups was similar.

Criteria for participation in the study included postmenopausal status, either natural or surgical, and the ability to complete 30 minutes of moderate treadmill walking; in addition, the participant could not be taking any prescription medications other than hormone therapy. Postmenopausal status was verified with baseline gonadotropin levels. All subjects signed a written consent form after reading an informed consent statement. Before testing, a medical history questionnaire was completed and reviewed to determine whether criteria for the study were met and to ensure there were no preexisting health risks (e.g., cardiovascular disease and diabetes).

Before testing, all subjects were also instructed to refrain from exercise and alcohol intake for 48 hours. In addition, a 3-day food diary was completed by each subject during the week before the experimental and control trials to ensure that the diets were similar for both groups and for all sessions. Nutritional data were analyzed by using a computer program (Nutritionist IV-N4, version 3, Salem, OR) for daily total kilocalorie (kcal) intake, percentage of total kilocalories that were carbohydrate, fat, and protein, plus polyunsaturated:saturated fat ratio. None of the nutritional data were significantly different between experimental and control trials for either group or for experimental trials between HRT and untreated groups. Moreover, these values were all close to the Recommended Dietary Allowance (RDA) for this population.

**Preliminary Session (Session 1)**

During a preliminary session, the subject's body composition was determined by using a four-site

<table>
<thead>
<tr>
<th>Variable</th>
<th>HRT</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2\text{max}}$ (mL/kg/min)</td>
<td>28.17 $\pm$ 1.7</td>
<td>23.79 $\pm$ 2.8</td>
</tr>
<tr>
<td>HR$_{\text{max}}$ (bpm)</td>
<td>177.71 $\pm$ 5.7</td>
<td>169.69 $\pm$ 4.1</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.43 $\pm$ 3.3</td>
<td>53.00 $\pm$ 2.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.69 $\pm$ 4.4</td>
<td>70.40 $\pm$ 5.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.01 $\pm$ 2.3</td>
<td>164.82 $\pm$ 1.4</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>26.47 $\pm$ 2.2</td>
<td>24.99 $\pm$ 2.4</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>30.74 $\pm$ 6.6</td>
<td>61.99 $\pm$ 11.5</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>20.33 $\pm$ 5.3</td>
<td>26.23 $\pm$ 3.0</td>
</tr>
<tr>
<td>E$_2$ (pg/mL)</td>
<td>87.63 $\pm$ 37.0</td>
<td>31.37 $\pm$ 5.4</td>
</tr>
</tbody>
</table>

*Note: Values are means $\pm$ SE.*
skinfold measurement (13), and \( \dot{V}O_{2\max} \) was determined by using a treadmill protocol developed for the older subjects in this study. The protocol called for 2-minute stages beginning at a speed of 2 mph and 2% grade and increased 0.5 mph and 2% grade each stage until 3.5 mph was reached. Thereafter, the speed remained constant at 3.5 mph while grade was increased 3% each stage.

Each subject’s \( \dot{V}O_{2\max} \) was determined as the highest \( \dot{V}O_2 \) value when either the primary criteria of a plateau in \( \dot{V}O_2 \) (<2.1 mL/kg per minute) with an increase in workload or two of the three secondary criteria were noted: [1] the predicted HR\(_{\max} \) was reached, [2] the respiratory exchange ratio was >1.0, or [3] the rating of perceived exertion (Borg 10-point scale) was 9 or 10 (14). Cardiac function was monitored with a 12-lead electrocardiograph (Q4500; Quinton Instruments, Bothell, WA). Oxygen consumption was measured and analyzed by using the Consentius metabolic analysis system (Consentius, Sandy, UT), which was interfaced with the electrocardiograph.

**Experimental Session (Session 2)**

The subjects reported to the Southeastern Louisiana University Exercise Physiology Laboratory at 7:45 A.M. after an overnight fast. At 8:00 A.M., a registered nurse inserted an IV catheter (20 g, 32 mm) and attached a normal saline lock with the subject in a supine position. At 8:30 A.M., 40 minutes before exercise (~40) and at 9:00 A.M., 10 minutes before exercise (~10), resting blood samples were taken from the catheter while the subject was in a sitting position. For each blood draw the first 3 mL of blood (with saline from the catheter lock) was withdrawn into a discard tube and a 28-mL draw followed. The catheter was then flushed with physiological saline (3 mL) to maintain patency.

At 9:10 A.M., after a 5-minute warm-up, the subjects began 30 minutes of treadmill exercise at approximately 80% of \( \dot{V}O_{2\max} \). Oxygen consumption was monitored and recorded throughout the test, and the exercise intensity was maintained by adjusting the speed and the grade of the treadmill. One blood draw was completed midexercise (+15); additional blood draws were taken in a sitting position immediately after exercise, as well as 10, 20, 35, 50, 65, and 80 minutes after exercise (during recovery).

**Control Session (Session 3)**

For the control session, each subject reported to the exercise physiology lab at 7:45 A.M. after an overnight fast, and the same blood sampling protocol used in session 2 was completed; however, the treadmill exercise was excluded. All blood draws were conducted with the subject in a sitting position.

**Blood Analyses**

For each blood draw, samples were collected in two 10-mL whole blood Vacutainers (Becton Dickinson Systems, Rutherford, NJ) for endocrine determinations, one 5-mL ethylenediaminetetraacetic acid (EDTA) tube for hematocrit and hemoglobin (Hg), and one 3-mL sodium fluoride-potassium oxalate tube for plasma lactate analysis. Plasma volume changes (15) were determined from the hematocrit and Hg values to control for hemoconcentration/hemodilution shifts that could alter hormone levels (16). The blood lactic acid concentrations were indicative of the relative degree of anaerobiosis during the exercise. Whole blood was centrifuged, and the serum was aliquotted and frozen (−20°C) for subsequent determination of DHEA, DHEAS, and F, Estradiol, FSH, and LH were also determined in baseline samples to verify the reproductive hormone status of the women (hypoestrogenic and elevated FSH values) and to provide a complete endocrine profile for each subject.

Hematocrit was analyzed with use of microcapillary tubes and a hematocrit centrifuge (Readacrit, Clay Adams, Parsippany, NJ). Hemoglobin was analyzed spectrophotometrically (Spectronic 1001 Plus; Milton Roy, Houston, TX) with use of a colorimetric assay (Sigma Chemical, St. Louis, MO). Lactate was determined spectrophotometrically following an enzymatic procedure (Sigma Chemical).

Serum DHEA was determined by RIA with use of commercially available kits (Diagnostic Systems Laboratory, Webster, TX). Serum DHEAS, F, E\(_2\), FSH, and LH were determined with use of an automated chemiluminescent enzymatic immunoassay (IMMULITE; Diagnostic Products Corporation, Los Angeles, CA). All hormone serum samples from each subject were determined in the same assay to avoid any changes in interassay variability. Intraassay coefficients of variation (CVs) for DHEA, DHEAS, F, LH, FSH, and E\(_2\) were all <5%. Interassay CVs for DHEA, DHEAS, F, LH, and FSH as well as E\(_2\) for the low, middle, and high pools were all <10%, with the exception of the low pools for DHEA (13.58%) and E\(_2\) (14.51%) and the high pool for F (10.08%).

**Data Analysis**

The area under the curve (AUC) was determined for DHEA, DHEAS, and F by using a trapezoidal method after subtracting the averaged baseline hormone concentration (−40, −10) for each subject. The hormonal AUC for the experimental and control trials were compared with a dependent t-test to deter-
mine whether exercise affected hormone concentrations. The HRT and untreated AUC concentrations were compared by using an independent t-test to determine whether HRT affected the exercise-induced changes in hormone concentrations. All comparisons were considered statistically significant at P < 0.05. All values are means ± SE.

RESULTS

Experimental Workload

The percentage of VO₂max (mL/kg per minute), percentage of HR_max (bpm), and rating of perceived exertion (0–10) maintained during the experimental trials was not significantly different between the two groups. During the 30 minutes of treadmill exercise (session 2), the HRT subjects maintained 79.16% ± 1.2% VO₂max, 90.23% ± 1.8% HR_max, and a rating of perceived exertion of 5.1 ± 0.5. The untreated group maintained 80.19% ± 0.9% VO₂max 89.49% ± 2.5% HR_max, and a rating of perceived exertion of 5.3 ± 0.5.

Plasma Volume Shifts

Plasma volume changes were determined from the hematocrit and Hg values to control for hematocrit or hemodilution that could alter hormone levels. Resting values for hematocrit and Hg fell in the normal range for both groups (17). Plasma volume shifts for time periods -10 to + 15, +15 to 0, O-10, 10-20, 20-35, 35-50, 50-65, 65-80 minutes after exercise were as follows: -6.99% ± 2.8%, 5.23% ± 3.7%, 6.38% ± 1.5%, 1.18% ± 2.8%, -0.85% ± 1.7%, 1.40% ± 1.1%, 2.30% ± 0.8%, and -1.84% ± 1.9%, respectively, for the HRT group and -7.41% ± 3.8%, 4.97% ± 2.1%, 3.17% ± 0.99%, 0.88% ± 1.5%, 1.38% ± 1.4%, 3.23% ± 1.9%, -1.77% ± 1.7%, and 0.68% ± 1.2%, respectively, for the untreated group. These plasma volume values indicate that no hemocoagulation of >7.5% occurred during the experimental trial for either group.

Endocrine Profile

Baseline concentrations of FSH (mIU/mL), LH (mIU/mL), and E₂ (pg/mL) were within the normal range according to expected values for postmenopausal women (18, 19) (Table 1).

Responses to Exercise

The lactate concentration peaked at 52.43 ± 0.8 mg/dL (+15) for the women receiving HRT and 41.44 ± 6.3 mg/dL for the untreated women (+15) (Fig. 1). No statistically significant difference between the lactate concentrations was noted between the two groups midexercise.

The serum DHEA concentration peaked at 15.74 ng/mL ± 4.3 immediately after exercise for the women receiving HRT and 9.08 ng/mL ± 2.6 (+15) for the untreated women (Fig. 2). The DHEA AUC for women who were receiving HRT as well as for the women who were not treated was significantly greater for the exercise trial than for the control trial (P = 0.02 for HRT; P = 0.01 for not treated), and the DHEA AUC for the women who received HRT was significantly greater than that for the untreated women in the experimental trial (P = 0.02) (Fig. 2).

Serum DHEAS peaked at 97.83 µg/dL ± 12.78 10 minutes after exercise for the women who were receiving HRT and 86.60 µg/dL ± 16.81 10 minutes after exercise for the untreated women (Fig. 3). The DHEAS AUC values for the untreated women during the exercise trial were significantly greater than control values (P = 0.02). The DHEAS AUC values for the women who received HRT were higher than control values (P = 0.06). However, the DHEAS AUC for the HRT group was not significantly greater than that for the untreated group during the exercise trial (Fig. 3).

Cortisol peaked at 32.66 µg/dL ± 4.5 20 minutes after exercise for the HRT group and 22.47 µg/dL ± 2.9 10 minutes after exercise for the untreated women (Fig. 4). The F AUC for the women receiving HRT and for the untreated women was significantly greater for the exercise trial than for the control trials (P = 0.01 for the HRT group; P = 0.03 for the untreated group). The F AUC for the women receiving HRT was significantly greater than that
DISCUSSION

Although more research is needed to establish its effects, recent clinical data suggest that the replacement of DHEA in humans could be effective for enhancing insulin sensitivity (2), immune function (4), GH insulin-like growth factor I (IGF-I) (20), and one’s sense of well-being (20), while reducing serum triglycerides (2) and the risk of developing osteoporosis (20). We conducted this study to determine whether E replacement enhances the DHEA, DHEAS, and F responses to aerobic exercise in postmenopausal women.

We are aware of no previous study that has examined both serum DHEA and DHEAS exercise responses in postmenopausal women. Recently, it was shown that replacement doses of DHEA increase the bioavailability of IGF-I, which could attenuate the loss of lean tissue associated with aging (20). Baker et al. (7) found that eumenorrheic women who completed a 10-mile run had higher DHEA and DHEAS concentrations than nonathletic female controls. Cumming and Rebar (21) documented increases in DHEA concentrations in untrained and trained eumenorrheic women and in trained amenorrheic women in response to a graded exercise test on a cycle ergometer.

In other studies, only DHEAS was measured. These studies also have shown that DHEAS levels increase with exercise in young women. Keizer et al. (8) showed elevated DHEAS levels from an incremental, short-term cycle ergometer test in trained eumenorrheic women. Untrained subjects did not elicit a significant response. In addition, elevated DHEAS concentrations in response to rigorous cycling and running, including 15-, 25-, and 42-km competitions, have been noted in premenopausal women (10, 22). We found that exercise elicited significant DHEA responses in postmenopausal women. Moreover, the concentration of DHEAS in

Figure 2 (A), Mean DHEAS concentrations (±SE) for the HRT group (circles; n = 7) and the untreated (NHRT) group (triangles; n = 9) during the exercise (●, △) and control (○, ▽) trials; (B), HRT and untreated DHEA AUC concentrations for the exercise (●) and control (○) trials; statistical significance noted between (**) and within (*) groups.

for the untreated women for the exercise trial (P = 0.03) (Fig. 4).

Figure 3 (A), Mean DHEAS concentrations (±SE) for the HRT group (●, ○; n = 7) and the untreated (NHRT) group (△, ▽; n = 9) during the exercise (●, △) and control (○, ▽) trials; (B), HRT and untreated DHEAS AUC concentrations for the exercise (●) and control (○) trials; statistical significance noted within (*) group.
the untreated women was increased by treadmill exercise, and the effect of HRT on the DHEAS response to exercise approached statistical significance ($P = 0.06$).

The DHEA response to exercise was considerably greater than the DHEAS response. These findings are compatible with expected results in that DHEAS is found in higher concentrations and has a considerably longer half-life compared with DHEA (19); thus, a large increase in DHEAS would be required to observe a large alteration in concentrations. DHEA concentrations are a reflection of acute adrenal activity, whereas DHEAS concentrations usually indicate long-term adrenal function.

Our data suggest that HRT enhances DHEA responses to exercise but that it does not enhance DHEAS response to exercise. Lobo et al. (5) documented a DHEA response, but not a DHEAS response, to administration of 0.625 mg of conjugated Es. Administration of 2.5 mg of conjugated Es resulted in increased concentrations of DHEAS and DHEA. All the women in our HRT group were receiving E dosages of <2.5 mg, which may not have been sufficient to elevate DHEAS levels.

The DHEA responses, noted in both groups, offer a new finding for this population and support previous data obtained for younger females (7, 21). These DHEA exercise responses are most probably due to an increased secretion rate by the adrenal cortex that is caused by ACTH stimulation from the intensity of the exercise. The enhanced response in the HRT group is an unprecedented finding and could be an additional effect of the E therapy. Abraham and Maroulis (6) proposed that exogenous Es may potentiate the effect of ACTH on the zona reticularis region, which is the area of the adrenal cortex specifically responsible for androgen secretion.

Several possible mechanisms for exercise-elicited DHEAS increases have been offered previously. Kelzer et al. (8, 10, 22) most often attributed DHEAS elevations to an increased secretion rate. More controversial is the suggestion by other investigators (6), who believe that prolactin may stimulate androgen secretion through the action of Es. Furthermore, hemoconcentration was not the mechanism for the increases noted in the DHEA, DHEAS, and F concentrations, because peak percent changes in these hormones were well above the greatest percent plasma volume reduction.

Although no therapeutic effects have been established clinically with the elevation of DHEA levels, recent studies have suggested that DHEA replacement may have some remedial effects for this population (4, 20). Our data indicate that exercise alone can elevate DHEA levels in postmenopausal women and that HRT enhances these responses. However, further research to establish whether higher DHEA levels ameliorate the aging process clearly is warranted.

The effects of exercise on F levels has been studied extensively (10–12). Strenuous exercise elicits elevated ACTH concentrations (12). The exercise protocol in the present study was designed to activate the hypothalamic-pituitary-adrenal axis by administering an exercise intensity of approximately 80% of $\dot{V}O_{2\text{max}}$. We found exercise-induced increases in F concentrations in the HRT and untreated groups, indicating activation of the hypothalamic-pituitary-adrenal axis. Estrogen administration may increase the biosynthesis of F through the conversion of 17-OH pregnenolone to 17-OH P in response to ACTH (5, 23). Although we did not measure ACTH, it appears that the exercise-induced increases in ACTH, combined with influence of conjugated Es, would explain the F response in the present study. The elevated F responses in both groups support...
previous data. Furthermore, the enhanced response in the HRT group is a new finding. These data could have the following implications for the acute adrenal responses in this population. First, it is well known that a stressor such as exercise elevates F levels (12). Increases in this glucocorticoid might aid in the physiological inhibition of inflammation, maintenance of vascular reactivity (i.e., catecholamine effects), and energy metabolism during and/or after these conditions.

All exercise values for the untreated group remained within normal ranges for this population (18, 19). The enhanced HRT peak response only slightly exceeded expected norm values 20 minutes after exercise; however, these values fell in the normal range within 50 minutes after exercise. Thus, the enhancement of F in the HRT group during exercise could provide “repair and recovery” effects, catecholamine responses, and energy metabolism without any negative repercussions.

There was a significantly higher lactate value in the HRT versus the untreated group at one time point. The difference was seen immediately after exercise; however, this difference was not seen at 10 minutes after exercise or at any other time point. We do not believe that this indicates a difference in physical exertion between the two groups. Stanley et al. (24) indicated that elevated lactate levels may be due to lactate production and/or a reduction in the turnover or clearance rate of lactate, which could explain the variations noted between groups and individuals. Furthermore, during the exercise the two groups maintained a similar %Vo2max and a %HRmax and a similar rating of perceived exertion values.

To rule out the possibility that the order of the sessions had an effect on the results of this study, we compared baseline hormone values between the control and exercise sessions for both groups. No statistical significance was noted for either group for the two sessions had an effect on the results of this study, except for the enhanced peak response only slightly exceeded expected norm values 20 minutes after exercise; however, these values fell in the normal range within 50 minutes after exercise. Thus, the enhancement of F in the HRT group during exercise could provide “repair and recovery” effects, catecholamine responses, and energy metabolism without any negative repercussions.

There is little indication that the means by which menopause was induced in these women affected the DHEA responses to exercise in this study. It is well known that the adrenal is the most important source of DHEA and that the ovaries appear to contribute little serum DHEA (19, 25). Thus, grouping surgically and naturally menopausal women together would not have had a major impact on our results.

Moreover, basal DHEA values were not lower in the surgically induced menopausal women receiving HRT than in the naturally menopausal women receiving HRT or lower in the untreated surgically induced women than in the untreated naturally menopausal women. Furthermore, we compared individual DHEA, DHEAS, and F responses of the two naturally menopausal women, who were taking a progestin, with the other HRT subjects and observed no discernible differences.

In summary, this is the first study to show the acute adrenal responses of DHEA, DHEAS, and F concentrations to treadmill exercise in women receiving HRT and untreated postmenopausal women. Estrogen replacement therapy was shown to enhance exercise-induced increases of DHEA and F, but not DHEAS, in this population. Although the clinical significance of these findings is yet to be established, it is well known that exercise and HRT may have significant health-related benefits (e.g., for patients with cardiovascular disease or osteoporosis). However, future investigations are needed to establish whether increased DHEA levels, in response to these treatments, could offer additional benefits for this population.

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