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The role of sex hormones in physiological adaptation and athletic performance in women with hyperandrogenism: medical and ethical aspects

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Abstract

Introduction: Hyperandrogenism in women's sports is a topic that has been controversial for years and has been discussed and debated internationally. It concerns the participation of women with elevated testosterone levels in sports competitions, especially in disciplines where physical strength and performance are crucial. Gender categorization in sports has a biological basis and stems from significant physiological differences between men and women.

The aim: To ensure fair competition and equal opportunities for all participants.

Materials and methods: A systematic review explored the link between androgen levels and athletic performance improvement. Google Scholar and PubMed were searched in polish and english language.

Results: The issue of hyperandrogenism in sports often arises in the context of controlling the fairness of competition. Many researchers and sports activists argue that high levels of testosterone can give an unfair advantage, especially in sports requiring strength and speed. Therefore, the International Olympic Committee (IOC) and other sports organizations have introduced limits on testosterone levels in women competing in certain sports. It is also worth noting that hyperandrogenism is not always due to doping or unfair practices. Often it is a

physiological condition that can result from individual genetic characteristics. The approach to this issue requires consideration of both aspects of fair competition and the rights of athletes to compete without discrimination based on their natural physiological characteristics.

Key words: hyperandrogenism; female athlete; disorders of sex development; free androgen index; testosterone; Paris 2024

Introduction

Success in sports is the result of many elements, such as genetic predispositions, proper training preparation, proper nutrition, or the use of appropriate equipment. For many years, sports have been divided into classic gender categories: female and male. However, in recent years, we have increasingly heard about situations where athletes are denied the right to compete in his/her category due to personal characteristics or abnormal levels of testosterone, that do not fit within the framework of the classical binary division of sexes.

Unlike in other fields, in sports, gender division and the resulting exclusion are not treated as a form of discrimination but as something understandable and justified. A large part of our society believes that men are physically stronger than women, so using gender-based division here becomes a good way to create equal opportunities . It is noticeable that more and more women are participating in sport at a professional level, and over time, there is also a significant improvement in their performance. However, despite such progress, the advantage of men in sports results usually remains up to 20% compared to women. [1,2] Therefore, it was agreed that inter-gender competition would not be fair, and thus most disciplines have been divided into male and female categories.

The most commonly used factor in explaining differences between genders in sports results is the concentration of circulating testosterone, which is up to 15 times higher in men than in women. It is believed that androgens, precisely such as testosterone, are responsible for regulating various physiological processes occurring in tissues ultimately subjected to exercise. In adult athletes, the use of exogenous anabolic steroids improves sports performance by increasing muscle mass and strength, reducing fatigue, and stimulating erythropoiesis. [3]

Currently, the control of androgen levels in female athletes is mainly carried out in cases related to menstrual disorders. Hypothalamic inhibition of gonadotropin-releasing hormone (GnRH) secretion, resulting from the maintenance of a negative energy balance, is considered to be the main cause of a large proportion of abnormalities. Such disturbances are the result of intense training and restrictive diets maintained to achieve intended sports results, or they directly result from the overrepresentation of women with specific endocrinological characteristics in professional sports. [4]

Hyperandrogenism has become a popular and controversial topic in the world of women's sports in recent years, which we would like to present and systematize in the following review.

The aim

To explore how elevated levels of sex hormones, particularly androgens, influence physiological adaptations and athletic performance in women with hyperandrogenism. The article aims to contribute to the ongoing conversation about how to fairly and effectively integrate athletes with varying hormonal profiles into competitive sports while balancing medical ethics and athletic integrity.

Material and methods

A systematic review explored the link between androgen levels and athletic performance improvement.

Google Scholar and PubMed were searched in polish and english language using keywords like ‘hyperandrogenism’, ‘female athlete’, ‘sexual development disorders’, and ‘free androgen index’.

The role of sex hormones in physiological and athletic adaptation

Sex hormones such as estrogen, testosterone, progesterone have an essential function in the physiological adaptation of the body. They take part in the formation and differentiation of sexual characteristics but also for the normal course of pregnancy, menstruation and the changes that occur in the body in response to the changing environmental situation.

1. Estrogens

Estrogens, and the signaling pathways that they regulate, are key mechanisms that control bodily functions. The biological effects of estrogens are mediated by estrogen receptors, among which are the canonical estrogen receptor (ER) types α and β, which act as transcription factors. In addition, a G-protein interacting estrogen receptor (GPER) was identified in the 1990s, which also plays an important role in estrogen signaling. [5] This hormone also inhibits ovulation, which is why it and progesterone are used in contraception. They are also used to supplement natural estrogen levels when they are insufficient, as in some menstrual disorders, and to inhibit androgen formation and thus the growth of androgen-dependent cancers (prostate cancer). Estrogens appear to offer a number of beneficial effects for women, including protection against osteoporosis and heart attacks. [6] Although the effect of estrogens on muscle protein synthesis is not entirely clear, studies have been able to show an increase in muscle mass and strength in already postmenopausal women, especially when performing intense resistance exercise, which was explained by the hormones' effect on increasing the number of satellite cells or increasing the number of cross bridges in muscle.[7,8] Another interesting aspect is that estrogens, especially estradiol, significantly modulate substrate utilization during exercise, inducing mainly an increase in fat oxidation and a decrease in protein and CHO (carbohydrate) oxidation, mainly by a mechanism of reducing hepatic glucose production and muscle glycogen utilization.[9,10] It is worth mentioning that estrogens, using the estrogen receptor complex, are able to influence mitochondrial function, by regulating the expression of mitochondrial proteins such as PGC1α (regulator of cellular energy metabolism) or directly affecting the intensity of ATP production.[11]

2. Progesterone

The steroid hormone progesterone plays a key role in the reproductive processes involved in establishing and maintaining a pregnancy.

The establishment and maintenance of pregnancy. The physiological effects of progesterone are mediated by the hormone's interaction with specific intracellular progesterone receptors (PRs), which are expressed as two protein isoforms, PR-A and PR-B.[12] The hormone also has minimal effect on bone mineral density compared to estradiol, while medroxyprogesterone acetate (MPA) and estradiol induce a significant decrease in osteoclast activity. These factors should be taken into account when choosing a progestin for hormone replacement therapy.[13] The effect of progesterone on the hypothalamic-pituitary-adrenal axis by modulating LH secretion, thus establishing a feedback mechanism on ovarian steroidogenesis, has been widely reported in the literature.[14] Most existing studies suggest that progesterone has

testosterone-like effects and may have a real effect on protein synthesis and thus increased muscle mass in women, but this effect has been demonstrated mainly in postmenopausal women.[15]

3. Testosterone

Testosterone plays a key role in carbohydrate, fat and protein metabolism, significantly affecting the body's physiology. It is increasingly recognized that testosterone has a significant impact on body fat composition and muscle mass, especially in men. Deficiency of this hormone is associated with a number of adverse effects, such as increased fat mass, especially in the central area, which is particularly associated with abdominal obesity, reduced insulin sensitivity, impaired glucose tolerance, elevated triglyceride and cholesterol levels, and low HDL cholesterol levels. All of these factors are characteristic of metabolic syndrome (MS) and type 2 diabetes mellitus (DM II), which increases the risk of cardiovascular disease.[16] The action of testosterone is based on the androgen receptor (AR, or androgen receptor), which is expressed in both male and female muscle cells; moreover, in men, activation of the aforementioned receptor simultaneously directly results in the activation of muscle protein synthesis via the Akt/mTOR pathway and can inhibit muscle protein degradation pathways.[17,18] In men, there is a correlation between an increase in circulating testosterone levels and the performance of short-term intense resistance training.[19] The situation is different for women, here hormonal changes in response to intense exercise are difficult to interpret, due to menstrual variability, but a large body of research does not indicate a sharp increase in testosterone levels as a result of performing resistance exercise, in addition, strength and total muscle mass are not clearly related only to the level discussed, suggesting that in women the activation of muscle protein synthesis also relies on other hormones.[20,21]

Hyperandrogenism in female sports

The most important factor explaining the difference in sports between men and women is the concentration of testosterone and dihydrotestosterone (DHT). Although the concentration of testosterone in the blood is not an indicator of success in women's sports, there are grounds to claim that its very high concentration improves results in the population of women with androgen sensitivity.[21] Androgen derivatives such as 11-ketotestosterone and 11-keto dihydrotestosterone are also potent androgen receptor agonists, but their potential biological role is not fully understood.[22] It should also be noted that in the world of sports there are two

categories, male and female. In the late 1990s, the IAAF (International Association of Athletics Federations) and the International Olympic Committee stopped testing athletes based on gender, admitting that it created more problems than it brought benefits. However, after an incident with Caster Semeny, a runner from South Africa, gender tests were reintroduced in 2009 because of winning at the World Track and Field Championship in Berlin. She was accused of winning the gold medal because she was a man. An IAAF investigation found that Semeny suffered from DSD (differences of sex differentiation), which resulted in high testosterone levels, giving her an advantage over other competitors.[23] In May 2011, the IAAD adopted new regulations regarding the participation of athletes with hyperandrogenism in the women's category. Female athletes could compete if the testosterone concentration in the blood was <10 nmol/l.[24,25] In 2018, the IAAF updated its regulations, lowering the maximum permissible level of natural testosterone to 5 nmol/L. This change in regulations was supported by scientific research, which demonstrated that women with naturally elevated testosterone levels, due to Differences in Sexual Development (DSD), have a significant performance advantage over other female athletes.[27]

Legal aspects of hyperandrogenism in women's sports

Tests to verify the gender of female athletes have been controversial since their introduction in the 1940s, but are still used in various forms. World Athletics rules, which require "suspected" female athletes to undergo medical tests to prove their femininity, underwent a popular and legal reassessment when athletes such as Dutee Chand and Caster Semenya challenged them before the org. Court of Arbitration for Sport- CAS.[1,26]

Already in 2011 the IAAF and in 2012 The International Olympic Committee introduced new rules called Hyperandrogenism Regulations stipulating women with hyperandrogenism. Namely, at that time, the maximum limit of acceptable serum testosterone levels was set for a person considered to be a woman, able to compete in athletics in their respective category.[39] The limit for qualifying testosterone levels was lowered from 10 to 5 nmol/L. A review of published data obtained by liquid chromatography-tandem mass spectrometry analysis showed that the normal range of circulating testosterone in women is 0.1 to 1.8 nmol/l, and the normal range in men is 7.7 to 29.4 nmol/l. In women with mild hyperandrogenism, such as polycystic ovary syndrome (PCOS), circulating testosterone levels do not exceed 4.8 nmol/l.[1,28]

In 2021, The International Olympic Committee (org. International Olympic Committee - IOC) published a position statement outlining a non-binding framework for equity, inclusion and

non-discrimination based on gender identity and gender reassignment, outlining ten important principles.[28] One such principle was “no presumption of advantage,” which was criticized in a later joint position statement by the International Federation of Sports Medicine (org. International Federation of Sports Medicine FIMS) and the European Federation of Sports Medicine Associations (org. European Federation of Sports Medicine Associations - EFSMA).[30]

Medical implications of hyperandrogenism

Information on the impact of hyperandrogenism on women's physical fitness has become more complete over the years, and the pace of medical development allows us to deepen our knowledge of this subject. Hyperandrogenism in women may be associated with a number of disorders such as virilization or hirsutism and may be the cause of disease processes or the result of genetic diseases. However, increased androgen concentration has some beneficial effects on sports performance.

1. PCOS - polycystic ovary syndrome

Polycystic ovary syndrome seems to be a common diagnosis among professional women and Olympic athletes.[22]

It is observed that athletes with PCOS achieve significantly better results in the toleration test (BEEP-TEST) and show higher maximum oxygen uptake (VO2 max) during the treadmill endurance test than other athletes with the same BMI.[31] Moreover, women with PCOS leading a sedentary lifestyle, compared to the control group without PCOS, showed greater muscle strength in the barbell press while lying on a horizontal bench, leg extension exercises and in hand compression strength, regardless of their body structure.[32] These observations suggest that mild hyperandrogenism resulting from PCOS may improve women's physical fitness and performance, which plays a role in their subsequent decision to engage in competitive sports. Reverse causality was not observed, namely practicing sports is not associated with an increased risk of PCOS.[33]

2. FHA - functional hypothalamic amenorrhea

Amenorrhea in female athletes is generally attributed to intense physical training, and in the 1970s the condition was described as "athletic amenorrhoea", i.e. loss of menstruation as a

result of intense physical training.It is caused by inhibition of the hypothalamic-pituitary-gonadal (HPG) axis, which disrupts the pulsatile release of gonadoliberin (GnRH) from the hypothalamus, which stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Reduced secretion of GnRH and, consequently, LH and FSH results in weakened ovarian synthesis of steroid hormones, including estradiol, progesterone and testosterone. HPG is inhibited in many mechanisms, including activation of the hypothalamic-pituitary-adrenal axis during physical exercise, when corticotropin and cortisol together with endorphins released in response to physical activity inhibit the secretion of GnRH by the hypothalamus.[25,34]

Furthermore, athletic amenorrhea is a hypometabolic state, as demonstrated by low concentrations of insulin and insulin-like growth factor I (IGF-I) and high concentrations of growth hormone (GH) and IGF-binding protein-1. IGF-I stimulates the release of GnRH and LH, therefore the decrease in IGF-I activity may partially explain the reduction in LH secretion. Moreover, in athletes who do not menstruate, the level of leptin, the satiety hormone involved in the pulsatile secretion of GnRH, is significantly reduced.[35]

3. 46 XY DSD - Disorders in sex development with karyotype 46,XY (differences of sex differentiation)

In a study conducted on a large group of female athletes, it was found that the incidence of 46 XY DSD is at least 7 per 1000, which is significantly higher compared to the general population. The increased incidence of 46 XY DSD among female athletes suggests that this condition may improve physical performance. However, the physical fitness of athletes with such a rare disease was not compared with the results of the control group because these values are not representative. Only a few case studies have been described in which it was shown that treatment aimed at lowering testosterone levels worsened average results by 5.7% over a 2-year period.[36]

4. Androgen insensitivity syndrome (AIS)

Another common cause of the female phenotype in people with an XY karyotype. In AIS, androgen receptors do not function properly or at all. Therefore, even though testosterone is produced (and may appear high in blood tests), the body cannot respond to it in the usual way; it may have no effect (in complete AIS - the phenotype is completely female-typical) or have some effect (partial AIS - the phenotype varies). Athletes with complete AIS are excluded

from the regulations because they are not “suitable athletes”, but athletes with partial AIS may be covered by the regulations.[37]

Ethical aspects of hyperandrogenism in sports

The rules in modern sport provide opportunities for women to achieve victories, especially in competitions where androgenization influences the athlete's performance. These victories would likely not be possible if gender categories were mixed. Success in sports should result from a combination of talent and dedication to training. These issues are highlighted by the International Olympic Committee and the International Associations of Athletics Federations (IAAF, today known as "World Athletics"), which have adopted specific rules regarding eligibility for women with hyperandrogenism.[38]

In 2011 and 2013, during the IAAF World Championships, it was demonstrated that results obtained in middle-distance running significantly correlated with testosterone levels, which were shown in athletes in the highest percentile compared to those in the lowest, with performance differences approaching nearly 3%.[39]

To address this issue, the IAAF established an upper limit for circulating testosterone levels in female athletes, and over the years, these limits have become even more stringent to ensure that the achieved results are even more comparable to those of athletes without confirmed hyperandrogenism, aiming for a more equitable competition for all participants in this gender category.[40]

From an individual perspective, female athletes with congenital hyperandrogenism may feel a sense of injustice because endogenously elevated testosterone levels are not considered doping. On the other hand, it would also be unfair for a female athlete with normal testosterone levels to compete against an athlete whose testosterone level is several times higher, giving her a significant performance advantage and implying a better final performance outcome during competition. Despite any reservations, these restrictions are an important element in ensuring fair competition in women's sports. It is important for women not to be discouraged from engaging in extreme effort, especially in the constant quest to improve their own performance and overcoming barriers, which is required in professional sports. Furthermore, regulations limiting the levels of certain hormones are intended to eliminate the temptation to use doping, which could be used to level the playing field between athletes.

The World Medical Association has issued an opinion stating that: "Medical treatment for the sole purpose of altering the performance in sport is not permissible".[11] This is beyond dispute. However, if we look at the matter from another perspective, it should be questioned whether World Athletics, by banning the use of performance-enhancing drugs, while at the same time accepting the use of drugs that reduce androgen concentration and thus performance, is not displaying a kind of "double standards". It is known that every treatment carries some form of side effects, so it is important to carefully analyze the benefits and risks for women resulting from the discontinuation of testosterone and the possibility of potential thromboembolic events due to the use of oral contraceptives.[12] Throughout this issue, it is important to remember that sport for these women is primarily a passion but also a lifestyle and a means of living. Therefore, all these athletes, regardless of the regulations in force, should always be treated with due respect and kindness.

Olympic Games- Paris 2024

The 2024 Paris Olympics have once again triggered debates about gender verification and hyperandrogenism, especially with regard to the participation of athletes whose sexual characteristics do not conform to typical definitions of male and female. Of particular note are the cases of Imane Khelif of Algeria and Lin Yu-ting of Taiwan. Both athletes were disqualified from last year's World Championships due to failing gender eligibility tests, but have since been allowed to compete at the Paris Olympics.[41]

Conclusion

In sports, success depends on many aspects, such as genetics, training, nutrition and equipment. Conventionally, sports are divided into gender categories, but there is growing controversy over this division, especially for individuals with personal characteristics that do not fit into the classic gender framework. Testosterone plays a key role in sports performance and gender differences. High testosterone concentrations are usually found in men and can improve physical performance. The control of androgen levels in women is gaining popularity, especially in cases associated with menstrual disorders. Hyperandrogenism in women's sports raises many contradictions and ethical challenges. Sports organizations such as World Athletics (formerly the IAAF) and the International Olympic Committee have introduced rules regarding acceptable testosterone concentrations in women. These decisions were

intended to ensure fair competition, but were met with criticism. Therefore, such organizations are working all the time and issuing more and more statements and regulations to resolve the controversy. The medical and ethical implications of hyperandrogenism are gaining increasing attention in sports medicine. Studies show that certain endocrine disorders can affect women's athletic performance, requiring careful monitoring and appropriate decision-making in the context of both health and equality in sports. Over the years, international sports organizations have implemented various rules and regulations to address these issues. These rules often include thresholds for hormone levels that athletes must meet in order to compete in the women's category. Despite these efforts in Paris 2024, Khelif and Lin's cases emphasize that the current regulations are still not adequate to handle all of the scenarios fairly. They also point to a wider issue: the difficulty of drawing a clear line between natural biological variations and conditions that may give an unfair advantage.

The discussion of hyperandrogenism in women's sports is complex and requires consideration of many aspects, such as medicine, ethics and gender equality.

Author's contribution

Conceptualization AK, KG, PP, KB; methodology AK, KG, PP, KB; software AK, KG, PP, KB; check AK, KG, PP, KB; formal analysis AK, KG, PP, KB; investigation AK, KG, PP, KB; resources AK, KG, PP, KB; data curation AK, KG, PP, KB; writing - rough preparation AK, KG, PP, KB; writing - review and editing AK, KG, PP, KB; visualization AK, KG, PP, KB; supervision AK, KG, PP, KB; project administration AK, KG, PP, KB; receiving funding-not applicable

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