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MINI REVIEW

Andrological aspects of physical exercise and sport medicine

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Abstract Appropriate physical activity is one of the bases of healthy lifestyle. In fact, physical exercise and playing sport may be associated with both improvements and injury to both general and reproductive health. A biologically normal testosterone secretion appears fundamental in males to guarantee both a physiological exercise adaptation and safe sport participation. The reproductive system is highly sensitive to the effects of exercise-related stress and the reproductive hormones may both increase and decrease after different acute or chronic exercises. Exercise and sport participation may positively or negatively influence andrological health status depending on the type, intensity and duration of performed physical activity and on individual health status. 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. Preventing and treating andrological problems in active healthy and unhealthy individuals is as important as promoting a correct lifestyle. Physicians need to be educated on the relationships between the male reproductive system and sport participation and on the great role of the pre-participation physical examination in the prevention of andrological diseases.

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Physiological and clinical relationships between exercise, sport and the male reproductive system exist. Besides the physiological role of sexual hormones in exercise adaptation and sport performance, the andrological aspects of physical exercise and sport concern the possible risks and benefits for reproductive and sexual health. This is due to both the high prevalence of lifestyle-related diseases influencing reproductive and sexual functions (e.g. obesity, metabolic syndrome, diabetes and cardiovascular diseases) and to the high participation and professionalism in sport. In addition, the worldwide abuse of prohibited substances may negatively influence the male's reproductive system in many competitive and non-competitive athletes.

Hypothalamus–pituitary–testicular (HPT) axis and physical exercise

Many hormones (e.g. catecholamines, growth hormone, adrenal steroids, androgens, etc.) influence health status, exercise/sport performances and the physiological adaptation to exercise-related stress in athletes [1, 2]. In addition to classic reproductive and sexual effects (e.g. sexual behaviour, penis growth, erection, secondary sexual characteristics and spermatogenesis), and also depending on the role of CAG repeat polymorphism on androgen receptors biological activity [3], endogenous testosterone exert a wide spectrum of actions in males. Particularly, testosterone can differently influence: (a) body composition (e.g. muscles growth, fat mass, bone density), (b) central nervous system maturation and functions (e.g. behaviour characteristics, aggression and cognitive processes), (c) endocrine and metabolic pathways (glucose metabolism, insulin and leptin), (d) muscles physiology and motor behaviour, (e) erythropoiesis and (f) adaptation to stress [4–11].

The reproductive system is highly sensitive to the effects of exercise-related stress. However, few and conflicting data are available when the HPT axis responses to different sports and, particularly, to standardized exercises are considered. The effects of exercise on HPT axis depend on the type, intensity and duration of performed exercise and are related to many endogenous and exogenous conditioning factors (e.g. energy balance, energy availability, psychological factors, etc.) that may justify the observed discrepancies in the literature.

In our opinion, acute exercise, depending on its characteristics, demands a physiological increase in testosterone. In fact, the majority of investigations showed that total and/or free testosterone acutely increased immediately after acute strenuous and/or prolonged sub-maximal endurance and resistance exercises [12–19]. Unfortunately, the mechanisms responsible for testosterone increase after acute exercise are still unknown. Probably due to exercise standardization and/or to individual variability gonadotropins levels have been reported unchanged, increased or, rarely, decreased after both sub-maximal and maximal acute exercise [20–24]. Consequently, other mechanisms, such as a possible adaptation of secretory capacity of the Leydig cells, adrenergic and/or lactate stimulation, modifications of clearance rate, plasma volume reductions and changes in testicular blood flow should be investigated [15].

Studies on the effects of chronic exercise (e.g. training) on HPT axis compared trained and untrained men in a resting state by using both retrospective and prospective approaches. Retrospective studies frequently showed a reduction of free and total testosterone concentrations in endurance-trained men, and the few prospective studies showed contradictory results probably due to the features of the training period, the magnitude of training stimulus and the volume of training load employed [15, 25]. In addition, modifications of androgen receptors status have also been described [15, 26].

The best known HPT axis abnormality in highly trained or over trained athletes is the reduction of serum total and free testosterone concentrations. The exposure to endurance training may induce chronic basal resting testosterone concentrations at the extreme low end of normal range for age, or reduced from 40 to 80 % with respect to age-matched sedentary controls (e.g. so-called exercise-hypogonadal male condition), with possible clinical consequences due to testosterone reduction [27].

Exercise-related hypogonadal males showed a reduced LH response to GnRH, probably due to GnRH resistance or compromised pituitary LH secretion [27, 28]. The HPT axis alterations in males subjected to chronic endurance training (reduced gonadotropins and testosterone levels, altered LH pulsatility, reduced biological/immunological LH ratio) are the consequence of stress-related (e.g. PRL, cortisol, endorphins, leptin and ghrelin) physiological adaptation and/or of altered energy balance/availability [24, 27–32].

Regarding the effects of exercise training per se on semen parameters, no homogeneous data are available. While some Authors described alterations in the sperm parameters in athletes [33–36], other investigators did not show semen alterations [37–39]. Probably, besides doping consequences, semen alterations could be found only in athletes with a very high volume of training, this indicating the possible presence of an exercise volume threshold over which a range of modifications of both gonadal hormones and semen profile appear [39–42].

Male hypogonadism and sport participation

Even if a significant association between exercise capacity and circulating total testosterone and SHBG serum concentrations was not found by some Authors [43], a biologically normal secretion of testosterone is necessary, similarly to other hormones, to guarantee both a physiological exercise adaptation/performance and safe sport participation in male individuals. Because of the multiple genomic and non-genomic effects of testosterone, untreated male athletes with hypo-testosteronemia due to true hypogonadism (e.g. Klinefelter syndrome, congenital hypogonadotropic hypogonadism, anorchia, hypogonadotropic hypogonadism secondary to pituitary adenomas, etc.) are theoretically exposed to specific risks for health and for their physiological adaptation during exercise [44–46]. However, evidence-based criteria do not exist. Hypogonadal athletes are at increased risk of osteoporotic fractures in case of falling or trauma (e.g. cyclists, combat sports), of cardiovascular accidents related to high exercise-strain, of worsened sport-related anaemia, and of reduced balance in stress hormones (e.g. cortisol). In addition, testosterone deficiency alters the endocrine-metabolic and neuromuscular adaptations to exercise, reduces muscles strength, aggressiveness in competition and the re-synthesis of proteins during recovery and increases the risk of overtraining. On these basis, and because we observed that the history of clinical symptoms of hypogonadism may be inaccurate to diagnose testosterone deficiency in trained individuals [47], in our opinion a testosterone replacement therapy should be considered in all athletes with low serum testosterone due to true hypogonadism (i.e. not related to anabolic androgens abuse), independently from the presence of classical symptoms of hypogonadism and if contraindications are absent.

Currently the World Anti-Doping Agency (WADA) permits athletes to assume, for therapeutic purposes, many prohibited substances (e.g. testosterone, LH, and so forth) after obtaining a Therapeutic Use Exemption (TUE) (www.wada-ama.org). Interestingly, a TUE is not granted if the therapeutic need of a prohibited substance is a consequence, wholly or in part, of prior non-therapeutic use of a prohibited substance—for example in secondary hypotestosteronemia due to anabolic androgens steroids abuse—or when the prohibited substance is given to increase "low-normal" levels of any endogenous hormone. Physicians responsible for treatments with such prohibited substances in hypogonadal athletes should be aware of the need to perform an accurate clinical evaluation. Moreover, they should confirm the diagnosis with hormonal and instrumental evaluations, use officially marketed substances, and respect the official therapeutic indications and authorized formulations/doses in order to guarantee a physiological androgens status and to avoid abuse [3, 48–50].

Male sexual function, exercise and sport

Exercise and sport may positively or negatively affect male sexual functions (sexual desire, erectile function and ejaculation) [27, 51]. Well-balanced physical training is of great benefit to maximize erectile function and sexual health, to prevent and treat both sexual diseases and diseases causing sexual disorders (e.g. metabolic syndrome, cardiovascular diseases, diabetes and obesity) [52–60]. Otherwise, a long duration and/or high intensity chronic exercise (e.g. marathon runners, long distance runners, etc.) may induce hypogonadism and, consequently, erectile dysfunction and/or decreased sexual desire [27, 61]. Besides the effects of traumatic injury to the male reproductive system during competitions, non-traumatic bicycle injury may also affect erectile function in cyclists [62–64]. In addition, drug abuse (e.g. doping with androgens, β-blockers, diuretics, stimulants) may negatively affect sexual desire, erection and ejaculation in male athletes.

Varicocele in athletes

Varicocele is the most frequent andrological disease in athletes of different ages with a prevalence of 29 % or higher [65–67]. Even if few studies exist, the percentage of spermatozoa with forward progression and normal morphology may be reduced in athletes with varicocele with respect to non-athletes with the same degree of varicocele [68]. At least in theory, different exercise-related systemic and local factors—reduced gonadotropins secretion, increased anti-gonadic hormones, increased temperature, increased endo-abdominal pressure, reduced oxygen availability—might represent an "aggravating factor" for both the evolution of varicocele and the genesis of varicocele-linked testicular and seminal alterations in athletes [68, 69].

Effective management of varicocele in athletes [70] is to guarantee safe sport participation and to protect fertility. It involves the identification of athletes with varicocele whose sport activity may expose them to additional risks (e.g. exacerbation of the disease, testicular pain or testis trauma). It is important therefore to recognize athletes requiring treatment or clinical monitoring [70].

Androgenic–anabolic steroids abuse (doping)

The non-therapeutic use of androgenic–anabolic steroids (AAS) is one of the main causes of iatrogenic diseases due to drug abuse in the world [71, 72]. AAS are commonly abused, often together with other anabolic hormones such as GH, insulin. Common areas of abuse involve: (a) in one-third of cases as sport performance enhancers (track and field, weightlifting, football, swimming, rowing, boxing, etc.) (b) in two-third of abusers, as "muscle volume enhancers" in bodybuilders, for "cosmetic" purpose in the so-called body beautiful subculture or as performance enhancers for occupational purposes (security, police, armed forces, etc.) and, finally, (c) without any medical rationale as possible "fountain of youth" in aged people.

In addition to many systemic effects and health risks, AAS abuse inhibits gonadotropins secretion, endogenous testosterone production and spermatogenesis [73–75]. Even if the extent of AAS abuse in paediatrics and pre-adolescents is not well known, in very young male abusers AAS may induce precocious puberty, excessive androgenization with reduced testis size, stunted growth and premature closing of epiphyseal growth plates [76–78]. AAS-induced sperm alterations include oligozoospermia, azoospermia, decreased sperm motility, and abnormal sperm morphology [79–81]. These often result in decreased fertility in males. After AAS withdrawal the inhibited HPT axis functions will restore, but not always, within several months. In bodybuilders with a history of long-term AAS abuse, at least 6/12 months are needed for a full recovery of testicular functions [82–85]. Clomiphene may successfully restore AAS-induced male HPG dysfunction [86] and gonadotropins have been used to recover from AAS-linked azoospermia [87].

Phosphodiesterase type 5 inhibitors (PDE5i), exercise and sport

Experimental studies have indicated that sildenafil positively influences exercise capacity and cardiovascular adaptation in subjects affected by cardiopulmonary diseases [88, 89] and in healthy subjects in hypoxic conditions with different individual responsiveness [90–92].

Even if cardiovascular mechanisms probably predominate [93], PDE5i use, or abuse, may positively or negatively affect exercise capacity by also influencing endocrine and/or metabolic pathways. Particularly in healthy males, 20 mg of tadalafil administered 8 h before exercise increased salivary cortisol response to acute aerobic exercise [94] and blood lactate concentrations after anaerobic power exercise [95], with respect to placebo. In addition, we found that a two-day administration of tadalafil reduced the hypothalamus–pituitary–adrenal axis responses to exercise test until exhaustion in vivo [96], and that in C2C12 skeletal muscle cells tadalafil influences aerobic and anaerobic energy metabolisms depending on its doses and duration of exposure [97].

The possible relationships between PDE5i and exercise adaptation are relevant: (a) in terms of therapeutic use to improve exercise capacity in unhealthy individuals, (b) to guarantee safe sport participation in athletes treated with PDE5i for ED and (c) to avoid the fraudulent use of PDE5i as performance enhancers, raising the difficult question of whether PDE5i should be prohibited by WADA.

Sport medicine and male reproductive system

The role of sports medicine as epidemiological filter and health prevention system throughout pre-participation physical examinations (PPE) in athletes is of great interest in social medicine, particularly when young athletes are concerned [98]. The main purpose of the PPE, is not only to give specific sports eligibility certification, when mandatory, or disqualifying unfit individuals from practicing sports, but rather to ensure also that subjects predisposed to and/or affected by a disease can practice sports safely [65].

Unfortunately, beyond the problem of an athlete's sudden death, few studies have focused attention on the efficacy and/or the role of the PPE in diagnosing diseases which, while not influencing sports eligibility, are of clinical interest for directing a subject towards secondary prevention, specific clinical assessment and/or monitoring over the course of his life [99]. A genital examination adequately performed during the PPE could guarantee the early diagnosis and prevention of many andrological diseases in male athletes including varicocele, testicular tumours, and cryptorchidism. In addition, a thorough anamnesis and physical examination during PPE, associated if necessary with other clinical investigations [100], can detect early clinical signs of drug abuse. As such, it is a possible screening method for doping. Just as important, however, is that it can signal a need for adequate educational and/or therapeutic interventions. Sport physicians should be aware of the importance of an early diagnosis and management of andrological diseases in athletes, and the PPE represents a great opportunity to protect andrological health.

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