Altered DHEA and DHEAS Response to Exercise in Healthy Older Adults

Sarah Aldred, Manjit Rohalu, Kate Edwards, and Victoria Burns

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are hormones produced by the adrenal cortex that decline in concentration with age. Decreased DHEA levels are associated with age-related disease and oxidative stress but might be increased in younger adults by exercise. Studies are presented assessing the response of DHEA and DHEAS to varied-intensity exercise in older age. DHEA increased significantly in young adults ($14.5 \pm 6.1$ ng/ml rising to $21.1 \pm 7.5$ ng/ml; $p < .01$), whereas DHEAS decreased significantly ($2.56 \pm 1.11$ µg/ml falling to $1.90 \pm 0.8$ µg/ml; $p < .05$), after submaximal exercise. DHEA and DHEAS levels were significantly lower in older adults than in younger adults ($p < .01$), and there was no observed response of either hormone to exercise in older adults. Lipoprotein protein carbonylation is presented as a measure of oxidative status and significantly decreased in younger adults postexercise. Participants with higher DHEA postexercise had lower LDL protein carbonyl concentrations (Pearson’s coefficient $-0.409$, $p < .05$).

Keywords: hormones, physical activity, oxidative stress

Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are hormones produced by the adrenal cortex. The levels of both decline in concentration with age. These decreased levels have been associated with immune-system dysfunction and activation (Ledochowski, Murr, Jager, & Fuchs, 2001), increased oxidative stress (Bastianetto, Ramassamy, Poirier, & Quirion, 1999), and atherogenesis (Khalil et al., 1998). DHEA has a number of reported beneficial effects; in fact, it has been termed the wonder hormone because of its action in improving mood state in the clinically depressed (Wolkowitz et al., 1997), improving psychological well-being in the elderly (Morales, Haubrich, Hwang, Asakura, & Yen, 1998), and correcting hormone levels in patients with adrenal deficiencies (Hunt et al., 2000). DHEAS is the most abundant circulating steroid in the human body, with a very long half-life. It is a common belief that DHEAS serves as the circulating pool for DHEA and is readily desulfated back to DHEA, catalyzed by steroid sulfatases for use in testosterone or estradiol synthesis. In a recent study, however, there was no evidence of desulfation (Hammer et al., 2005).
Exercise is beneficial to health, and improved metabolic and biochemical parameters seen in chronic diseases associated with aging, such as heart disease and diabetes, can be attributed to regular physical activity. Indeed, metabolic syndrome is a multifactorial condition linked to chronic conditions of physical inactivity (Issa & Hanna, 2003). Physical activity and exercise are also known to decrease reported depression and increase feelings of psychological well-being and promote emotional health (Neuman et al., 1998), responses that might be, in part, attributed to hormonal responses to exercise.

Exercise is known to elicit an adrenal response (Consitt, Copeland, & Tremblay, 2002), and indeed there are a number of studies that have reported increased cortisol after an acute bout of endurance or resistance exercise (Kindermann et al., 1982; Kraemer & Ratamess, 2005). The number of studies that have assessed the effect of exercise on DHEA and DHEAS levels within the same study, however, is limited. Studies that have investigated these hormones have often been done in postmenopausal women (Giannopoulou, Carhart, Sauro, & Kanaley, 2003) or under race conditions, when intensity and duration of exercise cannot be controlled (Bonen & Keizer, 1987). When levels after endurance exercise have been reported, findings are mixed (Bonen & Keizer; Corrigan, 2002), and the effect of exercise intensity has not been assessed. Therefore, although previous studies have reported DHEA and/or DHEAS concentration with reference to exercise (Bonnefoy et al., 2002; Kemmler et al., 2003), there is a need to qualify the response of DHEA and DHEAS to a specific exercise intensity in different populations and in a controlled setting.

In addition to a number of potentially interlinked responses, decreases in DHEA have been associated with increased oxidative stress, and DHEA has been shown to have antioxidant properties (Bastianetto et al., 1999; Khalil et al., 1998). Furthermore, we have shown that DHEA has antioxidant properties to protect low-density lipoprotein (LDL) against oxidative damage in vitro (Aldred & Griffiths, 2004). Oxidative damage to LDL is one of the initiating processes in atherosclerosis and formation of the atherosclerotic plaque (Raitakari et al., 1997) and has been implicated in a number of the contributing factors associated with heart disease (Berliner & Heinecke, 1996).

Exercise can alter the balance of oxidative and antioxidative species in the human body, and although it was first assumed that because of an increased oxygen metabolism, exercise would induce an increased release of reactive species to cause damage to proteins, DNA, and lipids (Balakrishnan & Anuradha, 1998; Packer, 1997), more recent research has indicated that exercise-induced radical species are key to adaptive processes (Jackson, 1999; Mc Ardle, Pattwell, Vasilaki, Griffiths, & Jackson, 2001; Roberts, Vaziri, & Barnard, 2002). For example, exercise training has been shown to increase antioxidant enzymes such as superoxide dismutase and glutathione peroxidase (Elosua et al., 2003) and can increase levels of water- and lipid-soluble endogenous antioxidants such as ascorbic acid and alpha tocopherol (Powers, DeRuisseau, Quindry, & Hamilton, 2004). It is possible that an exercise-induced increase in DHEA levels might also contribute to total antioxidant capacity.

The response of DHEA and DHEAS to exercise in young and older adults requires verification, and the studies presented here aimed to further the understanding of the responses of DHEA and DHEAS to different-intensity exercise across different age groups. In addition, the oxidative status of volunteers after
exercise was assessed in a subset of younger and older men and women, to assess a possible correlation with DHEA concentration.

**Methods**

**Moderate- to High-Intensity Exercise**

**Participants.** Participants were 19 healthy, recreationally active students, 10 men and 9 women, at the University of Birmingham, age 24.21 ± 3.15 years. Seven healthy volunteers, 3 men and 4 women, age 65–75 years were recruited via two general-practice medical surgeries in Birmingham, UK, for the older adult group. All participants were classified healthy by the medical practices and were not prescribed any medication at the time of the study. Participants gave informed consent, ethical approval for the study was obtained from the Coventry research ethics committee, and research and development permission was given to use general-practice surgeries by the south Birmingham PCT and Heart of Birmingham PCT. There were no differences between men and women in age or body-mass index. None of the participants smoked, had a history of immune or cardiovascular disease, were suffering from an acute infection or illness, were pregnant, or were currently taking medication (with the exception that all the young women were taking birth control). All participants were asked to abstain from vigorous exercise for at least 24 hr and alcohol, caffeine, and food for at least 12 hr before testing.

**Submaximal Exercise Task.** In the young group, participants undertook a four-step incremental cycle-ergometer test, with each step lasting 4 min. The workloads performed at each step were 84, 133, 182, and 231 W for men and 70, 98, 126, and 154 W for women. These workloads were selected after pilot testing to elicit similar heart rates in men and women. On average, the final workloads were 77% of W_max for women and 81% of W_max for men. Participants were instructed to pedal at 70 rpm throughout.

In the older adult group, participants undertook a submaximal task that consisted of treadmill walking (h/p/cosmos) with a gradually increasing speed and angle of elevation. The speed increased by 0.5 km/hr every 2 min, with elevation rising 2° every 2 min; speed and elevation increases occurred alternately. Douglas bag collections (30 s) were made at 55%, 65%, and 75% of HR_max, worked out by the formula 208 – (age × 0.7) (Tanaka, Monahan, & Seals, 2001). This formula is known to be a more accurate predictor of heart rate in older individuals than the common 220 – age formula. On average, final workloads were 58% of W_max for women and 62% of W_max for men.

VO_2, VCO_2, total expired air volume, and temperature of expired air were all recorded. All gas analyzers (Servomex) were calibrated using known gas volumes before the start of our gas analysis.

All participants were made aware of the exercise procedure and became familiarized with the mouthpiece used.

**Low/Moderate-Intensity Exercise**

**Participants.** Twenty-one healthy human volunteers (9 men age 20–23 years, VO_2max 44.5 ± 7 ml · kg⁻¹ · min⁻¹, and 12 women age 18–23 years, VO_2max 32 ± 8
ml · kg⁻¹ · min⁻¹) from the University of Birmingham participated in the young group, and 7 healthy volunteers (3 men, VO₂max 32 ± 7 ml · kg⁻¹ · min⁻¹, and 4 women, VO₂max 23.1 ± 2.9 ml · kg⁻¹ · min⁻¹) age 65–75 years were recruited via two general-practice medical surgeries in Birmingham, UK, for the older adult group. All the participants in the older adult group were classified healthy by the medical practices and were not prescribed any medication at the time of the study. Participants gave informed consent, ethical approval for the study was obtained from the Coventry research ethics committee, and research and development permission was given to use general-practice surgeries by the south Birmingham and Heart of England PCTs. None of the participants smoked, had a history of immune or cardiovascular disease, were suffering from an acute infection or illness, were pregnant, or were currently taking medication (with the exception that all the young women were taking birth control). Restrictions on caffeine intake and exercise were as for the moderate- to high-intensity-exercise study.

**Exercise Task.** The exercise task comprised a steady-state cycling test at 60% W_max for 40 min in the young group and a steady-state treadmill test at 50% W_max for 30 min in the older adult group. An incremental cycle exercise test to volitional exhaustion was undertaken in the young group, and an incremental submaximal treadmill test was undertaken by the older adult group, to determine individual W_max and VO₂max. Heart rate was monitored throughout (Polar Electro, RS200), and Douglas bag collections were taken for 30-s periods at 10, 20, and 30 min to monitor expired air.

**Blood Sampling.** An intravenous Teflon catheter (Quickcath, Baxter) was introduced into an antecubital vein and connected to a posiflow adaptor (BD Biosciences). The catheter was kept patent with regular flushing using isotonic saline 0.9% sodium chloride (Hill et al., 1998). Blood was drawn immediately after the formal resting baseline and directly after exercise. At each draw, blood was collected into an iced 4.5-ml tube containing ethylene diaminetetra-acetic acid (EDTA K3E 15%, 0.054 ml BD Vacutainer, Meylan Cedex), which was centrifuged (3,000 rpm at −9 °C for 10 min) and the plasma aliquotted and stored at −70 °C until analysis.

**DHEA and DHEAS Analysis.** DHEA and DHEAS levels were assessed by ELISA (DRG Instruments GmbH). Briefly, plasma samples and standards (20 µl or 25 µl) were plated in a 96-well plate with prebound antibody to DHEA or DHEAS. Enzyme conjugate (DHEA or DHEAS conjugated to horseradish peroxidase; 100 µl) was applied to the wells and incubated for 1 hr at room temperature. The ELISA was visualized with TMB substrate (100 µl) and the reaction stopped with sulfuric acid (0.5 M, 100 µl) before reading at 450 nm. For reference, plasma cortisol was determined similarly using a sandwich ELISA (DRG Instruments GmbH). Plates were again read at 450 nm.

**LDL Oxidative Damage Assessed by Protein Carbonylation.** LDL was prepared by ultracentrifugation (Chung et al., 1986) and assessed for protein carbonyl content as a marker of oxidative stress by ELISA modified from the method of Carty et al. (2000).
Results

Moderate to High Intensity
DHEA in plasma significantly increased in the young group after submaximal exercise (14.5 ± 6.1 ng/ml rising to 21.1 ± 7.5 ng/ml; \( p < .01 \); Figure 1). This response was proportional to that of cortisol (100.6 ± 38.4 ng/ml rising to 120.2 ± 34.5 ng/ml). There was a significant correlation between the DHEA and cortisol responses when assessed by Pearson’s correlation coefficient (.775, \( p = .02 \)). DHEA levels were seen to return to, and remain at, preexercise levels after 30 min of recovery. DHEA levels were significantly lower in older participants than in younger participants \( (p < .01) \). DHEA levels in older adults did not change significantly after submaximal exercise \( (0.630 ± 0.16 \text{ ng/ml preexercise and } 0.637 ± 0.18 \text{ ng/ml postexercise}; \ Figure 1) \).

The circulating DHEAS concentration was seen to significantly decrease immediately after submaximal exercise \( (2.56 ± 1.11 \mu g/ml \text{ falling to } 1.90 ± 0.8 \mu g/ml; \ p > .05) \) in young people, but DHEAS levels did not change after submaximal exercise in older adults \( (0.56 ± 0.23 \mu g/ml \text{ preexercise and } 0.55 ± 0.23 \mu g/ml \text{ postexercise}; \ Figure 2) \). Again, DHEAS levels were significantly lower in the older adult group \( (p < .01) \).

Low/Moderate Intensity
DHEA levels increased after steady-state exercise in young men and women \( (19.3 ± 4.1 \text{ ng/ml preexercise and } 25.9 ± 6.7 \text{ ng/ml postexercise}; \ p < .01) \). DHEA levels did not change significantly in the older adult group after steady-state exercise \( (0.714 ± 0.14 \text{ ng/ml preexercise and } 0.727 ± 0.17 \text{ ng/ml postexercise}; \ Figure 1) \).

![Figure 1](image_url) — Dehydroepiandrosterone (DHEA) in young and older adults before and immediately after exercise of different intensities, \( M ± SD \). *Mean value \( (p < .01) \) significantly lower pre- than postexercise. **\( p < .01 \); old significantly lower than young.
Aldred et al.

DHEAS levels were seen to decrease significantly after exercise in young men and women (2.0 ± 1.1 µg/ml preexercise and 1.8 ± 0.8 µg/ml postexercise; \( p < .05 \)), but levels remained unchanged in the older age group (0.65 ± 0.28 µg/ml preexercise and 0.66 ± 0.28 µg/ml postexercise; Figure 2).

DHEA (\( p < .01 \)) and DHEAS (\( p < .01 \)) levels were significantly lower in the older adult group than in the young group.

**LDL Oxidative Damage Assessed by Protein Carbonylation**

The concentration of DHEA postexercise was negatively correlated with the level of LDL oxidation, where the DHEA concentration was higher postexercise. Participants with higher DHEA postexercise had lower LDL protein carbonyl concentrations (Pearson’s coefficient –.409, \( p < .05 \)). LDL protein carbonylation significantly decreased after steady-state exercise (Figure 3) in the young age group (4.38 ± 0.71 nmol/mg protein preexercise and 4.05 ± 0.95 nmol/mg protein postexercise; \( p < .05 \)) and was also lower in the older adult group (5.00 ± 0.36 nmol/mg protein preexercise and 4.96 ± 0.4 nmol/mg protein postexercise), but this group demonstrated a severely blunted response. LDL carbonylation in older adults was significantly higher than that observed in younger volunteers (\( p < .05 \)).

**Discussion**

Exercise is known to stimulate an adrenal response (Consitt et al., 2002). For a number of years it has been reported that circulating levels of androgens, including testosterone, increase after an acute bout of exercise. DHEA and its sulfon conjugated derivative DHEAS are major secretory products of the human adrenal
cortex, but the number of studies that have assessed both hormones in tandem after exercise in different age groups is limited. The results presented in these studies demonstrate that in young healthy adults DHEA levels increase, whereas DHEAS levels decrease, after an acute bout of exercise. This response is not observed in older adults.

Because DHEAS is often termed the circulating pool for DHEA, exercise activity might increase DHEA availability by the conversion of DHEAS to DHEA. DHEA and DHEAS are interconvertible by sulfatases and sulfotransferase in peripheral and adrenal tissues (Racchi, Balduzzi, & Corsini, 2003), and exercise might be an important stimulus to favor the production of DHEA. DHEA is a precursor for the sex hormones testosterone and estradiol. Testosterone is known to increase after exercise (Kraemer & Ratamess, 2005). Exercise is also known to increase circulating levels of estradiol in plasma (Walberg-Rankin, Franke, & Gwazdauskas, 1992). Taking our results together with those of others, it might be appropriate to postulate that an increase in DHEA stimulated by exercise might promote and enable this increase in testosterone and estradiol, which is also commonly seen after exercise.

In the young test group the results presented concur with studies that have demonstrated that DHEA levels can be increased by a short bout of exercise (Boudou, de Kerviler, Erlich, Vexiau, & Gautier, 2001; Giannopoulou et al., 2003). The observed changes demonstrate that submaximal exercise and steady-state lower intensity exercise caused a significant increase in DHEA from baseline. Cortisol was also seen to increase after exercise (results not shown). There was a significant correlation between the DHEA and cortisol responses. In contrast to DHEA and cortisol, DHEAS levels decreased in response to both submaximal and steady-state exercise in men and women. These responses in DHEA or

Figure 3 — Low-density lipid (LDL) protein carbonylation in older adults and young pre- and immediately postexercise, $M \pm SD$. *$p < .05$; significantly lower post- than preexercise.
DHEAS concentrations were not seen the in older adult group in either low- or moderate-intensity exercise.

It is well known that DHEA and DHEAS levels decrease with age, to only 2–5% at age 70 of the levels observed at age 30. It is therefore possible that baseline levels are too low to observe a response in DHEA or DHEAS to exercise in older adults or that a detectable response is not possible in this age group at this intensity (reviewed in Copeland, Chu, & Tremblay, 2004). This might directly be caused by the anatomy or physiology of the adrenal glands in older age. It might not be ethically possible to assess older adults at the same intensity and duration as younger adults, the intensity and duration necessary to produce a measurable response.

Individuals with higher DHEA levels postexercise had lower LDL oxidation. Taken together with previous in vitro studies from this laboratory (Aldred & Griffiths, 2004), it might be suggested that DHEA has antioxidant properties that can specifically protect LDL from the damaging effects of free radicals. Although LDL carbonylation was seen to decrease after exercise in older adults, the observed change was not significant and was much less than the decrease in LDL carbonylation observed in the younger age group (7.5% decrease in young adults vs. 0.7% decrease in older adults). In addition, observed LDL carbonyl levels were higher in older adults than in younger adults. Along with neuroprotective and memory-enhancing effects, DHEA has been shown to display antioxidant properties in other studies (Bastianetto et al., 1999). A mechanism for the protective effects of DHEA in preventing LDL oxidation was put forward by Khalil et al. (1998). Results showed that DHEA was able to inhibit the oxidation of LDL when it was subjected to oxidative damage by reducing conjugated dienes and TBARS formation. In addition, when DHEA was incubated with vitamin E, it was able to reduce vitamin E consumption when LDL was subjected to oxidative stress. It was therefore postulated that DHEA exerts its antioxidative effect by protecting or regenerating endogenous vitamin E levels in LDL. DHEA has also been shown to interfere with the generation of superoxide radicals (Whitcomb & Schwartz, 1985) and protect liver microsomes from oxidative damage (Aragno et al., 2004).

A number of studies have presented contradictory results for the response of both DHEA and DHEAS to exercise. Studies show decreased DHEA (Kemmler et al., 2003), increased DHEAS (Tremblay, Copeland, & Van Helder, 2004; Kemmler et al.), or no response of either DHEA or DHEAS (Consitt, Copeland, & Tremblay, 2001; Copeland, Consitt, & Tremblay, 2002; Giannopoulou et al., 2003). As is demonstrated here by the different responses observed in young versus older adults, however, when the participant groups used across the reported literature include trained and untrained men and women, premenopausal and postmenopausal women, and men and women of different age groups and where the exercise stimuli are also inconsistent and include resistance and endurance exercise, variation in reported DHEA and DHEAS responses should be expected. These factors should be considered when evaluating “inconsistencies” between studies reporting the response of adrenal hormones to exercise.

The studies presented here represent exercise undertaken on a cycle ergometer and a treadmill. All studies involving the older adults used treadmill walking/slow-running exercise. The use of different exercise tasks is a limitation when comparing the results of the studies presented, although studies supporting signifi-
cantly different DHEA or adrenal outcomes from endurance versus endurance exercise are not reported. Studies showing significantly different DHEA responses to resistance versus endurance exercise are available in the literature (Tremblay et al., 2004; Consitt et al., 2001; Copeland et al., 2002). Cycling and running might elicit recruitment of different muscle fibers or proteins on a cellular level in skeletal muscle, but an adrenal response can be achieved by either cycling or running, or, indeed, by psychological stress (Shirtcliff, Zahn-Waxler, Klimes-Dougan, & Slattery, 2007). In addition, studies have shown that at similar exercise intensities running and cycling can stimulate physiologically similar responses other than hormonal responses (Caputo, Mello, & Denadai, 2003). It was believed that older individuals in the UK would be no longer accustomed to riding a bicycle and that walking or jogging on a treadmill would be more similar to their accustomed daily activity.

For ethical reasons, when a maximal exercise test to exhaustion was undertaken by young adults, a submaximal test was undertaken by the older age group; however, both young and older adults were assessed for moderate- to high-intensity-exercise response using a submaximal test. The average workloads achieved in the submaximal test were 70% $W_{\text{max}}$ for the younger group versus 60% $W_{\text{max}}$ for the older group. Steady-state exercise tasks were of low to moderate intensity for both old and young participants: 60% $W_{\text{max}}$ in young versus 50% $W_{\text{max}}$ in old. These exercise intensities were set based on ethical and realistically achievable parameters, and the differences in workload should be noted when taking into account the results presented.

It has been demonstrated recently that DHEAS level in older individuals might be a predictor of the ability of biochemical systems to adapt to physical activity (Huang et al., 2006). If borne out, these results might have significant implications for age-related disease and the prescription of exercise to prevent and retard disease. Further studies are required in older adults, perhaps testing different exercise intensities, in different settings, in the healthy and disease sufferers, to further understand the response and implications of a response of DHEA and DHEAS to exercise bouts in older adults.

References


epiandrosterone inhibit 12-O-tetradecanoylphorbol-13-acetate stimulation of super-
oxide radical production by human polymorphonuclear leukocytes. *Carcinogenesis*,
6, 333–335.

Dehydroepiandrosterone (DHEA) treatment of depression. *Biological Psychiatry*, 41,
311–318.