

Assessment of endocrine stress status in athletes – new twists to the tale

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Abstract

Objective. Cortisol concentration at rest seems to be an insensitive marker for endocrine stress status in athletes. Therefore, the aim of this review was to identify potentially more sensitive parameters which could be used to monitor endocrine stress status during chronic exercise training. In order to gain more insight from studies not directly related to exercise science, this review also includes findings from studies investigating responses to psychological stress in healthy individuals and in patients suffering from chronic disease.

Data sources: Medline.

Study selection and data extraction. Key words (e.g. exercise stress, psychological stress, overtraining, chronic fatigue, dehydroepiandrosterone (DHEA), chronic inflammation). Only studies published in peer-reviewed journals included in the International Science Index were used. Care was specifically taken not to over-represent any particular research group's articles.

Data synthesis. A qualitative synthesis was done, based on all papers included in the review.

Conclusions. Four main conclusions were drawn: (i) instead of considering changes in mean cortisol concentration over time for a group of athletes, high- and low-responders should be identified at baseline and their responses considered separately; (ii) it may be more useful to express cortisol concentration as a ratio to either testosterone or DHEA-sulphate (DHEAs) concentration than assessing either the catabolic or anti-catabolic variable on its own; (iii) in response to stress, cortisol binding globulin (CBG) and sex hormone binding globulin (SHBG) do not seem to play

major roles in the regulation of circulating concentrations of bioactive cortisol and testosterone respectively; and (iv) it is crucial to allow sufficient recovery from the most recent exercise session to ensure that proper resting blood samples are obtained for assessment of chronic effects of training on endocrine status.

Introduction

Acute exercise stress results in physiological changes in the endocrine stress-axis that are usually only transient. Repeated exercise bouts in quick succession may however prevent the full recovery of basal homeostatic balance with regards to the hormonal axes, between bouts. In training regimens followed by elite athletes, insufficient recovery time from exercise is frequent, rather than the exception. These athletes are also under constant psychological stress (both sport-associated and every-day life stress), which may further contribute to their overall stress status. Unless athletes are able to adapt and cope with the increased stress, they may react poorly to additional stressors, resulting in inability to train at the previous level and decreased performance in competitive events. Alternatively, they may be unable to adequately down-regulate the stress response, which may lead to chronic over stimulation. Chronically elevated serum cortisol concentration has been linked directly to cellular protein catabolism²¹ and athletes with a greater stress hormone response to acute exercise have a greater perturbation of several immune function indices.¹⁷ These possible outcomes are likely to impact negatively on the careers of professional athletes.

The most consistent endocrine change reported in earlier studies investigating the endocrine response to an acute exercise stressor, is that of increased concentrations of serum cortisol.^{32,39,42} However, in response to chronic exercise training, many studies report an unchanged resting serum cortisol concentration over time.^{11,12,44} Although this may suggest that the endocrine stress status of these athletes is not compromised by their training regimens, reports of a decreased acute cortisol response to exercise in highly trained athletes³⁶ and in athletes suffering from the overtraining syndrome^{35,54,55} argues against full recovery between exercise bouts. This may occur only in some individuals or in response to some training programmes, possibly those that allow insufficient recovery time. Subtle or gradual adaptive changes in the endocrine stress status after training are difficult to assess, so that the effects are only noticeable once the overtraining syndrome sets in.³⁸

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Whether or not the endocrine stress status of athletes can be assessed from analysis of a simple resting blood sample is still controversial.⁵⁵ Therefore, researchers have continued to assess the endocrine stress axis in athletes, with the addition of related variables and more comprehensive protocols,³⁸ in attempts to better understand possible interactive and balancing responses, and with the hope that more sensitive markers of a maladaptive response may be uncovered.

Here we provide an overview of the more recent literature on the catabolic endocrine stress-axis and selected anti-catabolic variables' response to chronic stressors. Particular attention will be paid to exercise as a stressor, but since the additional effects of psychological life stress cannot be excluded in a human population, an overview of relevant literature pertaining to psychological stress will be included. Where possible, the outcomes of the recent research will be translated into possible future implications for clinical assessment of athletes presenting with fatigue.

Before considering chronic training-induced changes in the anabolic or catabolic endocrine systems, we will review new insights into the response of this system to acute exercise. Important questions recently highlighted include: (i) is the stress-response more sensitive to exercise intensity or exercise duration, or both? (ii) does a similar exercise stress test affect all individuals to the same extent? (iii) do repeated exercise bouts have a cumulative stress effect and is this influenced by the duration of recovery time? and (iv) is the anabolic:catabolic balance disturbed in response to exercise stress, or are the concentrations of endogenous anti-catabolic agents also increased in parallel to that of cortisol?

Assessment of acute endocrine stress response in athletes

Prior to assessment of the acute endocrine stress response, it is imperative that the baseline assessment is as accurate as possible. Factors that should be controlled, or taken into account, prior to any sampling include diurnal variation of hormone levels in circulation, nutritional status of the athlete and the time, duration and intensity of the most recent exercise bout.

Exercise intensity v. duration

As mentioned in the introduction, an increased serum cortisol concentration is consistently reported in response to acute exercise.^{32,39,42} According to some studies, the magnitude of this response is dependent mainly on the intensity of exercise rather than the duration.^{32,39} However, others report greater increases in cortisol concentration after long-duration low-intensity exercise (\approx 3 hours at 55% VO_{2max}) compared with shorter-duration higher-intensity exercise (on average 37 ± 19 minutes at 80% VO_{2max}).⁴⁶ Although these results seem to be contradictory, the shorter duration exercise in the latter study showed an increase in cortisol concentration of about 33% from baseline to post-exercise. This magnitude of response is similar to that observed by Kuoppasalmi *et al.*³² after 45 min-

utes and 90 minutes (27% and 43% increases respectively). Therefore, these results suggest that for shorter duration exercise (up to 90 minutes), intensity may play a larger role than duration in the stress response. However, for more prolonged exercise, the cortisol response may be more dependent on duration, since a 73% increase in cortisol concentration from baseline was observed after 3 hours of exercise.⁴⁶ This may have been due to added metabolic stress, or simply a longer duration for cortisol to accumulate. A tracer study in endurance-event horses indicated that the accumulation of cortisol during exercise is a function of increased production, rather than decreased clearance.³⁴ This suggests that exercise training and participation in competitive events of various intensities and durations may be factors contributing individually, or in combination, to elevated resting cortisol of athletes. Indeed, Luger *et al.*³⁶ reported that only highly trained runners exhibited elevated cortisol concentrations at rest when compared with sedentary or moderately trained subjects.

Divergent responses

Not all reports agree with the assumption that the cortisol response to exercise is fairly similar in all athletes after a standardised exercise test. In part, the conclusions drawn may depend on whether or not the exercise workload is given in absolute terms or relative to individual maximal capacity. Luger *et al.*³⁶ demonstrate that highly trained runners had a lower cortisol response to an absolute workload than did sedentary or moderately trained individuals. This could be interpreted in two ways. Either these athletes did not perceive the workload as stressful, or their hypothalamic-pituitary-adrenal (HPA)-axis was less responsive to the stress. Although the former explanation is highly plausible, the same athletes had lesser adrenocorticotrophic hormone (ACTH) and cortisol responses to administered corticotrophin-releasing hormone,³⁶ thus favouring the latter explanation. In a different study investigating HPA-axis responsiveness to acute stress, even in moderately trained men, subjects could be classified as either low- or high-responders on the basis of their ACTH secretion in response to strenuous treadmill exercise after administration of a mild dose of the synthetic glucocorticoid dexamethasone.⁴³ (The use of dexamethasone in this study by Petrides *et al.*⁴³ excludes the possibility that recent similar acute stress exposure could have confounded the results.) High-responders exhibited significantly greater ACTH and cortisol responses to strenuous exercise (90% VO_{2max}) than low responders. In another study, without dexamethasone, an acute exercise bout (10 minutes of running at 70% VO_{2max}) after a prolonged endurance exercise bout (2 hours of running) resulted in increased serum concentrations of cortisol in 50% of participants, while the other 50% showed either no change or a decrease from baseline concentrations.⁵⁷

Although the experimental protocols differed substantially in the studies discussed above, it is possible that the first group in the latter study by Viru *et al.*⁵⁷ may be similar to the high responders to exercise stress in the study by Petrides *et al.*⁴³ Viru *et al.*⁵⁷ also administered a third test, a 1-minute anaerobic test,

performed before the 2 hours of running and after the post-exercise acute aerobic test, to assess anaerobic muscle power. This showed that anaerobic muscle power in the group with a cortisol response to the 10-minute test was higher after the 2-hour run than at baseline, while it was significantly lower in the second group, who were unable to sustain a responsive HPA-axis throughout the long and complicated protocol. Whether this was an innate inability or an acute down-regulation, or a pre-pathological condition as a result of prior chronic stress exposure, is unknown. What is known, is that hypercortisolism is associated with down-regulation of either glucocorticoid receptor number or its affinity for glucocorticoids in various tissues.^{1,18,23,33,40,51} More investigation is needed to gain more information about the divergent response to stress, since an ability to identify high- and low-responders amongst athletes could impact on individualised approaches to training, and could objectively inform clinical assessment.

Anabolic response

In contrast to that of cortisol, serum testosterone concentrations may remain unchanged during exercise, but decrease in the recovery period. The magnitude of decrease seems to be dependent on both exercise intensity and duration: while short-duration intense exercise (120 m sprint lasting \approx 15 s) in one study did not result in a significantly decreased testosterone concentration,³² another short-duration, high-intensity protocol (3 x 300 m sprints lasting 2 minutes in total) resulted in a 25% decrease in mean testosterone concentration within 3 hours post-exercise,³¹ and moderate (21 km run at 4.3 km/h) and intense exercise (14 km run at 3.3 km/h) resulted in a \approx 30% and \approx 40% decrease in mean testosterone concentration at 3 hours post-exercise respectively.^{31,32} The decreased testosterone levels were reported to take between 24 hours and 3 days of recovery to return to baseline concentrations.^{13,32} Therefore, while the activity of the pituitary-adrenocortical system during exercise appears to be a good indicator of the capacity to respond to stress, pituitary-testicular system changes occurring during the recovery period may be a more sensitive marker of the chronic effects of the effort expended.

Cumulative responses

The effects of repeated bouts of exercise, and the influences of recovery duration between successive bouts, were recently investigated in elite endurance athletes. Repeated bouts of exercise (separated by 3 hours) were shown to have an additive stress effect, with increases in cortisol concentrations in response to the second bout of exercise that were much greater than those reported after the first bout.⁴⁷ In a similar study by the same group, the additive effect of exercise was influenced by the duration of recovery allowed between bouts. Subjects had smaller increases in cortisol, ACTH, epinephrine and norepinephrine concentrations in response to a second exercise bout after 6 hours of recovery between bouts than after only 3 hours of recovery.⁴⁸ In contrast to this cumulative effect of repeated exercise bouts on the catabolic stress hormone response, concentrations of anabolic hormones such as growth hormone and testosterone were reportedly unaffected

by the number of bouts per day or the recovery time between bouts.⁴⁸ However, these anabolic agents were determined only immediately after exercise, and not during recovery, which was earlier established to be more useful,^{31,32} so it is not possible to make such a clear-cut conclusion regarding the anabolic response to multiple bouts of exercise. It is also not clear whether testosterone production is also affected in a manner similar to cortisol production in low-responder athletes. From a clinical view point, no recommendation regarding the usefulness of multi-session, same-day exercise testing can be made at this point.

Cortisol-limiting agents

Although total cortisol concentration is commonly used as an indicator of acute stress, the total concentration of cortisol in the circulation does not necessarily reflect the concentration of bio-available (unbound) cortisol. Furthermore, the effect of other unbound, but physiologically opposing (anti-catabolic) agents may also contribute to lessen the net effect of cortisol released in response to stress. Very few studies have investigated these issues in athletes. In highly trained athletes, cortisol concentrations were increased after an ultramarathon as expected, but cortisol binding globulin (CBG) concentrations remained unchanged from baseline, suggesting that the net effect was that of increased free cortisol.⁴² In addition, sex hormone binding globulin (SHBG) was also reported to be unaffected by either short, high-intensity, or longer, moderate-intensity exercise, so that changes in total testosterone concentrations were associated with parallel changes in the fraction of free testosterone in the circulation.³¹ From these few studies, hormone binding globulins do not seem to play a significant role in the regulation of the concentration of bioactive hormone available in circulation in response to exercise, and need not be added to chemical pathology assessments of the stress response to exercise.

Other anti-catabolic agents which may have a regulatory role in the cortisol response to stress are dehydroepiandrosterone (DHEA) and its less active sulphated conjugate, DHEAs. The latter comprises more than 99% of the hormone present in circulation. DHEAs may be locally converted to the more active form, DHEA, by steroid sulphatase enzymes which are present in many cell types, e.g. leukocytes and fibroblasts.⁵⁶ Laboratories measuring salivary concentrations of this hormone usually assay the non-sulphated conjugate whereas other laboratories generally choose to assay serum DHEAs. The literature discusses the role of DHEA using results of the 2 forms interchangeably. The recent finding that an acute endotoxin injection increased the serum cortisol:DHEAs (dehydroepiandrosterone-sulphate) and cortisol:17-OH-progesterone ratios in a dose-dependent manner in patients suffering from chronic inflammatory disease,⁵³ suggests that in response to a stressor, cortisol production may be favoured at the expense of the adrenal androgens. Although the stress response to endotoxin may differ in some ways from the stress response to exercise, recent evidence indicates that intense military training (26 days) results in decreased plasma testos-

terone and DHEAs levels.¹⁹ However, in elite female athletes, an acute bout of exercise (simulated handball match) did not alter DHEA concentrations,¹⁰ suggesting that DHEA is not always responsive to a whole body stressor. More investigation is needed to determine if expression of the concentration of cortisol as a ratio to DHEA concentration may possibly be a better indicator of change in catabolic status than measurement of cortisol concentration alone in exercise stress.

Effects of chronic training on endocrine stress status

Given the factors mentioned above that complicate cross-sectional studies, studies with a longitudinal design may more accurately reflect chronic changes in the endocrine response to exercise training.

Cortisol

In a study comparing the effect of endurance, sprint and mixed training protocols lasting 10 weeks each,²⁹ the results indicated that higher-intensity endurance training with bouts of short duration (80% $\text{VO}_{2\text{max}}$ for 30 minutes, 3 times per week) did not alter resting cortisol concentrations, or the cortisol response to maximal exercise. However, both interval sprint training (2 x 4 20-second sprints at 96% of maximum heart rate, 3 times per week) and a combination of the 2 (alternating endurance and interval sprint protocols, 6 times per week) resulted in increased resting cortisol concentrations (baseline: means of ≈ 330 v. post-training: ≈ 450 nmol/l for both groups). This would suggest that higher-intensity and higher-volume training regimens, especially those which include sprint training on several days per week, results in a higher stress condition at rest. However, when comparing pre-training mean resting cortisol concentrations, those of the interval sprint group and the combined protocol group were significantly lower than that of the endurance protocol group (means of ≈ 330 v. 540 nmol/l), while post-training resting cortisol concentrations were similar in all groups. Although the subjects used in this study were healthy active individuals, randomly divided into the 3 training categories, the higher initial resting cortisol concentrations reported in the group subsequently exposed to the endurance protocol, may have been a confounding factor. In another study, a training protocol of shorter duration (10 days) also resulted in unchanged resting concentrations of cortisol after a 100% increase in training volume in cyclists (both exercise type specific and cross-training protocols were used).⁴⁴

ACTH response

Although these studies both concur with earlier studies that cortisol concentration at rest is not an indicator of chronic endocrine stress, they also showed that ACTH concentrations remained similar at rest and in response to an acute exercise test ($\text{VO}_{2\text{max}}$ test) in all groups. Although ACTH may therefore not be a useful clinical marker, it plays a pivotal role influencing cortisol release on the one hand, but also precursors to anabolic substances on the other (Fig. 1).

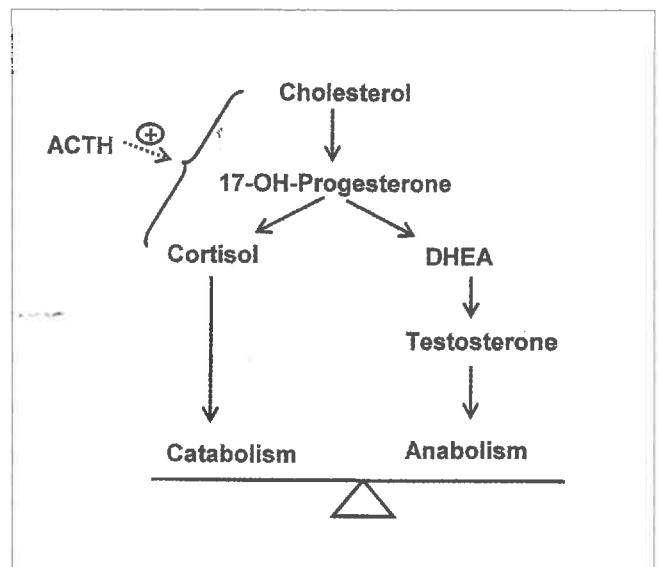


Fig. 1. Interactions between catabolic and anabolic endocrine variables relevant to the stress response. Solid arrows indicate chemical conversions; broken arrows indicate up-regulation of a synthetic pathway.

Anti-catabolic variables

The finely regulated homeostatic role of the endocrine system is illustrated by the fact that the net effect of cortisol does not only depend on factors playing a role in its release, such as ACTH, but also on variables with an opposite effect to that of cortisol, such as DHEA and testosterone (Fig. 1). Additional insights may be gained from examining the relationships between hormones with an opposing action to that of cortisol in response to training. Results obtained in human studies investigating the DHEAs response to exercise training are varied, as indicated in Table 1. These results suggest that the DHEAs response is not related to fitness level. Rather, we propose that the results from these studies indicate that the initial DHEAs response to unaccustomed, but moderate training workloads, as in the studies of Pritchard *et al.*⁴⁵ and Filaire *et al.*,⁹ is an increased DHEAs concentration that could counteract the effects of repeated transient elevations in the circulating cortisol concentration in response to the repeated training bouts. In addition, changes in DHEA concentration were previously reported to be a better indicator than testosterone, of the salivary androgen response to exercise in female athletes.¹⁰ However, if the unaccustomed training is more severe, such as in the study by Keizer *et al.*,²⁸ DHEAs concentration is reduced. Similarly, elite athletes compared with controls have lower circulatory DHEA,¹⁰ and DHEAs concentrations decreased in response to rapidly increased, excessive exercise training, even in well-trained athletes.¹¹ This suggests that changes in the DHEAs concentration at rest may be a better marker of exercise stress than cortisol concentration itself. This interpretation of the exercise literature is in support of the earlier suggestion in the medical literature that the cortisol: DHEAs ratio may be a useful indicator of risk of long-term stress-related pathology.²² Although the available evidence suggests that

TABLE 1. Previously reported responses of resting dehydroepiandrosterone (DHEA) and its sulphated form to exercise training

Reference	Subject group	Training intervention	Duration	DHEA or DHEAs
Pritchard <i>et al.</i> ⁴⁵	Sedentary	2x/day cycling for ≈1 hr at ≈50 - 55% VO _{2max}	3 months	↑
Filaire <i>et al.</i> ⁹	Elite handball & volleyball players	Seasonal training: 12 hr/wk (5 days/wk)	16 weeks	↑*
Keizer <i>et al.</i> ²⁸	Sedentary	2-3x/wk running PLUS 1x/wk cycling; Incremental from 20min at ≈60% VO _{2max} to 50-75 min at ≈80% VO _{2max}	3 months	↓
Filaire & Lac ¹⁰	Elite handball players	—	—	↓*†
Flynn <i>et al.</i> ¹¹	Distance runners	100% ↑volume	10 days	↓

Values were obtained in plasma or serum samples, unless otherwise indicated.

* Salivary DHEA concentrations.

† Values in comparison to that of sedentary controls.

sports medicine clinicians could consider this parameter in their assessments of athletes, further definitive research is required. Whether DHEAs is proved to be a relevant marker for the stress status of athletes or not, may still take some time given the long duration of training monitoring studies. DHEA is available as a 'nutritional' supplement (Nippoldt), but it is a banned substance.^{7,27} One could argue that this is the strongest evidence that DHEA does play an important role in elite athletes! However, its mechanism of ergogenic action in athletes is not clear. Although it affected several androgenic endocrine parameters positively in postmenopausal women,¹⁵ it did not enhance serum testosterone or change the adaptation to resistance training in healthy young men.³

In contrast, 2 studies on previously sedentary individuals reported that moderate training resulted in an increased resting testosterone concentration,⁴⁵ while training at greater intensity resulted in a decrease in resting testosterone concentration.²⁸ In a third study in athletes, resting testosterone concentrations decreased in response to 10 days of doubled normal training volume, while resting cortisol concentration remained similar.⁴⁴ These data are indirect evidence that unaccustomed, large increases in training volume may lead to an inability of the endocrine system to maintain a net anabolic effect, which may be detrimental to exercise performance. It may therefore also be useful to calculate the ratio of cortisol to testosterone at rest, to give a better indication of changes in the anabolic-catabolic balance in response to a training programme in elite athletes.

The usefulness of measuring the cortisol:testosterone ratio in response to exercise training was previously investigated in professional cyclists.²⁴ Three months of performance-enhancing intensive training with progressively increasing volume (1 month each of cycling 405 km/wk, 510 km/wk and 740 km/wk) resulted in a 26% increase in the cortisol:testosterone ratio at rest in these athletes. This was the result of both a 39% increase and a 15% decrease in resting cortisol and testosterone concentrations respectively. However, training did not have a statistically significant effect on either the resting cortisol or testosterone concentrations, or their responses to an acute bout of exhaustive exercise. An earlier study reported that more than 24 hours of rest may be required for testosterone to return to baseline concentrations after an acute bout of exercise.¹³ Furthermore, in endurance athletes, repeated

bouts of acute exercise on the same day were shown to have cumulative effects on the neuroendocrine response, with higher increases in epinephrine, norepinephrine, ACTH, cortisol and growth hormone concentrations during, and larger decreases in testosterone concentration after the second bout of exercise despite 3 hours rest between bouts.⁴⁷ In a subsequent study with differing resting periods, this cumulative effect was reported to be inversely related to the recovery time allowed between bouts.⁴⁸ These results highlight the importance of obtaining proper resting blood samples to prevent confounding effects of prior acute exercise bouts, during assessment, to ensure accurate interpretation of data regarding the effects of chronic exercise.

In summary, the significance of an increased resting DHEAs concentration after a chronic, unaccustomed increase in exercise training load remains to be elucidated. However, these results support the theory that there is a shift away from androgen and towards glucocorticoid production at times of increased physiological and psychological stress.⁴¹ Assessment of ratios of parameters with potentially opposing functions, e.g. cortisol:testosterone and cortisol: DHEAs may therefore provide a more comprehensive indication of endocrine stress and its net effects at tissue level, not only for researchers but also for clinicians assisting coaches in monitoring the stress response of their athletes to training.

Endocrine responses to overreaching and overtraining

Very few studies are available with data generated on actual overtraining syndrome (OTS) sufferers. Most information available originates from interpretation of, and extrapolation from, short-term overreaching studies, which will be discussed in the next few paragraphs, along with the few studies available on truly overtrained athletes.

In a study searching for an objective marker for overtraining, 10 overtrained athletes, diagnosed on the basis of clinical history, had an average resting cortisol concentration of 396 ± 74 nmol/l, which is within the normal range of 220 - 750 nmol/l.⁵⁰ In another study, plasma concentrations of cortisol, epinephrine and norepinephrine were reported to remain unchanged over the course of a training season in 10 elite

swimmers, of whom 3 were diagnosed with OTS during the course of the season.²⁵ In a study of cyclists subjected to an overreaching training protocol (2 weeks each of normal training, intensified training and recovery),²⁰ no change was reported in the resting plasma catecholamine concentration in response to altered training, although performances in maximal tests, intermittent tests and time trial tests were reduced after the intensified training, but returned to normal again after the recovery training period.

In order to determine whether the endocrine adaptation to overreaching or overtraining is dependent on the type of exercise, a 2-week overreaching training protocol was followed by runners.¹¹ Runners were required to either perform running exercise only (200% of usual training volume), or to cross-train (running at 100% of usual training volume plus cycling to yield an added 100% of energy expenditure as per usual running training). Similar to results from other more moderate training studies, resting ACTH and cortisol concentrations remained unchanged during both training protocols. However, resting testosterone concentrations decreased significantly by day 5. There was no difference in this measure between the 2 protocols, indicating that the endocrine response to excessive training is not exercise type specific, at least not when both types of exercise are of endurance type. The decreased testosterone concentration indicates the possibility that, although cortisol concentration was not increased, overreaching may coincide with a decreased anabolic status, which may in part explain the decrement in exercise performance seen in the OTS.^{2,4,30,55}

The results of the previous study reviewed show that 2 different additive exercise stressors have similar effects on the endocrine stress response to that of 1 severe exercise stressor. Acute psychological stress elicits a similar endocrine stress response to exercise, at least pertaining to the HPA-stress axis. Since athletes are under severe psychological pressure to perform, even when training, this chronic psychological stress may contribute to increasing their overall stress status. Psychological stress may even be more prolonged than the stress of exercise training sessions themselves.

Endocrine responses to psychological stress and chronic fatigue syndrome – potentially useful lessons

Inducing psychological stress in human subjects in an experimental situation is not as simple as in laboratory animals, since the effects of prior exposure to stress in human subjects are difficult to control and may have confounding effects on the results obtained. Therefore, animals are often used as a more standardised model to investigate the physiological responses to psychological stress.

Studies in rats determined that short duration immobilisation stress of different severities (tube restraint v. prone restraint on a wooden board) yielded different magnitudes of corticosterone response.¹⁴ Furthermore, peak corticosterone concentrations were only achieved after stressors lasting more than 1 hour,^{14,26} after which these peak concentrations were maintained for the duration of the immobilisation protocol.²⁶ With

chronic intermittent stress protocols, the corticosterone concentration after acute stress increased with each successive episode, but recovery to baseline concentrations was more efficient over time,^{14,37} indicating both enhanced responsiveness and enhanced clearance. However, this habituation of recovery was shown to be stressor-specific, since a novel stressor elicited a typical 'acute' stress response again.^{14,37} Therefore, the speed of recovery of corticosterone concentrations to baseline may be a good indicator of adaptation to a psychological stressor. This approach to stress-axis assessment should be tested in the athletic population.

Similar to the results obtained in rodent models,^{14,37} repetition of experimentally induced psychological stress (Stroop Color Word Interference task, public speaking and mental arithmetic in front of an audience) in healthy humans (2 sessions, separated by 7 days) was recently reported to result in habituation.¹⁶ Smaller increases in ACTH and cortisol concentrations in response to the stress on day 8 were observed, while epinephrine and norepinephrine did not habituate. However, the ACTH and cortisol responses to both acute experimentally induced¹⁶ and chronic work-related psychological stress⁴⁸ could be divided into 2 distinct patterns, 1 of low-response and 1 of high-response. High-responders had a highly variable diurnal pattern with higher early morning cortisol concentrations (although still within the normal range) and several peaks during the morning, with a much lower evening cortisol concentration (the typical normal diurnal curve), whilst low-responders showed low diurnal variability and low morning cortisol concentrations (a flattened diurnal curve).^{16,49} This was observed despite similar values for perceived stress in the 2 responder groups and no *a priori* reason to propose a divergent response in either study. The implication of these 2 studies for our understanding of exercise-stress is that it may not be possible for training studies to group all athletes together without confounding the results. Although, high- and low-responders have also been reported in response to acute exercise stress,⁴³ studies of longer duration exercise interventions have not been assessed in this way. Preliminary data from our group suggest that there is indeed a divergent cortisol response to longer term exercise training – recreationally competitive cyclists with resting serum cortisol concentrations within the normal reference range (150 - 650 nmol/l) at baseline exhibited significantly increased cortisol concentrations after 8 weeks of intensified cycling training (increased volume and intensity), while those with elevated cortisol concentrations at baseline (> 650 nmol/l) exhibited significantly decreased cortisol concentrations at rest after training (Fig. 2). However, all subjects increased performance over the course of the intervention protocol. These results may have important implications for training monitoring, since a blunting of the endocrine response to exercise may precede decreases in performance, so that preventative measures may be taken to prevent a long-term negative effect on performance.

Since athletes are adapted to exercise stress, it may be more appropriate to assess their stress responsiveness to a novel stressor, rather than to more exercise. Dexamethasone has been used as a stressor to investigate the responsiveness

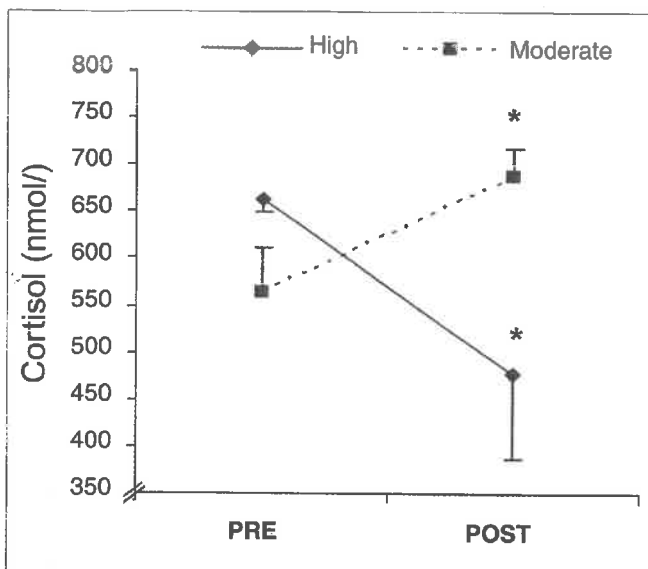


Fig. 2. Differences in mean resting cortisol responses to 8 weeks of intensified cycling training (increase in both volume and intensity) obtained in subjects with either high (N = 3) or moderate (N = 4) baseline cortisol concentrations. Error bars indicate standard deviations. PRE = pre-training, POST = post-training, * value significantly different from pre-training ($p < 0.05$), as calculated using paired Student's *t*-tests.

of the stress-axis in a non-athlete human population^{6,8,33} and in rats,⁵ but is a substance banned by the IOC.²⁷ Another alternative is to challenge the endocrine-stress-axis with ACTH. In a study comparing 19 patients suffering from the chronic fatigue syndrome (CFS) to 10 healthy controls,⁵² basal DHEA and cortisol concentrations, as well as the cortisol:DHEA ratio, were found to be similar in the two groups at rest. However, 30 minutes after administration of 1 μ g of ACTH, there were some significant differences in the adrenal responses. While there was no significant difference in the DHEA response (average increase of 28 ± 7 ng/l in CFS v. 27 ± 10 ng/l in controls), there was a significant difference in the magnitude of change in cortisol concentration between the 2 groups (average increase of 272 ± 31 nmol/l in CFS v. 360 ± 27 nmol/l in controls, $p = 0.05$). Long-duration psychological stress therefore seems to be characterised by decreased adrenal sensitivity to ACTH. This result is comparable to that reported in ultra-endurance athletes, who, when compared with recreationally exercising controls, exhibited similar diurnal cortisol secretion (main effect for group: $p = 0.94$), but a significantly increased ACTH secretion (main effect for group: $p < 0.005$).⁵⁸ These results point toward a decreased adrenal sensitivity to ACTH, probably as a result of both chronic psychological and chronic physiological stress. It is possible that decreased adrenal sensitivity precedes the decreased hypothalamic sensitivity shown earlier by Barron *et al.*² in overtrained athletes. We suggest that a standardised ACTH challenge test should be developed for monitoring stress responsiveness in competitive athletes.

Summary

It is clear from the reviewed literature that both the anabolic and catabolic endocrine responses to stress are complex, with many different, opposing factors contributing to the net effect

exhibited. The main effects of different types of stressors on catabolic and anabolic variables are summarised in Table II.

TABLE II. Effects of different stressors on serum cortisol, testosterone and DHEAs concentrations in humans*

Type of stressor	Cortisol	Testosterone	DHEAs
Acute unaccustomed	$\uparrow\uparrow$	$\downarrow\downarrow$	\uparrow
Acute moderate	\uparrow	\leftrightarrow	\leftrightarrow
Chronic excessive/severe, insufficient recovery	$\uparrow / \leftrightarrow$	\downarrow	\downarrow
Chronic moderate	\leftrightarrow	$\uparrow / \leftrightarrow$	\leftrightarrow

* Responses reported do not reflect the divergent responses reported in low versus high-responders.

Recently, Urhausen and Kindermann reviewed the sport science literature⁵⁵ and came to the conclusion that assessment of the catecholamine response to incremental exercise was the only useful endocrine marker for monitoring training stress and overtraining in athletes. However, due to the methodological complexity of its measurement, catecholamine assessment is not feasible for routine monitoring. The different approach that we followed in the current review was to include relevant psychological- and disease-related stress literature. Integration of these studies highlights the possibility of comprehensive monitoring of training stress in athletes in a manner dependent on the determination of concentrations of endocrine variables that are currently routinely analysed in many analytical and clinical laboratories.

The approach we suggest for athletes would be similar to that previously suggested in the medical literature for monitoring risk for pathology related to prolonged cortisol hyperactivity.²² Our conclusion that this is a relevant approach is based on the following.

1. Psychological and physiological stressors seem to elicit a similar response from the endocrine stress-axis, which means that athletes are subjected to cumulative effects of the 2 types of stressors. Cortisol concentration increases after an acute stressor, in a manner dependent on both intensity/severity and duration, with cumulative effects of repeated bouts. However, the cortisol response adapts to a moderate stressor over time, with cortisol concentrations reaching lower peak values and returning to baseline concentrations quicker after each successive stress exposure. This effect was shown to be stressor-specific, so that a new type of stressor will again increase the cortisol response.

2. Chronic exposure to a severe stressor may not allow habituation, with cortisol concentrations remaining similarly elevated after subsequent exposures, or failing to resolve during recovery.

3. A divergent response of cortisol to a stressor was described after both physical and psychological stress exposure, that of low- and high-responders. The separation of adaptation and maladaptation to exercise stress may be related to this short-term observation. An advantage of regular monitoring of elite athletes is that a baseline characterisation as either a low- or high-responder can be made in the off-season. The approach we suggest is based on available evidence,

albeit in populations other than athletes or in studies with relatively small sample size or relatively short duration of intervention. Nevertheless, the evidence discounts suggestions that catecholamines are the only relevant endocrine marker of training stress.

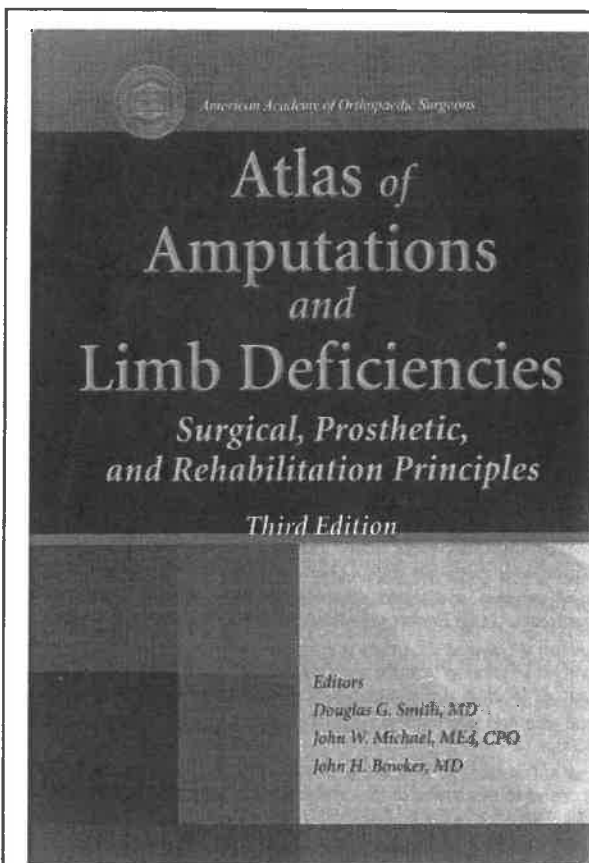
Stress seems to increase glucocorticoid production at the expense of androgen production, albeit with variable results reported thus far for DHEA. The various opposing effects of different stressors on catabolic vs. anabolic variables (Table II) suggest that assessment of absolute concentrations of individual variables on their own, without considering the interaction of these opposing variables, is not sufficiently accurate to monitor endocrine stress status. We further suggest that testosterone concentration may be a useful parameter to measure as an indicator of recovery status, since it returns to baseline after sufficient recovery, but remains decreased after severe stress exposure with insufficient recovery. It would also be imperative in future studies to include symptomatic assessments of athletes' recovery as well as objective assessments of performance. This review sets the basis for future longitudinal assessments that are now required to validate (or invalidate) these suggestions.

On a cautionary note, the above guidelines can only be applied successfully when analyses are performed on proper resting blood samples, to exclude the confounding effect of acute stress responses, especially given the difference in response times for cortisol and testosterone. Therefore, clinicians and exercise physiologists should allow sufficient recovery time after recent exercise training sessions to ensure that the athlete is truly in a rested state at the time of sample collection. This will also be a particularly important aspect of study design for future investigations of endocrine recovery rate in response to a standardised challenge.

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