# The hypothalamic-pituitary-gonadal axis dysfunction in men practicing competitive sports

## *Zaburzenia czynności układu podwzgórze-przysadka-gonady u mężczyzn uprawiających wyczynowo sport*

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KEYWORDS:

- competitive sport
- overtraining
- hypogonadism

ABSTRACT

Regular physical activity is widely recommended for primary and secondary prevention of many diseases. Among others, it has been proven to reduce the risk of coronary heart disease, stroke, diabetes, hypertension, colorectal cancer, breast cancer and depression. In addition, physical activity plays an important role in regulating the body's energy balance, and therefore controls body weight. Physical inactivity was identified as the fourth leading risk factor for global mortality (6% of deaths worldwide) after factors such as elevated blood pressure (13%), smoking (9%) and high blood glucose (6%). The purpose of this article is to illustrate the physiological and pathological changes that occur in the hypothalamic--pituitary-gonadal axis (HPG) secondary to exercise and training. Relatively short and intensive exercise usually increases, while more prolonged exercise usually decreases serum testosterone concentrations. Reduced or low-normal circulating testosterone levels involve health consequences such as an increased risk of abnormal spermatogenesis, infertility problems, and compromised bone mineralization. In addition, the administration of prohibited substances, such as anabolic androgenic steroids, to competitive and non-competitive athletes is an important cause of iatrogenic andrological diseases.

SŁOWA KLUCZOWE:

- sport wyczynowy
- zespół przetrenowania
- exercise hipogonadyzm

STRESZCZENIE

Regularna aktywność fizyczna jest szeroko zalecana w pierwotnej i wtórnej profilaktyce wielu chorób. Udowodniono między innymi, że zmniejsza ryzyko choroby wieńcowej, udaru mózgu, cukrzycy, nadciśnienia, raka jelita grubego, raka piersi i depresji. Ponadto aktywność fizyczna odgrywa ważną rolę w regulacji bilansu energetycznego organizmu, a zatem kontroluje masę ciała. Brak aktywności fizycznej uznano za czwarty czynnik ryzyka globalnej śmiertelności (6% zgonów na świecie) plasujący się tuż za podwyższonym ciśnieniem tętniczym krwi (13%), paleniem tytoniu (9%) oraz wysoki poziom glukozy we krwi (6%). Celem niniejszej pracy jest zilustrowanie zmian fizjologicznych i patologicznych zachodzących w osi podwzgórze-przysadka-gonady, a wtórnych do ćwiczeń fizycznych i treningu. U mężczyzn stężenie testosteronu wzrasta wraz z krótkim i intensywnym wysiłkiem fizycznym, podczas gdy dłużej trwające i bardziej wyczerpujące ćwiczenia zwykle zmniejszają stężenie testosteronu w surowicy. Obniżone lub niskie stężenie krążącego we krwi testosteronu pociąga za sobą konsekwencje zdrowotne, takie jak zwiększone ryzyko zaburzeń spermatogenezy i problemy z płodnością, upośledzoną mineralizację kości. Również stosowanie przez sportowców wyczynowych i amatorów zabronionych substancji, takich jak sterydy anaboliczno--androgenne, jest ważną przyczyną jatrogennych zaburzeń andrologicznych.

### Introduction

Regular physical activity is widely recommended for primary and secondary prevention of many diseases. Among others, it has been proven to reduce the risk of coronary heart disease, stroke, diabetes, hypertension, colorectal cancer, breast cancer and depression (1, 2 ). In addition, physical activity plays an important role in regulating the body's energy balance, and therefore controls body weight. Physical inactivity was identified as the fourth leading risk factor for

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global mortality (6% of deaths worldwide) after factors such as elevated blood pressure (13%), smoking (9%) and high blood glucose (6%) (3, 4).

In order to improve cardiopulmonary fitness, muscle strength, bone quality and reduce the risk of depression, WHO recommends that adults aged 18-64 spend at least 150 minutes a week on moderate aerobic physical activity, or exercise for at least 75 minutes weekly, intensive aerobic exercise. Such exercises should last at least 10 minutes a day (1, 5).

Different international health organizations warn about the elevated degree of sedentarism in the general populations, especially in the most developed countries (6, 7).

Appropriate physical activity is one of the bases of healthy lifestyle. Therefore, it seems necessary to promote programs of physical activity that improve health and quality of life of citizens; however, not having adequate knowledge on how to perform these activities might, on occasion, lead to negative side effects. Some women who play sports or exercise intensely are at risk for a problem called "female athlete triad". Female athlete triad is a combination of three conditions: disordered eating, amenorrhea, and osteoporosis.

Normal endocrine function is essential for optimal performance, adaptations to exercise, and maintenance of optimal body composition (8, 9). Effects of long-term training on the reproductive system in female athletes have been widely studied. However, the literature on the endocrine adaptations of male athletes is less robust. Normal functioning of the hypothalamic-pituitary-gonadal axis is also essential for the onset and maintenance of reproductive function, in addition to immune and musculoskeletal function (10).

The aim of this article is to illustrate the physiological and pathological changes that occur in the HPG axis secondary to exercise and training. In men, testosterone levels increase with acute bouts of exercise, but the long-term effects are less pronounced, indicating lower testosterone levels in endurance athletes. Limited energy availability can negatively affect hormone levels in endurance athletes.

## The hypothalamic-pituitary-gonadal axis in men

The HPG axis, which is regulated by a negative feedback system, is central to male reproduction. The testes are the male gonads and are responsible for production of both testosterone and sperm. The hypothalamus releases every 90 to 120 minutes in a pulsatile manner a hormone known as gonadotropin-releasing hormone (GnRH) which, in turn, stimulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release from the pituitary. Hormones such as prolactin, corticotropin-releasing hormone, glucocorticoids, catecholamines, insulin, insulin-like growth factor (IGF-1), leptin, adiponectin, ghrelin, and, neurotransmitters such as opiates, modulate the release of GnRH. LH is responsible for testosterone production by stimulating the interstitial cells of Leydig. FSH is main in proper spermatogenesis. This leads to an increase in the synthesis of many substances, including inhibin B and androgen-binding protein (ABP), ensuring a sufficiently high testosterone concentration in the testes. Testosterone and estradiol present in blood serum, by negative feedback inhibit LH secretion, and inhibin B – FSH by pituitary gonadotropic cells (11, 12).

About 95% of testosterone is synthesized in men in the testes called Leydig cells. Less than 1% of testosterone is produced in cells of the adrenal cortex, and less than 5% comes from the transformation of its peripheral precursors (13, 14). Normal testosterone concentrations in adult males range between 12 and 30 nmol/l: testosterone concentrations in blood follow a circadian rhythm with higher levels in the morning hours and about 25% lower levels in the evening (15).

The biological effect of testosterone results from the combination of the hormone with an androgen receptor. A small portion of circulating testosterone becomes a precursor to produce two other hormones. Up to 10% of testosterone under the influence of 5α-reductase is reduced in the 5α position, which leads to the formation of dihydrotestosterone (DHT). The 5 alpha-reductase type 1 is predominantly expressed in the non-genital skin, liver and brain. 5 alpha-reductase type 2 is expressed at relatively high levels in the prostate, genital skin, epididymis, seminal vesicles and liver (44). DHT is the most biologically active androgen that also binds to the androgen receptor, and its affinity for this receptor is 4 times stronger than that of testosterone. The effects of this action are mainly observed in the prostate, skin, liver and hair follicles. Testosterone can also be aromatized to estradiol and act in this way via the estrogen receptor. About 0.1% of testosterone undergoes this process. The effect of this action can be observed within the central nervous system and in bones (16, 17).

During puberty, testosterone influences the growth of the body and the development of somatic sexual characteristics (e.g., penile growth), inducing and maintaining spermatogenesis and sex drive. During maturity, the correct level of testosterone is responsible for maintaining spermatogenesis and sexual activity, and has an anabolic effect on the liver, hematopoietic and immune systems. It enables the maintenance of cognitive functions and the correct body composition, including muscle structure and mass, bone mineral density, affects fat metabolism (18).

Testosterone is an essential hormone in male athletes. Changes in testosterone levels can be disturbing because it plays an important role in neuromuscular adaptation, muscle maintenance, strength and aggressiveness during competition (19, 20).

## Effects of physical exercise on the hypothalamic-pituitary-gonadal axis in men

The acute responses of major physiological systems to a single training session can be large and robust. They are usually proportional to exercise intensity (for endurance events), but the relationship of response is not always linear in nature (21).

Relatively short, intense exercise usually increases, while more prolonged exercise usually decreases serum testosterone levels (22).

Increased testosterone concentrations have been observed during relatively strenuous running, weight training, rock climbing, and ergometer cycling (23, 24). Short term sprint increased blood testosterone levels in adolescent boys (25). Acute exercise-induced testosterone increases were also observed in older men, but they were significantly lower (26).

In addition to age, many factors can influence the acute HPG response to acute exercise:

- characteristics of the exercises (e.g., type, intensity and duration);
- individual factors (e.g., genetics, training, nutrition, hydration, body composition, mental stress, visual anxiety, motivation, endocrine diseases);
- stress hormone responses to exercise (e.g., catecholamines, cortisol);

- use of medicines or other substances (e.g., glucocorticoids, non-steroidal anti-inflammatory drugs, phosphodiesterase inhibitors, amino acids and androgenic anabolic steroids) (27).

We don't know the mechanism of rapid increase testosterone concentration after acute physical activity. But it results in better adaptation and efficiency of both muscle activity and functional abilities during exercise (28).

No conclusive evidence about gonadotropin response to an acute exercise is available. In fact, LH and FSH levels have been reported to be increased, decreased, or unchanged by short-term strenuous exercise . The exercise-associated increment in circulating testosterone is considered not to be mediated by LH, due to the inconsistent LH response and to the evidence that testosterone levels increase more quickly than LH in response to exercise (10).

Various mechanisms have been proposed to explain the sharp rise in testosterone concentrations during exercise:

- increased testosterone synthesis and/or secretory capacity of Leydig cells – due to LH-independent mechanisms related to exercise (e.g., catecholamines, lactate);
- changes in water distribution/perspiration related to plasma volume, testicular blood flow;
- testosterone metabolic clearance (i.e., in case of decreased hepatic blood flow and modified serum albumin and SHBG levels) (28, 29).

The response time of testosterone differs from that of other circulating steroids, suggesting that specific testicular mechanisms are involved. Catecholamines also increase significantly during exercise. Beta-adrenergic blockade inhibits the testosterone response to exercise (30). Several studies have shown that the sympathetic nervous system and circulating catecholamines are involved in increasing testosterone secretion during acute exercise by stimulating Leydig cells (25, 28).

The exercise-related acute testosterone increase seems to be not a simple secondary effect but a physiological mechanism of adaptation.

Ultimately, the exact mechanisms involved in increasing testosterone levels in specific exercise protocols have not yet been determined.

**Prolonged, submaximal exercise and chronic exercise training**

Athletes want to improve their performance by constantly increasing their training loads. It has been estimated that the exercise training loads of athletes have increased on average by 20-25% over the past decade (31, 32).

In contrast to the short-term testosterone increment during and immediately after short, intense exercise, a suppression of serum testosterone levels occurs during and subsequent to prolonged exercise, in the hours following intense exercise, as well as during chronic exercise training (22).

Men who engaged in intensive exercise training can develop low resting testosterone levels, alterations in their HPG axis, and display hypogonadism. Specifically, such conditions in men may derive acutely and be associated with low energy availability (i.e., Relative Energy Deficiency in Sports) or excessive training load (i.e., overtraining). However, manifestations of a more chronic based hypogonadism that persists on a more permanent basis (years) exist and is termed the "Exercise Hypogonadal Male Condition" (33, 34).

Because there is a lack of common and consistent terminology in this research field, the following definitions are presented:

- Relative Energy Deficiency in Sports (RED-S) refers to impaired physiological function including, but not limited to, metabolic rate, menstrual function (in woman), bone health, immunity, protein synthesis, cardiovascular health caused by relative energy deficiency. Syndrome is energy deficiency relative to the balance between dietary energy intake and energy expenditure required for health and activities of daily living, growth and sporting activities (35);
- overtraining – an accumulation of training and/or non-training stress resulting in long-term decrement in performance capacity with or without related physiological and psychological signs andsymptoms of maladaptation in which restoration of performance capacity may take several weeks or months (36);
- "Exercise Hypogonadal Male Condition." or "exercise hypogonadal male".

In 2005 Hackney et al. proposed the use of the term "Exercise Hypogonadal Male Condition" (EHMC) for exercise trained men who showed lowered testosterone. Hackney et al. showed that highly trained or overtrained male athletes had 40-80% lower levels of testosterone compared to controls (34). Men with this condition have certain characteristics:

- low resting basal testosterone concentrations, typically only 50-75% that healthy, age-matched sedentary men;
- low testosterone concentrations do not appear to be a transient phenomenon related to the acute stress of exercise training;
- in many cases, it appears an adjustment in the HPG axis has occurred (to allow a new lower set-point for circulating testosterone). That is, gonadotropins also display lower compensatory levels;
- a history of early involvement in organized sport and exercise training exist. It has resulted in these men having many years of daily exposure to physical activity;
- the type of exercise training most frequently seen in these men is prolonged, endurance-based activities such as: distance running, cycling, race walking, and the triathlon training (37).

"Exercise-hypogonadal male" is not a typical hypogonadism. Male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (QoL). A diagnosis of male hypogonadism must compriseboth persistent clinical symptoms and biochemical evidence of testosterone deficiency (38). Testosterone threshold levels for diagnosis of hypogonadism are below 3-4 ng per ml (34).

There is a lack of consistency in the exercise literature determining what exactly constitutes exercise hypogonadism. Many researchers have tried to establish a cut-off value to determine when testosterone levels are lowered enough to apply the distinction "exercise hypogonadism". Regardless of the terms used to refer to testosterone levels in exercising men, it is important to note that even were testosterone is reduced, for many of these individuals it is low but within the normal range and seldom found to reach clinical definitions of hypogonadism (34). The manifest symptoms of hypogonadism include the absence or regression of secondary sexual characteristics, bone mineral density, muscle atrophy, abdominal obesity, anemia, oligospermia, erectile dysfunction, decreased libido, decreased energy and depressed mood, increased irritability, difficulty concentrating (38).

Researchers have proposed two major rationales and mechanisms for testosterone reductions:

- testosterone production being disrupted by inhibitory factors such as other hormones in a stress response cascade;
- inadequate energy intake disruption of the HPG axis regulatory function (34).

Relative to the first mechanism, many investigators demonstrated blood cortisol elevations disrupt testosterone production peripherally at the testes (41). There are numerous research studies reporting findings of exercise induced short-term increases in cortisol levels, as well as these acute elevations in cortisol from an exercise session being associated with decreases in testosterone. Furthermore, evidence exists for circulating testosterone and cortisol to be negatively associated with athletes even in the resting and in basic condition (34).

The inhibitory effect of cortisol appears to be twofold; influence LH and FSH by suppressing GnRH, and also impair Leydig cell function by directly inhibiting steroidogenesis (41, 42).

Prolactin is another hormone that can lower testosterone levels. Elevated prolactin concentrations inhibit GnRH secretion, reducing gonadotropin secretion and affecting the central aspects of the HPG axis. Prolactin may also inhibit the gonadotropin action at the gonadal level.

In the case of the second proposed mechanism, short- and long-term caloric deficient results in testosterone reductions in men. It is well-recognized that a common finding is overtrained athletics is weight loss and suppressed appetite and sometimes anorexic tendencies.

Last year, Dwyer et.al. published a study about healthy men presenting with symptoms of hypogonadism in the setting of excessive exercise (more then 10 hours per week) or weight loss (above 10% of body weight). Healthy age-matched men served as controls. Patients had significantly lower BMI (Body mass index), testosterone, LH, and mean LH pulse amplitudes yet normal LH pulse frequency, serum FSH, and sperm counts. Some patients exhibited nocturnal, sleep-entrained LH pulses characteristic of early puberty, and one subject showed a completely apulsatile LH secretion. After decreased exercise and weight gain, men had normalized serum testosterone levels, and symptoms resolved. Thus, the effect of inadequate caloric intake or excessive exercise on testosterone seems more related to central HPG axis suppression. Bergendahl et al. found such gonadotrophin reductions were driven by suppressed GnRH release by the hypothalamus (43). This is a functional hypogonadotropic hypogonadism. Recently, Wong et al. proposed this dysfunction likely involves hypothalamic suppression due to dysregulation of leptin, ghrelin, and pro-inflammatory cytokines (44). The gonadal axis suppression transient and the axis functional, as the effect, can be reversible with weight gain; although the rate of testosterone returning to normal seems highly individualistic (34).

## Effects of physical exercise on spermatogenesis

Chronic physical exercise may induce a state of oligospermia, a reduction of the total number of motile sperm and an increase in abnormal spermatozoa (46).

Safarinejad et al. observed a negative effect of training on semen parameters in high-intensity athletes compared to moderate-intensity athletes (47). Arce et al. established an exercise threshold of 100 km of running per week for semen alterations to occur. They found alterations in sperm density, motility, morphology, and in vitro sperm penetration of standard cervical mucus in endurance-trained runners with compared to resistance athletes or sedentary subjects (46).

Wise et al. found that cycling over 5 hours a week was associated with low concentration and total sperm motility. Many studies also confirm deleterious effects of bicycling on semen parameters among competitive cyclists (48). It seems to be connected with mechanical trauma caused by compression of scrotum on the bicycle saddle, or with increase in scrotal temperature related to exercise itself or wearing of tight clothing.

Mountain trekkers should be aware of the potential effects of high altitude on fertility. An oxygen-poor environment has a direct effect on spermiogenesis, epididymal dysfunction, HPG changes and hyperprolactinemia. An exposure to altitudes higher than 2,000 meters may result in reductions in sperm concentration, motility and the number of spermatozoa with normal morphology (49).

Various mechanisms affect the reproductive function of men who exercise intensively. The disturbances in the HPG axis not only reduce testosterone synthesis but also worsen spermatogenesis. On the other hand, it has been reported that endurance exercise is associated with oxidative stress (50). During endurance exercise, a 10-20-fold increase in oxygen consumption in the entire body is observed, and oxygen uptake in active skeletal muscle increases by 100 to 200-fold (51). This increase in oxygen use may result in the overproduction of reactive oxygen species (ROS). Oxidative stress is caused by an imbalance between the ROS production, formed in cells during many metabolic processes, and the action of the protective antioxidant system of the body responsible for neutralizing and removing them. ROS excess is the cause of pathological reactions leading to damage of important biological molecules (i.e., lipids of cell membranes, proteins, sperm DNA), causing irreversible changes in their structure and leading to sperm dysfunction (52).

It seems that both the intensity and type of sport play a significant role.

Moreover, doping in sport has a negative impact on male reproductive function, not only on semen quality but having an effect on the endocrine regulatory axis as well as the testes and accessory ducts, and sexual performance. This effect has been observed to revert in approximately 1 year upon cessation of substance abuse, except in extreme cases.

## Conclusions

A biologically normal testosterone secretion appears fundamental in males to guarantee both a physiological exercise adaptation and safe sport participation. The male HPG axis function is also strongly affected by physical exercise. Relatively short and intense exercise usually increases, while more prolonged exercise usually decreases serum testosterone concentrations. Reduced or low-normal circulating testosterone levels involve health consequences such as an increased risk of abnormal spermatogenesis, infertility problems, and compromised bone mineralization.

We should remember that exercise can represent a potential cause of andrological problems.

On the other hand, moderate and low-level exercise have positive effects on the male reproductive potential. We need additional research in this area, with appropriate

standardization of assessment tools and research protocols, to draw more accurate conclusions about the effects of exercise on the male gonadal axis function. Future studies should clarify the direction and magnitude of the effects on semen and testosterone concentration in men participating in the most popular sport disciplines. In addition, prohibited substances administration (e.g., androgenic-anabolic steroids, and so forth) in competitive and non-competitive athletes represents the main cause of iatrogenic andrological diseases.

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