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ORIGINAL ARTICLE

Effect of acute DHEA administration on free testosterone in middle-aged and young men following high-intensity interval training

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Abstract With advancing age, plasma testosterone levels decline, with free testosterone levels declining more significantly than total testosterone. This fall is thought to underlie the development of physical and mental weakness that occurs with advancing age. In addition, vigorous exercise can also lower total and free testosterone levels with the decline greatest in physically untrained men. The purpose of the study was to evaluate the effect of oral DHEA supplementation, a testosterone precursor, on free testosterone in sedentary middle-aged men during recovery from a high-intensity interval training (HIIT) bout of exercise. A randomized, double-blind, placebo-controlled crossover study was conducted for 8 middle-aged participants (aged 49.3 ± 2.4 years) and an additional 8 young control participants (aged 21.4 ± 0.3 years). Each participant received DHEA (50 mg) and placebo on separate occasions one night (12 h) before a 5-session, 2-min cycling exercise (100 % $\dot{V}O_{2max}$). While no significant age difference in total testosterone was found, middle-aged participants exhibited significantly lower free testosterone and greater luteinizing hormone (LH) levels than the young control group. Oral DHEA supplementation increased circulating DHEA-S and free testosterone levels well above baseline in the middle-aged group, with no significant effect on total testosterone levels. Total testosterone and DHEA-S dropped significantly until 24 h after HIIT for both age groups, while free testosterone of DHEA-supplemented middle-aged men remained unaffected. These results demonstrate acute oral DHEA supplementation can elevate free testosterone levels in middle-aged men and prevent it from declining during HIIT. Therefore, DHEA supplementation may have significant benefits related to HIIT adaptation.

Keywords HIIT · Free testosterone · Lactate · LH · Luteinizing hormone

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Introduction

Testosterone, a potent anabolic hormone, plays an important role in antagonizing catabolic stress from daily physical challenges. Because of its hydrophobic nature, most of the circulating testosterone is bound to plasma proteins, including sex hormone-binding globulin (SHBG) and albumin. The SHBG-bound fraction is biologically inactive

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because of the high binding affinity to testosterone, whereas the albumin-bound testosterone is readily dissociable and thus bioavailable as is the small percentage of free testosterone that is normally circulating in the blood (Bhasin et al. 2010). In middle-aged men, there is a rise in SHBG levels, which results in a more substantial age-dependent decline in free testosterone than total testosterone (Harman et al. 2001; Yeap et al. 2007). Furthermore, this decline in free testosterone is directly correlated with the development of physical weakness (Hyde et al. 2010), mental illness (Moffat et al. 2004), and metabolic disorders (Wehr et al. 2011) with advancing age.

Dehydroepiandrosterone (DHEA) is an endogenous precursor of testosterone produced by the adrenal cortex (Kroboth et al. 1999) and exists primarily in a sulfated form (DHEA-S) due to the action of steroid sulfatase (Kroboth et al. 1999; Yamada et al. 2007). Since DHEA-S is the most abundant circulating steroid in the human body, the age-dependent decline in circulating DHEA-S may partly contribute to the decreased testosterone levels with advancing age (Lamberts et al. 1997). Although exercise training is generally recommended for middle-aged adults, several forms of exercise training can reduce DHEA-S levels (Tsai et al. 2006), resulting in a decline in total (Cumming et al. 1987) and free testosterone levels (Nindl et al. 2001; Tremblay et al. 2004).

Recently, high-intensity interval training (HIIT) has been promoted as an effective training method for improving aerobic fitness, weight loss, and general health (Gibala and McGee 2008). However, the effect of HIIT on total and free testosterone levels in middle-aged men is currently unknown. Furthermore, although DHEA appears to effectively raise testosterone levels in middle-age men, its effect on testosterone levels in middle-aged men when recovering from vigorous exercise has not yet been sufficiently documented. Therefore, the purpose of this study was to determine the effect of a low dose of DHEA supplementation (50 mg), received the night before a high-intensity intermittent exercise session, on plasma free and total testosterone levels of middle-aged men during a 24-h training recovery.

Methods

Participants

Sedentary young (aged 21.4 ± 0.3 years, $N = 8$) and middle-aged men (aged 49.3 ± 2.4 years, $N = 8$) voluntarily enrolled in this DHEA intervention study. All participants were informed of the possible risks and the experimental procedure 1 week before the experimental trials began. Participants with any form of nutritional supplementation or under testosterone administration were precluded from the study. All qualified 16 men were forbidden to participate in any form of vigorous exercise 1 week before and during the experiment. This human trial was conducted during 2009–2010 after approval of the appropriate university Institutional Review Boards.

Experimental design

We hypothesized that a single dose of DHEA supplementation can help to limit a decline of free testosterone levels in middle-aged men as a result of vigorous exercise. To determine the effect of a single dose of DHEA on the testosterone levels of middle-aged and young participants during recovery from vigorous exercise, we used a randomized, double-blind, placebo-controlled crossover design, with a 10-day washout period between the crossover trials. The dosage of DHEA (Sigma, St Louis, USA) was 50 mg and was based on previous studies, which demonstrated a substantially rise in DHEA-S level for middle-aged or older men after supplementation (Arlt et al. 1999; Yang et al. 2005). DHEA or placebo capsules were orally taken by participants 12 h before the exercise challenge under supervision of staff personnel. Both placebo, made from rice flour, and DHEA were encapsulated to eliminate the possible confounding effect caused by differences in look, smell, and taste.

In the morning, fasted participants arrived to the laboratory at 0800. About 250 ml of water were supplied to each subject upon arrival. At 0900, participants performed 2 min of cycling at 100 % $\dot{V}O_{2max}$ (maximal oxygen consumption) for five times with 1 min rest between each cycling interval. Blood samples were collected from participants immediately before exercise (0900), immediately after exercise, and 15 min and 24 h into recovery.

Maximal oxygen consumption ($\dot{V}O_{2max}$)

$\dot{V}O_{2max}$ was determined one week before the experimental trial on a Monark 839E cycle ergometer (Monark Ltd, Varberg, Sweden). $\dot{V}O_{2max}$ and maximal HR were determined during a continuous incremental cycle ergometer protocol. This protocol consisted of a 5-min warm-up and incremental increases in workload of 60 W every 3 min until exhaustion. VO_{2max} was verified by a respiratory exchange ratio (RER) of greater than 1.1 and a plateauing of VO_2 with increasing workload. O_2 and CO_2 concentrations of inspired and expired gases were measured with a MetaMax I system (Leipzig, Germany).

Blood sample

Blood samples (5 ml) were withdrawn from an antecubital vein and immediately split among tubes after collection. Part of a blood sample was added to 0.1 ml EDTA (24 mg/ml, pH 7.4), centrifuged for 10 min at 3,000 g, and the plasma collected. The rest of the blood sample was allowed to clot for 10 min at room temperature, centrifuged as before, and the serum collected. The plasma and serum samples were stored −80° C until biochemically analyzed. Plasma was used for the measurements of lactate, total testosterone, DHEA-S, cortisol, and luteinizing hormone (LH). The serum samples were used for free testosterone analysis.

Biochemical analyses

Total testosterone, free testosterone, DHEA-S, cortisol, and LH were measured according to manufacturer's instructions (Immuno-biological Laboratories, Inc., Minneapolis, MN 55432, USA) using a Genios ELISA Analyzer (TECAN Group Ltd., Salzburg, Austria). Plasma lactate concentration was measured using Lactate Assay Kit II (BioVision, Malpitas, CA, USA) according to a step-by-step procedure provided by manufacturer. Briefly, duplicate samples (50 µL) and reaction mixture buffer were added in a 96-well microplate. They were then incubated for 30 min at room temperature. Lactate concentration was estimated by measuring the optical density at 450 nm in a microplate reader on a Genios ELISA Analyzer (TECAN Group Ltd., Salzburg, Austria). All the samples were measured in duplicate, and the intra-assay coefficient of variances (with sensitivity) for DHEA-S, total testosterone, free testosterone, cortisol, and LH were 4.6 % (0.044 µg/mL), 3.3 % (0.083 ng/mL), 4.7 % (0.17 pg/mL), 6.2 % (0.36 ug/dL), and 5.7 % (0.12 mIU/mL), respectively.

Statistical analysis

Since the sample size of the study was small, the Shapiro–Wilk test was used to test whether the data were normally distributed, and Levene's test was used to confirm the homogeneity of variances. Because not all dependent variables tested were normally distributed, comparisons between paired data were analyzed using the nonparametric Wilcoxon's signed rank test. To analyze changes over time, a Friedman test was used, and when a significant F-ratio was found, Wilcoxon's signed rank test was used for post hoc analysis. The subject number for both groups were selected in accordance with a similar study design published elsewhere (Kraemer et al. 1991). In the present study, a minimum of three participants was required to attain 50 % power for determining the effect of DHEA supplementation on free testosterone in exercised middle-aged men. Data are presented as mean ± standard error (SE). A $P < 0.05$ was considered significance for all tests.

Results

Results for plasma DHEA-S concentration are shown in Fig. 1. Baseline circulating DHEA-S of the middle-aged men was substantially lower than that of the young control men ($P < 0.05$). Twelve hours after oral DHEA supplementation, DHEA-S increased significantly above baseline for both middle-aged (from 0.82 ± 0.13 to 5.16 ± 1.19 µg/mL, $P < 0.05$) and young men (from 2.13 ± 0.46 to 7.93 ± 1.57 µg/mL, $P < 0.05$). DHEA-S levels declined significantly after exercise (HIIT) for both age groups with DHEA supplementation.

Total and free testosterone results are shown in Figs. 2 and 3, respectively. Baseline total testosterone levels were not significantly different between the middle-aged and young control groups (Fig. 2). After exercise, total testosterone declined significantly for both middle-aged and young groups ($P < 0.05$), and this decline occurred regardless of whether DHEA or placebo were supplemented. Baseline free testosterone (Fig. 3) of the middle-aged group was ~75 % lower than that of the young control group (9.22 ± 2.81 vs. 2.76 ± 0.28 pg/mL, $P < 0.05$). Oral DHEA supplementation significantly elevated free testosterone for both middle-aged (2.76 ± 0.28 to 9.99 ± 1.86 pg/mL, $P < 0.05$) and young (9.22 ± 2.81 to 19.4 ± 2.80, $P < 0.05$) groups. Unlike total testosterone, free testosterone levels of both age groups were not significantly affected by exercise.

Luteinizing hormone and lactate are documented physiological stimulators for testosterone release from the testicles (Lin et al. 2001). Results for each are presented in Figs. 4 and 5, respectively. The average LH levels of the middle-aged group were significantly greater than that of the young group during the 24-h training recovery period. Baseline and exercise-induced changes in lactate concentrations were not different between middle-aged and young groups.

No significant difference was found in baseline cortisol concentrations between middle-aged and young men (Fig. 6). Cortisol increased significantly after exercise and to a similar extent for both middle-aged and young control groups. Oral DHEA supplementation did not affect cortisol concentrations. As expected, a significant drop of cortisol to baseline for both groups was observed following a 24-h recovery. However, the middle-aged group had a significantly lower cortisol level than the young control group at 24-h post exercise.

Results for total testosterone-to-cortisol (T/C) ratio and free testosterone-to-cortisol (FT/C) ratio are shown in Figs. 7 and 8, respectively. While the T/C ratio was not affected by DHEA supplementation, the FT/C ratio was

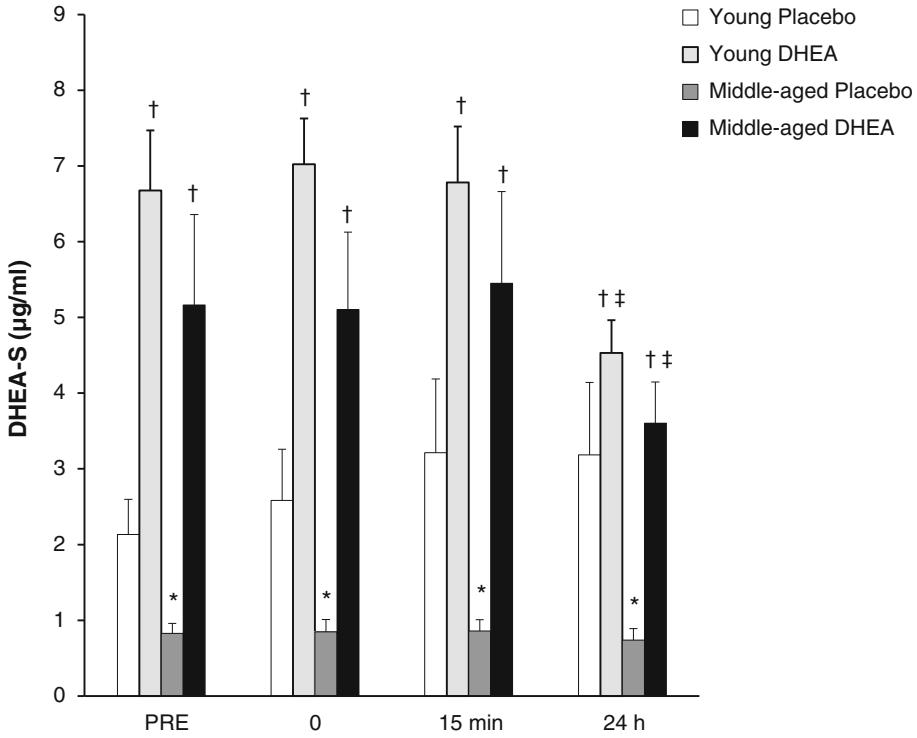

Fig. 1 DHEA-S response after an acute bout of high-intensity interval training (HIIT) for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; †significance against placebo at the same age level; ‡significance against pre-exercise baseline

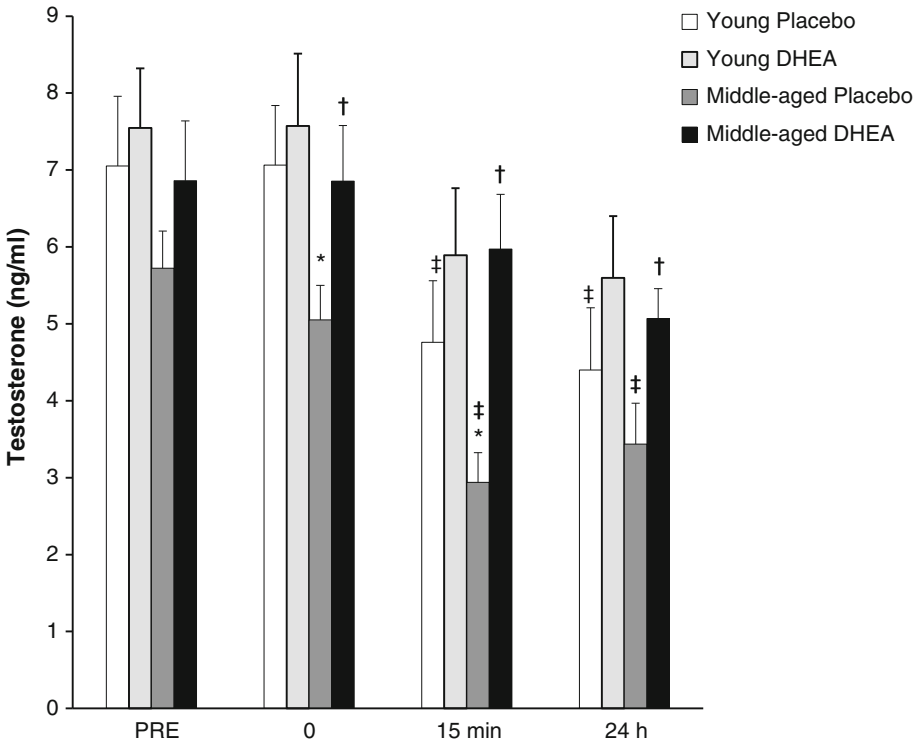

Fig. 2 Total testosterone response after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; †significance against placebo at the same age level; ‡significance against pre-cexercise baseline

increased significantly during the training recovery for both the middle-aged and young control groups. Exercise had no effect on the FT/C ratio but did tend to lower the T/C ratio immediately after exercise.

Discussion

Age-dependent decline in free testosterone is associated with development of several aging complications, such as

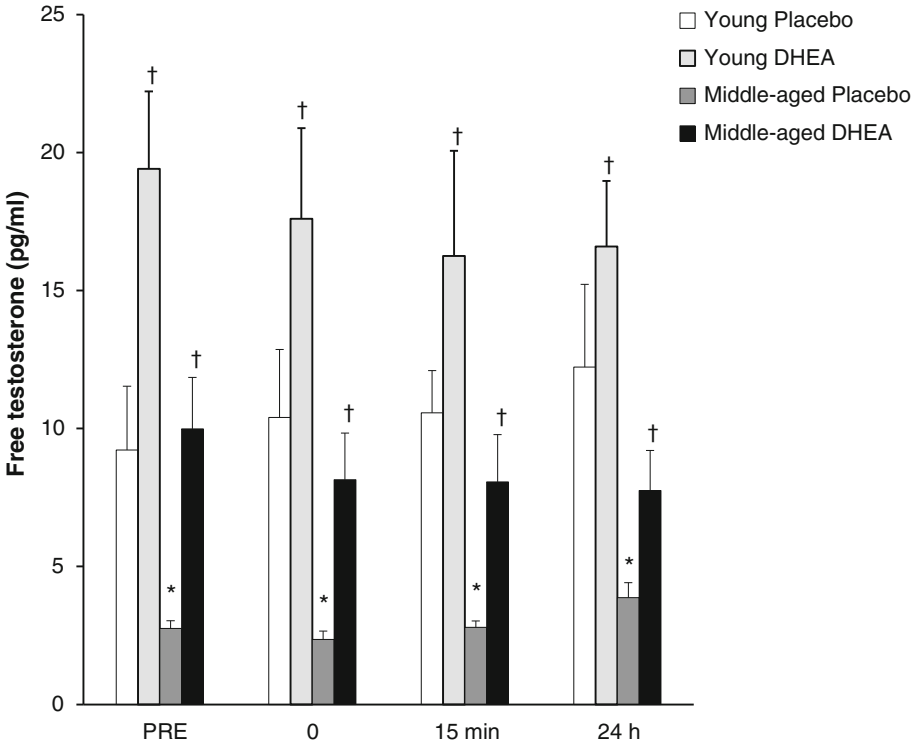

Fig. 3 Free testosterone response after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; †significance against placebo at the same age level; ‡significance against pre-exercise baseline

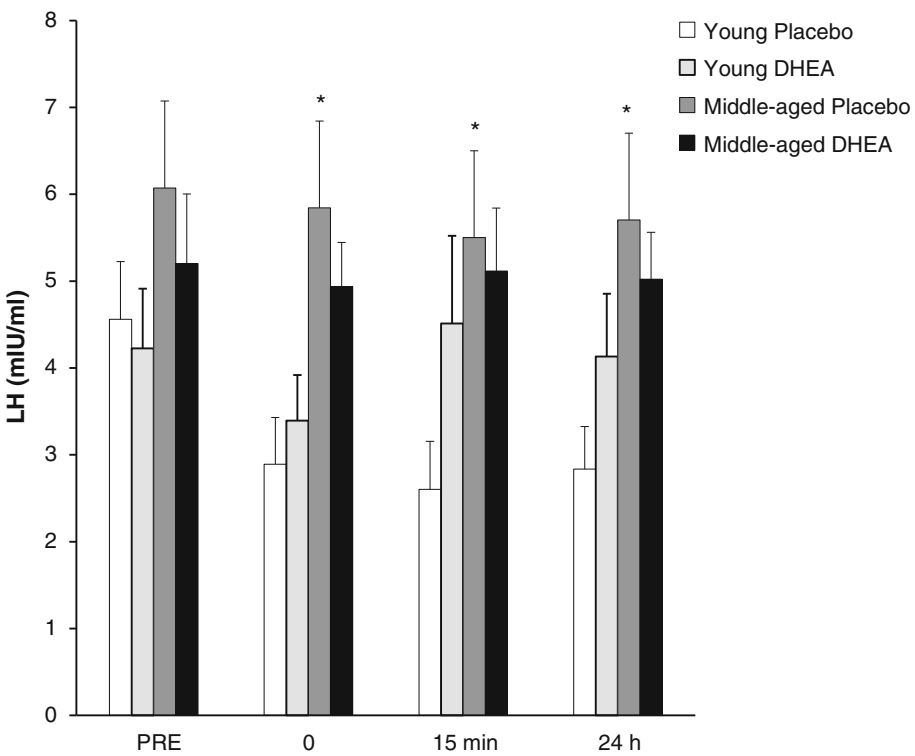

Fig. 4 Luteinizing hormone (LH) response after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. ‡ Significance against pre-exercise baseline

physical weakness (Hyde et al. 2010), mental illness (Moffat et al. 2004), and metabolic disorders (Wehr et al. 2011) in adults. Despite encouragement for middle-aged and older men to exercise train to improve physical fitness and health, decreased levels of total and free testosterone have been observed following vigorous exercise (Nindl et al. 2001; Tremblay et al. 2004). In this study, we report that HIIT decreased total testosterone levels of middle-aged men, but their free testosterone levels were not affected by this type of exercise training regimen.

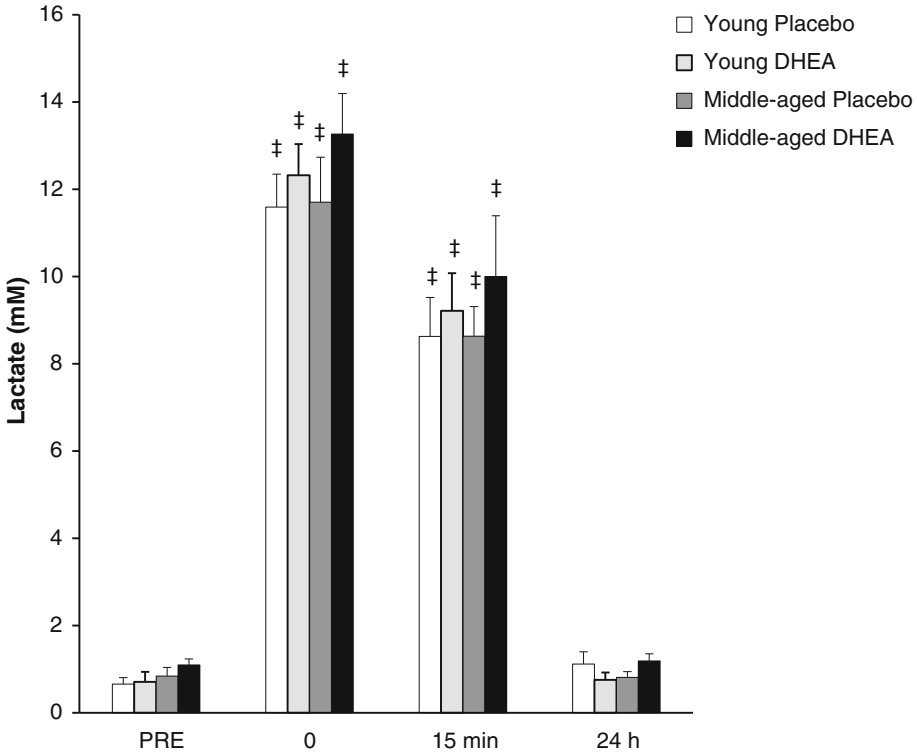

Fig. 5 Lactate response after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control

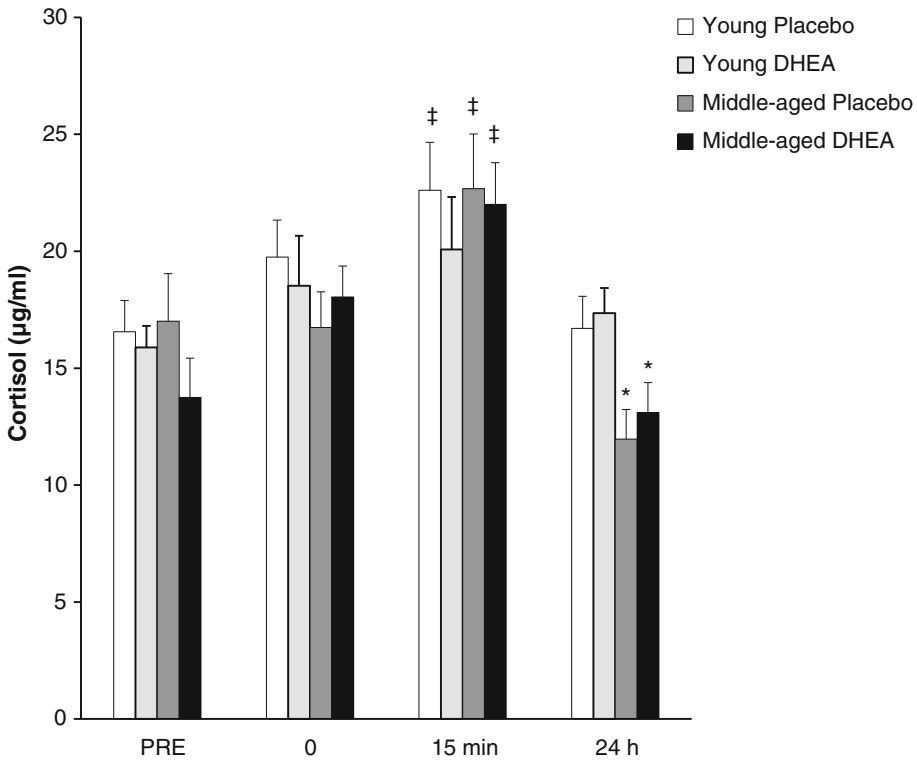

Fig. 6 Cortisol response after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; ‡significance against pre-exercise baseline

Moreover, we found that free testosterone during recovery from HIIT can be elevated effectively by oral DHEA administration for those middle-aged men with reduced free testosterone levels. The mechanism underlying the positive effect of oral DHEA administration on free testosterone does not seem to be associated with an increase in total testosterone availability, but rather a decrease in SHBP levels (Morales et al. 1998).

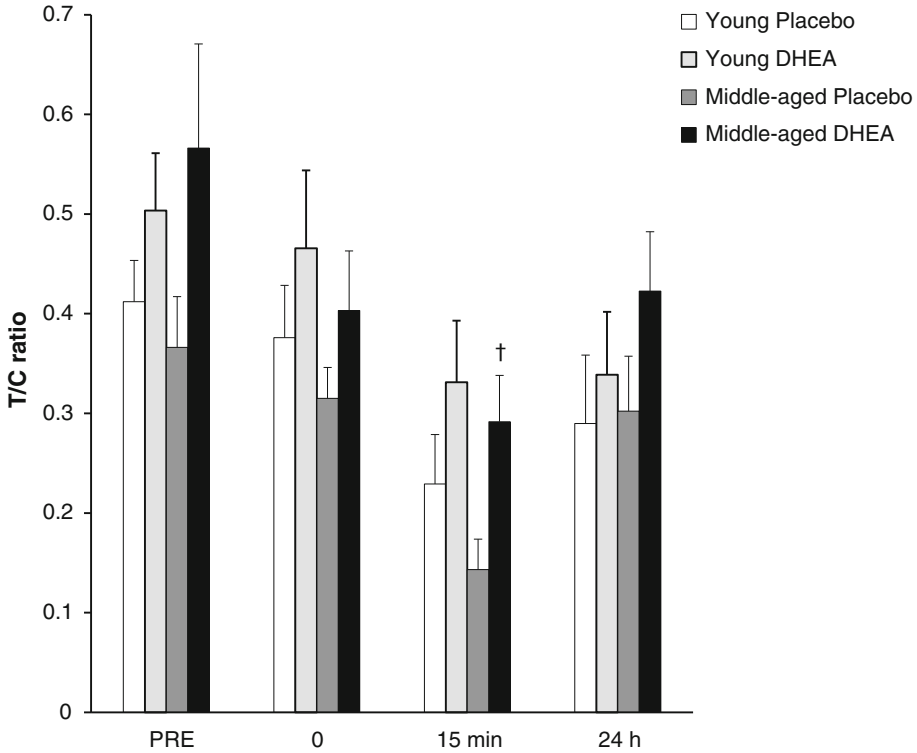

Fig. 7 Testosterone-to-cortisol (T/C) ratio after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; †significance against placebo at the same age level; ‡significance against pre-exercise baseline

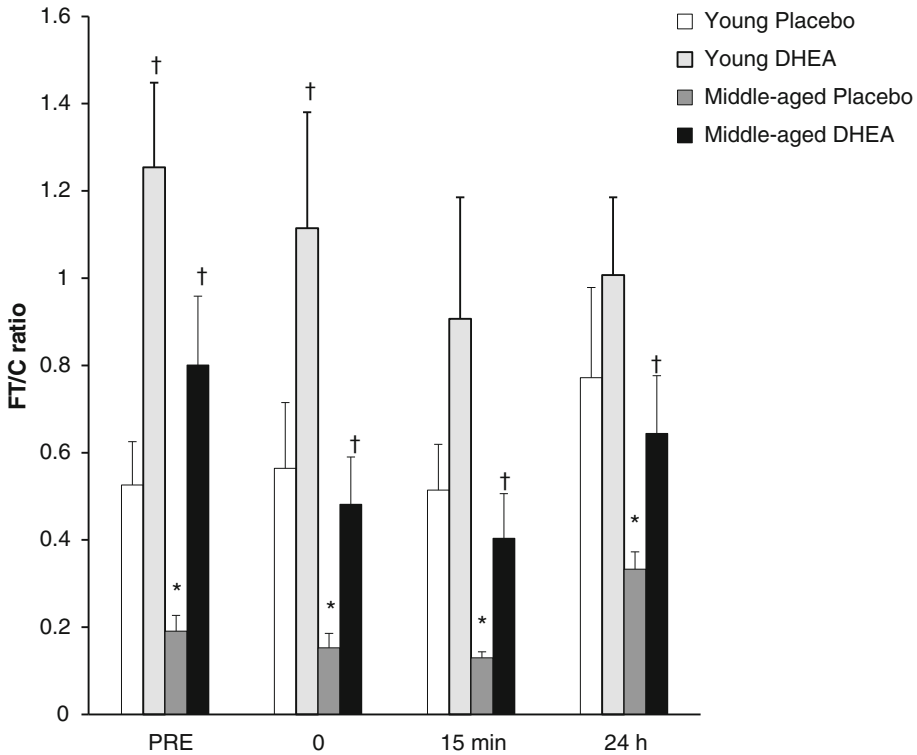

Fig. 8 Free testosterone-to-cortisol (FT/C) ratio after an acute bout of HIIT for middle-aged ($N = 8$, aged 49.3 ± 2.4 years) and young control men ($N = 8$, aged 21.4 ± 0.3 years) during DHEA and placebo trials. *Significance against young control; †significance against placebo at the same age level; ‡significance against pre-exercise baseline

We also report a greater baseline LH in middle-aged men compared to young men. It is generally thought that free testosterone, but not bound testosterone, provides feedback regulation for the release of LH from the hypothalamic-gonadotroph unit. Therefore, the greater plasma LH levels in middle-aged men compared to young men may result from reduced feedback from free testosterone inhibiting gonadotropin releasing hormone-LH

secretion. However, it has been reported that the aromatization of testosterone to estradiol is the direct stimulus for feedback inhibition of LH, rather than testosterone or free testosterone (Hayes et al. 2000; Leder et al. 2004; Schnorr et al. 2001). Thus, we speculated that the dose of DHEA administrated in our study may not have been high enough to raise the estradiol levels to observe a significant LH inhibition, despite being able to elevate the free testosterone levels of middle-aged participants.

High-intensity interval training was found to have no significant effect on LH for both age groups. This result is somewhat different from that of McMurray et al. (1995) who reported a small but significant lowering of the area under the LH curve after a 60-min endurance run. They also reported no differences in pulsatile LH release measured over 6 h of recovery. Cumming et al. (1985) reported an increase in circulating LH after exercise, but LH pulse frequency was reduced. Similar to our results, MacConnie et al. (1986) found that an acute 2-h treadmill run at 72 % VO_{2max} did not alter plasma LH concentrations of highly trained runners when measured over 8 h of recovery. Based on these findings and our results, we speculate that the effect of exercise on LH is small and may be influenced by the type, intensity, and duration of the exercise.

Our finding that the greater declines in circulating DHEA-S in the DHEA administered groups is similar to our previous finding that participants with high versus low endogenous DHEA-S levels have a greater decrease in DHEA-S under a physical challenge at high altitude (Lee et al. 2006). Circulating DHEA-S levels typically decrease under external challenges such as physical trauma and strenuous exercise (Kroboth et al. 1999), with better adaptation generally observed in individuals that have the highest endogenous DHEA decline. This suggests that this steroid is consumed for physiological adaptation (Huang et al. 2006; Lee et al. 2006; Liao et al. 2013). It has been reported that DHEA-S clearance increases during the rapid cell proliferation phase of the fetus (Gant et al. 1971; Williams et al. 2004). Thus, it is possible the decline in DHEA-S noted after exercise is associated with increased DHEA-S consumption for muscle cell regeneration, which is important for tissue remodeling and training adaptation.

Total testosterone levels were found to decline significantly in both middle-aged and young participants by 15 min post exercise and remain low for the next 24 h. Testosterone response to exercise appears to vary depending on training status. Jensen et al. (1991) reported a significant rise in testosterone after both resistance and endurance exercise in well-trained men, with testosterone returning to baseline level within 2 h. This temporal response appeared to be associated with a change in muscle androgen receptors (Ahtiainen et al. 2009). Schmid and colleagues (1982), however, reported that highly endurance-trained men have an increase, but less well-trained men, a decrease in blood testosterone levels in response to the same amount of exercise. Therefore, our finding that total testosterone declined post exercise rather than increase could have been due to the training status of our participants. Dietary content (such as L-carnitine content) can also influence the levels of blood testosterone and androgen receptor during training (Kraemer et al. 2006) and therefore could also have influence the outcome of our study.

It has been shown that lactate can directly stimulate testosterone release from testicular Leydig cell in rats (Lin et al. 2001). In the present study, our short-term HIIT substantially elevated blood lactate. However, we failed to detect any testosterone increase in response to this lactate surge. Since blood testosterone concentration is a balance between testosterone production and degradation, it is possible that the rate of testosterone degradation was faster than testosterone release from Leydig cells of human testes during and after HIIT. It is also possible that lactate does not stimulate testosterone release from the Leydig cells in humans.

The testosterone-to-cortisol ratio has been frequently used as a marker of anabolic and catabolic balance in athletes during training, as this hormonal ratio correlates well with changes in muscle size and power during long-term strength training (Hakkinen et al. 1988). Recently, Lane et al. (2010) suggested that the free testosterone-to-cortisol ratio should be utilized as a marker of training stress or imbalance since free testosterone has the biological effect. In the present study, free testosterone was elevated with DHEA administration and well maintained after HIIT. Villareal and Holloszy (2006) found that DHEA therapy potentiated the effect of 4 months of weightlifting training on muscle strength and volume in elderly men and women. By maintaining elevated levels of DHEA-S during and following HIIT, it is possible that DHEA supplementation could increase training adaptation to high-intensity exercise in middle-aged and older individuals as well. However, a long-term intervention study is needed to confirm this possibility.

The free testosterone level is closely associated with muscle mass and strength in the elderly (Herbst and Bhasin 2004; van den Beld et al. 2000). A number of recent studies reported that low levels of free testosterone are independently associated with increased cardiovascular mortality (Wehr et al. 2011; Yeap et al. 2010), higher prevalence of depression (Almeida et al. 2008), onset of Alzheimer diseases (Moffat et al. 2004), and frailty (Hyde et al. 2010) in adults. In this study, we found that an age-dependent decline in free testosterone was not affected by HIIT. However, supplementation of DHEA with HIIT was able to boost the level of free testosterone of middle-age men to

the level of our young control group. This result encourages future investigation to determine whether combining exercise training and DHEA supplementation can optimize the long-term benefits of exercise training for the elderly and help to limit or reverse the aforementioned clinical complications caused by aging.

We must note that one potential side effect of DHEA supplementation to middle-aged or older men is the increase in estrogen levels (Arlt et al. 1999; Labrie and Luciano 2010). In a recent report, middle-aged Japanese males that received 25 mg of DHEA daily for 2 weeks had a significant 27 % elevation in estradiol (Yamada et al. 2007). This increase, however, only raised the levels of estradiol to those of young male participants in the study. Whether this is an unwanted side effect in middle-aged men remains unclear.

Conclusion

In this study, we confirm that HIIT can lower total testosterone levels, but free testosterone appears to be unaffected. More importantly, we provide convincing evidence that oral DHEA administration can rapidly raise the free testosterone levels of middle-aged men to levels comparable to that of young men, and this increase is well maintained after acute HIIT.

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Conflict of interest All authors declare no competing interest.

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