Relationship between Cortisol, Cytokines and Stress on Training: A Scoping Review

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Abstract

The aim of this review was to provide an overview of cortisol and cytokines levels in saliva, and their relationship with stress on the physical training activities. This study was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A search strategy was undertaken using the following terms: “training stress", "cortisol", "cytokines", and "salivary”. Relevant articles published from January 2011 to December 2021 were identified from Google Scholar, ProQuest, Scientific Direct, PubMed Central (PMC). A total of 9 studies that met the inclusion and exclusion criteria were included in the present study.

The results showed that despite the conflicting results was found, most studies showed significant results of the increased cortisol and proinflammatory cytokines IL-1β, IL-6, IL-8, TNF-α in the negative mood, stress, anxiety, and depression conditions. The differences may be due to different requirements, types of training, or study design. Further studies are required to assess the role of salivary cortisol and cytokine as biomarkers for monitoring stress conditions in people who are closely related to training from the beginning of the selection, education, and assignment.

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Introduction

Stress is a biological change to an intrinsic or extrinsic stimulus, which based on the type, timing, and severity of the stimulus can drive various reactions in the body ranging from homeostatic changes to life-threatening effects and death.[1] Training is one of many physical stressors and causes changes in the human body's regulatory system. Training is one of the triggers of stress with increased energy requirements and causes an imbalance in homeostasis.[2] Endurance training, especially at high intensity, causes significant endocrine changes, both acute and chronic in the effective stimulus for the hypothalamic-pituitary-adrenal axis, resulting in a significant increase in circulating cortisol levels.[3] Physical activity causes significant changes in the endocrine system and affects metabolism.[4]

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Exposure to stress, both physical and psychological triggers the immune system to produce cytokines, which in turn activate the hypothalamus-pituitary-adrenal axis (HPA) causing the release of cortisol.[5] The stress response activates the HPA axis through neurons in the para vestibular nucleus in the hypothalamus in an effort to maintain body homeostasis. The HPA axis mechanism produces CRH which then triggers the pituitary to release ACTH which will stimulate the release of glucocorticoid hormone or cortisol as the end product. Cortisol is the end product of the HPA axis which has a biological role, namely anti-inflammatory and immunosuppressive effects. In general, cortisol plays a role in suppressing inflammatory reactions and as an immunosuppressant. Training stimulates the strong HPA axis. Endurance training has no permanent effect on hypercortisolism because the biologic markers on the HPA axis are the same as those of no resting phase in healthy men. During training, the HPA axis responds to many stimuli that reflect the regulatory and integrating functions of the HPA axis, known as neural homeostatic signals (stimulation of chemoreceptors, baroreceptors, osmoreceptors), circulating homeostatic signals (glucose, leptin, ghrelin, and atrial natriuretic peptide), and also inflammatory signals. (IL-1, IL-6, and TNF-α).[6]

The use of saliva as a sample for hormone analysis is of increasing interest to clinicians and researchers because saliva collection offers a non-invasive and stress-free alternative to plasma and serum collection for the determination of endocrine parameters such as steroids, amines, and peptides. The pH and analyte media (bacteria, ions, and inflammatory mediators) in saliva can affect hormone concentrations in plasma. Taking saliva as a sample can simultaneously determine the levels of steroids in plasma. Salivary steroids correlate with plasma steroid levels. Cortisol hormone can be done through a saliva test and is easier than other procedures in determining free cortisol levels. Salivary cortisol testing can also be used to examine the relationship of cortisol to stress.[7,8] This study aimed to present an overview of salivary cortisol and cytokines levels and their relationship with stress on the physical training activities.

Materials and methods

The relevant articles searched related to research questions according to the PCC analysis, namely How Cortisol Levels, Cytokines and Stress in Training Activities (Table 1).

P	Patient, Population	people who are closely related to training
C	Concept (intervention/phenomena of interest/outcome	Cortisol levels, cytokines, stress,
C	Context	training activities

Table 1. PCC analysis.

Identification and Selection

Collect and filter the literature obtained according to specific research questions focused on PCC. Search from Google Scholar source, PubMed Central (PMC), and ProQuest ScienceDirect using the keywords: stress training, cortisol, cytokines, salivary, with the relevant articles published from January 2011 to December 2021. Search using a Boolean Search Strategy Operator: "training stress" AND "cortisol" AND "cytokines" AND "salivary".

Eligibility Criteria

The eligibility criteria were done to obtain the most relevant articles. Inclusion criteria were articles published within a period of 10 years (January 2011 – December 2021), research journal articles, healthy human participants, athletes, or military, not restricted from the country, and psychological or physiological stress from training activities and not caused by disease, articles in English. Exclusion criteria were stress related to an illness.

Data Extraction

PRISMA guidelines were used for this study with search results from Google scholar: 174 articles, ProQuest: 23 articles, PubMed Central (PMC): 31 articles; Scientific Direct: 2 articles, the total number of articles is 230 articles. After sorting duplicate articles, there were 167 articles were found, then filtering based on inclusion criteria was carried out and 13 articles remained, the last selection based on exclusion criteria obtained 9 articles (Figure 2).

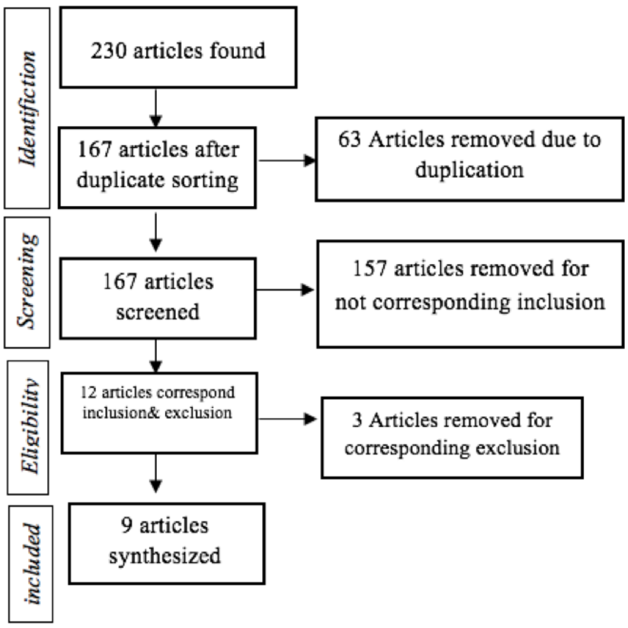

Figure 1. Study workflow and finding.

Results

Many of the studies included in this review found that psychological responses such as negative mood, stress, anxiety, depression, fear, and fatigue lead to an increase of cortisol and pro-inflammatory cytokines (IL-6, IL-8, IL1β, TNF-α) levels in serum and saliva during and after training.[5,10-15] However, other studies found different results that there were no significant changes of IL -10 and free IGF-1 levels before and after training,[16] and there was a significant decrease of cortisol level compared to controls (Table 1, 2).[17]

In firefighters, during a physical work simulation and sleep restriction for 3 days, the results of psychological stress sesponses using a mood scale showed a negative mood, increase levels of cortisol, IL-6, IL-8, IL-1β, and TNF α in saliva.[5] Responses of men in a six-week intensive preseason training program to examine for signs of overtraining showed a significantly increase in cortisol and salivary IL-6 for 1 - 6 weeks.[10] In highly trained endurance athletes, serum cortisol levels showed a positive correlation with training volume and sIL-6R was negatively correlated with cortisol concentration.[11] Salivary cortisol and cytokine IL-1β, IL-6, TNF-α were increased during and after prolonged hard training in ten young men university students.[12] In pre-competition track and field training, salivary cortisol athletes were found significantly increased compared to measurements 24 h earlier.[13]In combat training for 6 weeks, scores of stress, anxiety and depression were higher than at rest. Serum levels of cortisol, IL-6 and TNF-α increase during combat training.[14] The effect of boxing match on metabolic and inflammatory in Male elite Boxers showed an increase in serum cortisol, IL-1β, IL-6 and TNF-α.[15]

We found two studies which showed contradictive results. A study regarding the effect of acute exercise on the salivary levels of free IGF-1 and IL-10 found that there was no change in the levels of both biomarkers of sports training before and after acute exercise.[16] Another study revealed that salivary cortisol levels were significantly decreased in professional basketball players who performing five 2 h-lasting training sessions per week compare to the control group.[17]

As firefighters during a physical work simulation and sleep restriction for 3 days, the results of Psychological Stress Responses using a mood scale show a negative mood, increase levels of cortisol, IL-6, IL-8, IL-1β, and TNF α in saliva using Elisa method.[5] Responses of men in a six-week intensive preseason training program to examine for signs of overtraining showed a significant increase in cortisol and salivary IL-6 for 1 - 6 weeks.[10] In highly trained endurance athletes, Serum cortisol levels showed a positive correlation with training volume and sIL-6R was negatively correlated with cortisol concentration.[11] Salivary cortisol and cytokine IL-1β, IL-6, TNF-α increase in ten young men university students during and after prolonged hard training.[12] In Pre-competition track and field training, salivary cortisol athletes were found significantly increased compared to measurements 24 h earlier.[13]In combat training for 6 weeks, scores of stress, anxiety and depression were higher than at rest. Serum levels of cortisol, IL-6 and TNF-α increase during combat training.[14] The effect of boxing match on metabolic and inflammatory in Male elite Boxers showed an increase in serum cortisol, IL-1β, IL-6 and TNF-α.[15] But, another studies in acute exercise found no change in the levels of salivary free IGF-1 and IL-10,[16] and even in professional basketball players who performing five 2 h-lasting training sessions per week showed concentration of salivary cortisol decrease in comparison with the control group.[17]

Discussion

The study included in this review used a cross-sectional observational study design, with samples used to examine cortisol, cytokine in saliva and training stress levels in the form of saliva samples,[5,10,12,13,16,17] and using plasma blood samples,[11,14,15] taken before and after training. Cortisol and cytokine can also use other fluids, for example gingival crevicular fluid,[18] and the socket blood after tooth extraction.[19] Each training time period in this study was different, the shortest was 9 minutes in boxers,[15] 3 days of training,[5,13] 7 days,[12] 4 weeks,[14] 6 weeks,[10,14] 18 weeks,[11] and 6 months for a competitive training period.[16] Timing of sampling either blood or saliva for measurements for pre-training is just before training on the same day in the morning between 6.00 – 6.30 and immediately after completion of the training.

Measurement of cortisol levels using an enzyme-linked immunosorbent (ELISA) tool showed an increase after training compared to before (baseline).[5,10, 12-15] However, in a study of female basketball players during the competitive training season cortisol levels showed a significant decrease in athletes compared to the control group.[17]

Another study analyzing the relationship between salivary cortisol levels and performance in athletes on track and field detected a negative relationship. Similar trends were found for cortisol levels, suggesting that pre-competition increases in these two hormones can impair athletes' performance on track and field. Previous studies reported conflicting results regarding the impact of cortisol on performance, with cortisol being positively correlated with the performance of weightlifters and rugby players but negatively correlated with tennis players and golfers. This difference may be due to different requirements, different types of training, or different study designs. For example, the challenges that weightlifters face in competition both physically and mentally are very different from golf tournaments. Study design influences the impact of endocrine changes on performance, e.g., the importance of an opportunity whether competition or training, can also influence the impact of hormone levels on performance. Competition is important for an athlete to bring about optimal levels of emotion and arousal.[13] It has also been noted that the testosterone/cortisol correlation and its strength changes due to training induction, however, seem more likely that the testosterone/cortisol ratio represents actual physiological strain in training than overtraining syndrome.[20]

During training, the HPA axis responds to a variety of stimuli that reflect the regulatory and integrative functions of the HPA axis: neuronal homeostatic signals (stimulation of chemoreceptors, baroreceptors, and osmoreceptors), circulating homeostatic signals (glucose, leptin, ghrelin, and natriuretic peptides, atrial) and inflammatory signals (IL-1, IL-6, and TNF-α). In humans, blood sampling shows that the dynamics of HPA axis activation during training is associated with hypothalamic CRH stimulation and arginine-vasopressin secretion (with a prominent role for CRH), and adrenocorticotropic hormone synthesis and release. (ACTH) from pituitary corticotropic cells prior to cortisol elevation.[6]

The types of cytokines measured in this review writing varied according to the objectives of each research. Several studies investigated cytokines related to training on the pro-inflammatory cytokines IL-6, IL-1β, TNF-α,[5,10,12,14,15] anti-inflammatory cytokines IL-4, IL-10.[5,16] The results of cytokine measurements in this study showed an increase after training. Several studies on the interaction of psychological factors, the nervous system, and the immune system as well as biomarkers related to training activity, especially in athletes or the military, have been widely reported. Intense or prolonged training can lead to the production and elevation of pro-inflammatory cytokines. Cytokines such as IL-α, IL-1β, and IL-6 are part of the acute pro-inflammatory immune response to physiological stressors. During periods of overreaching, pro-inflammatory cytokines may be chronically elevated.[10] The anabolism and catabolism processes are important factors that they can maintain muscle mass. Anabolic factors consist of physical and chemical factors, while catabolic factors consist of muscle that is rarely used, oxidative stress, proinflammatory cytokines, acidosis, and glucocorticoid hormones. The increased level of cytokines can cause muscle wasting. Pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α can trigger muscle damage.[21]

Li et al. (2013) reported that prolonged combat training induces not only increased stress, anxiety, and depression but also gastrointestinal symptoms, pro-inflammatory immune activation, and increased intestinal permeability. Serum levels of cortisol, IL-6, and TNF-α, and segmental GI permeability increased during combat training compared to rest.[14] Cortisol exerts different effects on Th1 and Th2, resulting in changes in Th1/Th2 balance. In experimental animals that are given stress, the role of Th2 cells will be dominated by the release of type 2 cytokines, for example, IL-4, IL-5, and IL-6. These interleukins play an important role in the humoral immune response. IL-6 is a major endocrine cytokine that plays a major role in the immune stimulation of the human HPA axis.[22,23] Endogenous hormones are very important in physiological reactions and adaptations during physical work and influence the recovery phase after training, by modulating anabolic and catabolic processes. Testosterone and cortisol play important roles in protein metabolism as well as carbohydrate metabolism.[20]

Increasing in cortisol and IL-6 due to training stress have also been found due to other stressors such as academic stress[18] and dental anxiety.[24] Therefore, both biomarkers may help coaches, clinical sports professionals, researchers, personnel to better understand how to comprehensively monitor physiological changes, design training cycles that result in maximum improvement in performance achievement, and minimize the risk of overtraining and injury.[25] In addition, in military life which also is full of physical activity and training, stress can occur at any time. Training as a process of forming and enhancing military capabilities in their respective roles. The training of military personnel is also aimed at preparing for acute crisis situations, namely situations where there is a sudden change in the situation with the threat of loss of individual resources. A typical acute stressor is a threat that produces long-term or short-term stress.[26] Likewise, the stress in the military environment can occur during training.

Various measuring tools have been used to measure stress levels in training. Wolkow et al (2016) used the Mood Scale II to assess variations in circumstances mood over time, especially in field studies and sleep limitations, showing an increase in positive mood levels in training activities.[5] Another study used the Perceived Stress Scale-10 item (PSS-10) to quantify stress. Li, et al (2013) on quick reaction military personnel, stress levels were used by Hospital Anxiety and Depression (HAD) for anxiety and depression, and the results showed an increase during training compared to rest.[14] While others examined cortisol, cytokines, and training associated with the effects of prolonged training,[11,12] the effect of match performance or training on the field,[12,13,15,17] and training fatigue were measured by the Samn-Perelli scale.[5]

Conclusions

This review provides plentiful evidence supporting of an association between training or competition activities with the increased levels of cortisol and proinflammatory cytokines IL-1β, IL-6, IL-8, TNF-α, negative mood conditions, stress levels, anxiety, and depression among adult human subjects, athletes, or the military. We recommend future research to determine the role of cortisol and proinflammatory cytokines in monitoring stress conditions in people who are closely related to training from the beginning of the selection, education, and assignment, other than in daily life.

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Declaration of Interest

The authors report no conflict of interest.

No	Title, Author, Year	Sample	Cortisol and Cytokine	Result
1	Psychophysiological Relationship between Mood, Inflammation and Cortisol Changes in Physical Work Simulation Trainings and Sleep Deprivation of Firefighters. Wolkow A, et al. (2016)	Saliva was collected before and after training (3 days 2 nights) Every day in both conditions at the start (i.e., 6:30) and all day every i.e., 7:30, 9:00, 11:30, 13:30, 15:30, 17:30, 19:30, 21: 30 Mood Scale II to measure stress Samn-Perelli scale for fatigue rating	Cortisol saliva, pro-inflammatory cytokines (IL-6, IL-8, IL 1b, TNF-α), anti-inflammatory cytokines (IL-4, IL-10)	In negative mood, cortisol, IL-6, IL-8, IL-1b, TNF-α increase On Fatigue, cortisol, IL6, IL-8, IL-1b, TNF-α are increased. Cortisol, IL-6, IL-8, IL-1b, TNF-α increased: Control > sleep restricted

2	Changes in Saliva Testosterone at Rest, Cortisol And Interleukin-6 As Overtraining Biomarkers Anderson T, et al. (2016)	Passive saliva sample for sample afternoon; 15:00-17:00, 6 weeks	Salivary cortisol, testosterone, IL-6	IL-6 and cortisol significantly increased week 1 – week 6 fT decreased significantly week 1 – week 6
3	Combat training improves intestinal permeability, immune activation, and gastrointestinal symptoms in military personnel X. Li, et al. (2013)	Fasting blood samples for CRH and cortisol concentrations were collected between 06:00 and 06:15. 6 weeks Perceived Stress Scale-10 items (PSS-10) were used for stress quantification Hospital Anxiety and Depression (HAD) for anxiety and depression.	Systemic inflammation, stress markers (TNF-α IL-1, IL-6)	During combat training: stress, anxiety, and depression scores > compared to rest Serum levels of cortisol, IL-6 and TNF-α increased during combat training > rest.
4	Effect of Boxing Match on Metabolic, Hormonal and Inflammatory Parameters in Male Elite Boxers Yakup Kılıc , et. al. (2019)	Plasma samples of boxers, before and after matches, taken 1 week before the match so as not to affect their performance and 10 minutes of the game and 10 minutes at the end of the game (9 minutes exercise and 1 minutes rest).	Cortisol, growth hormone, testosterone, IL-1β, IL-6, IL-17α, TNF-α	Post-training increased in cortisol and growth hormone inflammatory markers IL-1β, IL-6, and TNF-α
5	Effects of acute training on growth factor-1 (IGF-1), salivary free insulin, and interleukin 10 in athletes Taye J. Lasisi, Ade F. Adeniyi (2016)	Saliva samples were collected before the start of the session and after the 60 minutes training. (30 minutes before and 30 minutes after).	Growth Factor-1 (IGF-1) and IL-10	Free IGF-1 and IL-10 levels in saliva did not show significant changes There was no relationship between salivary flow rate and free IGF-1 and IL-10 levels before and after training.
6	Acute Effects of Prolonged Hard Training Markers of Saliva Stress and Inflammatory Cytokines Tatsuya Usui, et al. (2011)	Saliva samples were taken at 60 min intervals during the session 10 min before training, saliva samples were collected (t = 0) rest session time of the same training session (t = 0, 60, 120, 180 minutes) for 7 days	Cortisol, IgA, and CgA, Salivary inflammatory cytokines, such as IL-1β, IL-6, TNF-α	During and after training: Salivary cortisol and CgA concentrations and levels of secretion are increased. After practice.: Decreased salivary IgA concentration and level of secretion During and after training: IL-1β, IL-6 increased

7	Redox Homeostasis and Metabolic Profile in Young Female Basketball Players during in-Season Training Rosamaria Militello, et. al. (2021)	Capillary blood and saliva samples were collected in the morning before the training session for 4 weeks	Salivary cortisol	The cortisol concentration showed decrease (51%; $p < 0.009$) in basketball players in comparison with the control group. The cortisol mean value was 915.09 ± 613.69 pg/mL for basketball players and 1867.68 ± 659.83 pg/mL for controls.
8	sIL-6R Related to Weekly Mileage Training and Psychological Health in Athletes Tom Cullen, et. al. (2017)	Blood samples at rest and after training 18 weeks all saliva samples were taken at the same time throughout the day 30 minutes before you can't eat and drink sIL-6R concentrations were measured weekly, while cortisol was measured monthly.	Cortisol sIL-6R	The concentration of sIL-6R was positively correlated with subjective measures of stress (r = 0.64, P = 0.004) and mood (r = 0.49, P = 0.02), but negatively correlated with sleep quality (r = j0.43, P = 0.05) and cortisol concentration (r = j0.17, P = 0.04). In a subgroup of 10 athletes, weekly training distances were measured, negatively correlated with sIL-6R the following week (r = j0.74, P G 0.005).
9	Status, Stress, and Performance of Track and Field Athletes during European Games in Baku (Azerbaijan) Benjamin Siart, et. al. (2017)	Saliva samples 3 days, 2 days, 1 day before the competition; competition day; 1 day after the competition. taken at the same time on the day before the competition (24 hours pre-comp; 24 hours before entering the Call Room). Additional samples were collected immediately after, 1 hour after, and 3 hours after the competition.	Cortisol	Salivary cortisol levels increased significantly from 24 hours before the competition (3.89 ± 1.77 ng/ml) to immediately before the competition (7.57 ± 3.72 ng/ml, paired Wilcoxon rank test, P = 0.005; V = 20, r = -0.67, N = 18). Morning cortisol levels were not significantly different between sample days.

Table 2. Cortisol levels.

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