BLOOD BIOMARKERS OF OVERTRAINING SYNDROME

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Effective physical training programs induce functional overreaching to improve athlete performance. However, athletes may develop overtraining syndrome (OTS) when an athlete's training is chronically intense, long, or frequent without cessation or adequate recovery. This article will discuss the importance of blood biomarker monitoring as a vital tool in OTS diagnostics and recovery.

OVERREACHING VS. OVERTRAINING

Athletes consistently strive for excellence, especially at the collegiate, professional, and Olympic levels. Ideally, strength and conditioning coaches and personal trainers develop training programs that help athletes achieve functional overreaching (FOR), which is an adaptive state that leads to acute fatigue based on deliberately planned training, followed by specific adaptations to imposed demands (SAID).

In other words, training programs should introduce stimuli that challenge the athlete physiologically and mentally, resulting in temporary performance reductions but ultimately leading to enhanced performance (also known as "supercompensation"). However, an imbalance between adaptation and recovery can lead to nonfunctional overreaching (NFOR). NFOR is a physiological state of consistent fatigue, stagnation, and noticeable reductions in performance (13). Beyond NFOR is OTS, which is a plateau or decrease in physical or psychological performance due to excessive training duration, intensity, and frequency or insufficient recovery practices (4). OTS, previously called "unexplained underperformance syndrome," is the culmination of a prolonged, elevated state of fatigue, continuously intense physical training, and inadequate recovery (5,12). It is often the result of prolonged maladaptation for months to a year, and recovery can take just as long (4,13). Mismanaged training programs place athletes at greater risk for OTS.

SIGNS AND SYMPTOMS OF OVERTRAINING

While a complete list of documented signs and symptoms of OTS is beyond the scope of this article, sports professionals must be aware of these indicators. Notable signs include chronic fatigue, performance declines, frequent or prolonged illnesses (e.g., cold or flu), depressive symptoms, and overall poor physical and mental wellness. Other indicators of OTS include prolonged muscle soreness or damage, disordered sleep patterns, anorexia (loss of appetite), unintentional body composition changes (e.g., unplanned weight loss), altered blood pressure, low glycogen stores (i.e., frequent bonking), decreased maximal oxygen consumption, altered resting heart rate, and decreased heart rate variability (13,18). Physical signs such as tiredness or the desire to rest are often noticed and indicate poor training adaptation (4). However, blood biomarkers could also be a valid measure to determine the presence of OTS.

BLOOD BIOMARKERS

Blood biomarkers are objectively measured characteristics of normal biological processes and can be diagnostic, predictive, or monitoring tools. They can also be used for risk assessment, safety, surrogate or endpoint data, and pharmacodynamics. In the context of OTS, blood biomarkers can indicate a correlational and potentially causal relationship with OTS. This article proposes that an athlete's comprehensive health and performance assessment include blood biomarker monitoring as a vital tool in OTS diagnostics and recovery.

The most common OTS blood biomarkers include testosterone (males), adrenocorticotropic hormone, cortisol, growth hormone, insulin-like growth factor-1 (IGF-1), creatine kinase, catecholamines, and C-reactive protein. Testosterone and cortisol appear to be the most sensitive to OTS, but these blood biomarkers have limitations. All blood biomarkers must be evaluated and considered within the framework of timely and comprehensive health and performance evaluation to accurately understand an athlete's performance, adaptation to imposed demands, and health.

TESTOSTERONE

Testosterone levels are one of the primary indicators of OTS in male athletes. Testosterone promotes protein synthesis, red blood cell production, glycogen replenishment, and reduces protein breakdown (12). Healthy total testosterone levels are unique to each individual and can vary based on age, sleep quality, weight, genes, and overall health status. A reference range between 280 – 1080 ng/dL in men is considered normal (19).

Some research studies have found that intense and prolonged physical training sessions can reduce testosterone levels and other associated hormones such as cortisol (4,12,13). In a cross-sectional study, 14 OTS athletes, 25 healthy athletes, and 12 healthy sedentary participants had their total testosterone, testosterone to estradiol ratio, and testosterone to cortisol ratio levels examined. The results showed that the healthy athletes had higher levels of total testosterone that the OTS athletes and sedentary participants. The OTS athlete's testosterone to estradiol ratio was about 50% lower compared to healthy athletes and sedentary individuals. There was no difference in the testosterone to cortisol ratio between the OTS athletes and the healthy athletes. Interestingly, researchers theorize that reductions in testosterone occur due to the conversion of androgen precursors into estrogens (7).

On the other hand, OTS researchers found that a 12-week recovery period that included increased energy intake, physical training cessation, emphasis on sleep quality, and stress management can mildly improve total testosterone and significantly improve testosterone to estradiol ratio levels. These studies highlight testosterone's sensitivity to an athlete's training and recovery program. Biomarkers such as total testosterone and testosterone to estradiol ratio are promising indicators of OTS (6).

ADRENOCORTICOTROPIC HORMONE AND CORTISOL

Adrenocorticotropic hormone (ACTH), produced by the adrenal glands, responds to stress and produces cortisol (a stress hormone). Healthy ACTH levels are 7 – 69 pg/dL in men and 6 – 58 ng/dL in women (19). Some experts have found that elevated ACTH levels may indicate OTS and others have suggested that OTS is characterized by decreased ACTH levels (1,18). However, several research reviews found no significant biochemical difference between healthy athletes and athletes with OTS (8,16). Due to inconclusive research findings, this is a lesser-priority biomarker.

ACTH stimulates the production of cortisol, leading some experts to wonder if blood cortisol concentrations should also be considered a potential indicator of OTS (1,13,16). Cortisol levels rise in response to stress, such as physical training, sleep loss, and exposure to environmental stresses (e.g., high altitude, extreme cold, extreme heat) (18). OTS scientists point out that low glycogen stores or food intake can significantly increase cortisol levels. In turn, this makes researching cortisol levels in response to exercise challenging (18). A cortisol response to an insulin tolerance test (ITT) score of <19.1 ug/dL is considered a risk factor for OTS, indicating adequate reliability for the diagnosis of OTS paired with other biomarkers and assessment data (6). Overall, cortisol can provide reliable insight into an athlete's training readiness, whereas ACTH cannot (17).

GROWTH HORMONE AND IGF-1

Growth hormone (GH), a hormone that plays a crucial role in promoting protein synthesis, cell growth, and tissue repair, is another common blood biomarker evaluated to detect the presence of OTS. GH, also known as somatotropin, is secreted by the acidophilic cells in the anterior pituitary gland. Healthy GH levels are <5 ng/mL in men and <10 ng/dL in women (19). Reduced resting GH levels are a potential indicator of OTS, making this a biomarker to monitor in athletes (6,13).

Furthermore, while GH is an acceptable biomarker to evaluate regularly in athletes, IGF-1 may be better. IGF-1 is a messenger produced in the liver that transmits the effects of GH to peripheral tissues and is a more accurate indicator of the mean plasma concentration of GH (12,20). Some research has demonstrated a correlation between high duration or intensity exercise reducing the liver's production of IGF-1 (18). Conversely, studies also indicate comparable baseline IGF-1 levels between healthy and OTS athletes (6,7,8). Mixed research findings are due to variables such as athlete training capacity, internal vulnerability to stressors, and other hormone levels (16). Experts recommend monitoring IGF-1 during an athlete's recovery from OTS and suggest that IGF-1 levels are a better indicator of OTS recovery rather than for diagnostic purposes (8).

CREATINE KINASE

Creatine kinase (CK) is another blood biomarker that can detect the presence of OTS in athletes (16). Creatine kinase, specifically creatine kinase muscle-muscle (CK-MM), is an enzyme typically used to measure muscle damage (e.g., rhabdomyolysis). Total CK levels between 20 and 200 units of enzyme per liter (U/L) are normal (19). Researchers found that OTS athletes have a median CK of 569 U/L, 163% above the median of healthy athletes and 542% higher than sedentary individuals (7). Moreover, scientists found that a 12-week recovery period in OTS athletes resulted in a 65.6% nonsignificant reduction of CK from baseline (p=0.071). The CK levels after the 12 weeks of recovery were comparable to healthy athletes (8).

Additionally, one study found that OTS athletes (n=43) have an average baseline CK level of 276 U/L, comparable to athletes with NFOR (269 U/L) and healthy athletes (257 U/L) (15). Immediately after strenuous exercise, CK levels were elevated to 493 U/L in the OTS athletes but were still similar to NFOR athletes (485 U/L) and healthy athletes (461 U/L). Interestingly, 72 hr after strenuous exercise, CK levels remained at 325 U/L in the OTS athletes, indicating a statistically significant (p<0.05) increase from baseline. Also, the OTS athlete's CK levels of 325 U/L were 133% higher than healthy athletes at the 72-hr time point (15). Other research studies have found CK levels higher in OTS athletes than in healthy individuals (9). Unfortunately, creatine kinase is non-specific, highly variable, and may be used to measure overreaching but not to diagnose OTS (6,18).

CATECHOLAMINES

Catecholamines, including epinephrine, norepinephrine, and dopamine, are very responsive to overtraining stimuli, namely increases in training volume (13). One study found that OTS athletes had baseline median epinephrine levels ~151% higher than healthy athletes and ~154% higher than sedentary individuals. Next, results indicated OTS athletes had median norepinephrine levels of ~123% higher than healthy athletes but with no statistically significant difference. However, the OTS athlete's norepinephrine levels were significantly higher than sedentary individuals (7). Despite these nonsignificant differences, epinephrine and norepinephrine should be measured when evaluating an athlete's bloodwork to ensure they are within reference ranges.

OTS researchers also found that OTS athletes had average dopamine levels of 227 g (per 12-hr period), which was significantly different from sedentary individuals with levels at 114 g (7). Elevated catecholamine levels represent chronic physiological stress and interdisciplinary support teams overseeing endurance athletes should monitor for intrasubject differences. Aerobic endurance athletes are at the highest risk of OTS due to their high-volume training demands (13).

C-REACTIVE PROTEIN

Another blood biomarker that could be collected as a part of a comprehensive blood panel is C-reactive protein (CRP). CRP is a non-specific, acute-phase protein the liver produces during an acute inflammatory process. Healthy CRP levels are <1.0 mg/dL (19). Researchers found that OTS athletes had a median CRP of 0.10 mg/dL at baseline and reduced levels to 0.04 mg/dL through a structured, 12-week recovery protocol (8). Unfortunately, several studies have failed to demonstrate any significant difference between CRP in OTS athletes and healthy individuals (7).

PRACTICE RECOMMENDATIONS FOR EVALUATION OF RESULTS

Deciding when to evaluate an athlete's blood biomarkers is complex, and there is no one right answer. Nevertheless, it is recommended that they are evaluated at a minimum at the beginning of each macrocycle, ensuring the athlete is fully recovered from the last macrocycle and ready to initiate a new training cycle uncompromised. If the personal trainer does not have access to the athlete until the beginning of a new sports season, this would also be an appropriate time to have their blood tested. Additionally, blood panels can be assessed during training cycles or seasons if the athlete appears with other signs of OTS, such as persistently sore muscles, fatigue or washed-out feeling, frequent colds or flu, sleep disturbances, depressive symptoms, loss of appetite, or amenorrhea (20).

Blood biomarker evaluation provides interdisciplinary support teams with objectivity in their athlete/team evaluation. Blood biomarkers allow for insight into any biological abnormalities an athlete cannot recognize or express. Best practices suggest that practitioners should account for the dynamic nature of normal biomarker values (e.g., dynamic stability), individual differences in athlete responses to identical stressors (e.g., inter-athlete variation), and the minimal change needed to influence a biological system's functionality (e.g., minimal clinically important difference [MCID]). The MCID ensures that biomarker results can be interpreted reliably, accurately, and promptly (10).

Interpretation begins with understanding the smallest change not due to measurement error (i.e., minimum detectable change [MDC]) and the smallest change deemed practically significant (i.e., MCID). The chosen MCID's magnitude is crucial for practical and informative biomarker monitoring in practice. Two primary methods for determining an MCID are: the anchor approach, which links changes in the biomarker to changes in an external reference variable (the anchor), and the statistical approach, which can rely on metrics like the standard error of measurement (SEM) or the between-subjects standard deviation of the biomarker (2,21,23). Additionally, the validity and reliability of biomarkers should be periodically assessed through prognostic-longitudinal studies (11,14). Biomarker monitoring is a highly-specialized process that varies based on the sport, the athlete's performance level, individual characteristics (e.g., age, sex, body composition, race), and available resources (e.g., time, budget, technology).

Blood biomarkers provide insight into an athlete's work capacity and unique recovery needs. Companies such as InsideTracker™, LabCorp™ (Labcorp on Demand), Everlywell™, and LetsGetChecked™ provide consumers with simple, at-home tests to measure many of the aforementioned blood biomarkers. However, the accurate interpretation of these results is not just crucial, it is a responsibility that personal trainers and fitness professionals must take seriously. Their understanding of blood biomarkers is key to optimizing athlete performance and recovery.

If an athlete has OTS based on abnormal biomarkers and other symptoms, then recovery is priority number one. Research on return-to-play protocols is still in development, but personal trainers should take a holistic approach and emphasize key foundations of recovery: quality sleep, well-balanced nutrition, and cessation of all strenuous physical training (12). When it is time to ramp up training, personal trainers are advised to follow the periodization format, the 10% rule (maximum training volume and/or intensity increase of 10% at a time), and continue focusing on recovery fundamentals (20).

GENERAL PRECAUTIONS

No single marker can be taken as an indication of impending or present OTS. OTS is multifactorial, and regular monitoring of performance and physiological, biochemical, immunological, and psychological assessments should be considered. Considering the time, equipment, training, and personnel required for blood biomarker collection, analysis, and interpretation, there are alternative assessments such as athlete-reported rate of perceived exertion (RPE) or reduced performance metrics (e.g., VO_2max) that provide evidence of OTS faster and with greater accuracy (9).

Experts discourage the general use of measuring resting blood hormone levels as a basis for OTS diagnosis due to the variability of research to date and the need for more standardization of reference ranges (16). In general, blood biomarker research is scant, and the studies available are either cross-sectional or experimental, with few having longitudinal elements. Other information available is from expert opinion or anecdotal information from individual athletes, reducing applicability to other athletes even in the same sport.

So far, most research on biomarkers related to athletic performance, fatigue, and recovery has concentrated on a limited range of variants and involved small, often heterogeneous participants, leading to unreliable and conflicting findings (22). Individual differences in training should not be limited to the common approach of focusing on potential biomarkers based on author biases or the existing literature, nor should it rely on small, statistically underpowered observational studies (3). Sports medicine and performance should transition toward an unbiased investigation of biomarkers, utilizing large observational and experimental study designs. The focus should be on ethical, evidence-based practices that benefit the athlete's career, health, and performance.

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