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TRANSGENDER WOMEN IN SPORT: IS IT JUST A MATTER OF SERUM TESTOSTERONE LEVELS?

SOMMARIO: 1. Introduction. 2. Physiological effects of testosterone and physical activity. 3. Effects of gender-affirming hormone therapy on key aspects of the physical performance. 4. Permanent effects of testosterone on male physiology. 5. Final considerations and future perspectives.

Abstract

Elevated serum testosterone levels and their physiological effects in men lead to an advantage in most sports. Based on biological sex, many sports competitions segregate athletes into two categories, male and female, to avoid inequalities. This division does not account for transgender people who experience an incongruence between biological sex and gender identity. The International Olympic Committee (IOC) allows transgender athletes to compete in women's divisions if their serum testosterone levels have been below 10 nmol/L for at least one year. However, this value is significantly higher than that found in cisgender women. Gender-affirming hormone therapy (GAHT) reduces circulating testosterone levels and causes certain changes in testosterone physiology in transgender women resulting in changes in the physical performance of these athletes.

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However, some testosterone-induced changes are irreversible and can affect the athletic ability and performance of transgender women. Therefore, this review aims to evaluate the physiological effects of testosterone and how these are modified by the GAHT, with the ultimate goal of making sport inclusive and equitable for all athletes.

1. *Introduction*

Sports performance is strongly influenced by physiological and metabolic factors, including muscle strength, anthropometric characteristics, cardiorespiratory capacity, and the ability to produce power. Exposure to testosterone in males is known to lead to physiological advantages in strength and endurance over females, resulting in a positive effect on athletic performance¹. For these reasons, sports competitions divide athletes according to their biological sex. However, the segregation of sports into men and women does not consider transgender female athletes and their inclusion in women's sports categories raises several concerns about the fairness of competitions between cisgender and transgender female athletes due to the higher levels of endogenous testosterone in the latter.

Guidelines have been established to allow transgender athletes to compete in the women's categories. The International Olympic Committee (IOC) requires transgender athletes to declare their gender as female for at least four years and to have testosterone levels below 10 nmol/L for at least 12 months prior to competition². In contrast, the International Association of Athletics Federations (IAAF) requires that transgender female athletes must have serum testosterone levels below 5 nmol/L for at least 12 months to compete³. However, these established serum testosterone levels are significantly higher than the average testosterone levels (1.7 nmol/L) generally present in healthy, premenopausal cisgender female athletes⁴, thus, causing contestations by cisgender women athletes.

To make sport inclusive and equitable for all athletes, it is necessary to understand the effects of testosterone on male physiology and investigate how GAHT may change the athletic performance of transgender women.

2. *Physiological effects of testosterone and physical activity*

Androgens are cholesterol-derived hormones synthesized by the gonads and adrenal glands whose main function is to develop and maintain

primary and secondary male characteristics, acting in both reproductive and non-reproductive tissues. The two major bioactive androgens circulating in humans are testosterone and its more potent metabolite, dihydrotestosterone, produced by the conversion of testosterone by the enzyme 5 α -reductase present in various tissues⁵.

Before puberty, serum testosterone levels are essentially similar in boys and girls, except for a brief period during neonatal life in males when higher levels prevail. The onset of male puberty is characterized by increased pituitary secretion of luteinizing hormone, which stimulates the Leydig cells in the testis to produce and secrete testosterone. In girls, testosterone also increases during puberty, peaking around age 25, but does not exceed 2 nmol/L. Circulating testosterone levels in adolescent boys after puberty are 15 times higher than in girls⁴, leading to anatomical and physiological changes that ensure better athletic performance and, in particular, acting on skeletal muscle, bone, and hemoglobin (Hb) levels.

On skeletal muscle, the effects of testosterone and dihydrotestosterone (DHT) are mediated by their binding to the androgen receptor (AR), a cytoplasmic receptor which, after binding to its ligand, migrates to the nucleus where it dimerizes with another AR/ligand complex and together bind to specific DNA sequences. This process results in an increased number and size of muscle fibers, an increased number of muscle satellite cells, an increased number of myonuclei, and an increased motor neuron size. Furthermore, testosterone has been experimentally shown to increase myostatin expression, mitochondrial biogenesis, myoglobin expression, and insulin-like growth factor 1 content⁴. All these effects result in increased muscle growth and, therefore, increased strength and power with improved athletic performance.

Testosterone stimulates the renal secretion of erythropoietin (EPO), the major trophic hormone for hemoglobin synthesis and red blood cell production, and regulates the expression of GATA-1 and GATA-dependent genes which increase sensitivity to EPO and, consequently, increase erythropoiesis. Additionally, testosterone inhibits BMP-Smad signaling in hepatocytes, leading to the suppression of transcription of hepcidin, an iron-regulating protein that results in reduced Hb levels⁶. The increase in the levels of Hb levels in the blood leads to an increase in the transport of oxygen from the lungs to the tissues and consequently an improvement in aerobic performance and endurance.

The effects of androgens on bones are mediated by both direct mechanisms through binding to AR, and indirect mechanisms through the aro-

matization of testosterone to 17β -estradiol to act on estrogen receptors, resulting in both cases in the stimulation of osteoblasts and osteocytes and inhibition of osteoclastic activity⁴. The different serum testosterone levels between the two sexes are responsible for skeletal dimorphism between males and females, leading to differences in bone size, mass, and function. This results in taller stature, increased power in jumping and throwing, and greater resistance to fractures than women.

3. Effects of gender-affirming hormone therapy on key aspects of the physical performance

GAHT in transgender women consists of the administration of estrogen in combination with an antiandrogen drug with the aim of reducing endogenous testosterone levels. In clinical practice, it is difficult to maintain serum testosterone levels in the desired range, such as that of cisgender women, due to the risk of side effects of estrogen hormone therapy. These include an increased risk of venous thromboembolic disease, hypertriglyceridemia, cardiovascular disease, hypertension, osteoporosis, and hyperprolactinemia⁷. Furthermore, circulating testosterone levels correlate negatively with body mass index. Therefore, normal-weight people have higher levels than overweight or obese people who have higher levels of the aromatase enzyme, responsible for converting androgens into estrogens⁸. Therefore, GAHT in transgender women requires careful and periodic monitoring to keep testosterone levels in the range of cisgender women and avoid possible complications.

The changes in hormone levels after GAHT in transgender women result in several physiological changes that can affect physical performance.

In men, the higher serum testosterone levels are responsible for the increase in muscle mass and the deposition of body fat predominantly in the abdominal area⁹. During the first year of GAHT, total body fat increases and total lean mass decreases in transgender women. The increased serum levels of estrogens, by binding to α estrogen receptors (ER), stimulate the proliferation of pre-adipocytes and increase activity of lipoproteins which promote the accumulation of body fat. Furthermore, estrogens act at the hypothalamic level and regulate energy expenditure, body weight, body fat distribution, and leptin sensitivity¹⁰.

Muscle cross-sectional area (CSA) represents the area of the muscle perpendicular to the direction of the fibers and is directly proportional to the maximum force it can generate. In transgender women, after 12

months of GAHT, CSA decreases in the quadriceps femoris and thigh muscles. However, the reduction in muscle mass in transgender women is less than the corresponding increase in transgender men. Hence, after 12 months of therapy, transgender women have a larger quadriceps femoris area than transgender men¹¹. This could be due to the protective effects of estrogen therapy, which exerts an anabolic action on muscle satellite cells via ER α and ER β , promoting muscle maintenance, repair, and regeneration¹².

A decrease in Hb and hematocrit (HCT) levels represent the most prominent and rapid change observed in periodic laboratory monitoring of transgender women. During the first three months of GAHT, serum levels of Hb and HCT reach values in the reference range of the perceived sex¹³. Transgender women with higher HCT levels have relatively higher testosterone levels, confirming the predominant role of testosterone on HCT levels.

Grip strength and muscle mass are considered indicators of muscle strength. In transgender women, after one year of GAHT, a decrease in grip strength is observed due to a decrease in serum testosterone levels. Indeed, testosterone affects the proliferation and differentiation of myoblasts and increases the number of satellite cells, promoting protein synthesis and, therefore, playing an important role in muscle mass and strength. The greatest decrease in grip strength and muscle mass in transgender women after one year of GAHT is observed in the last three months of therapy. In contrast, in transgender men where an increase in these parameters is observed in the first three months of therapy¹⁴, probably because the muscles take longer to decrease the protein content due to the lack of testosterone than to increase in protein content due to testosterone administration. After 12 months of GAHT, grip strength was above average for cisgender women. Thus, values closer to the ranges of cisgender women could be achieved after a longer GAHT duration. Finally, estrogen concentration is not associated with a change in grip strength¹⁵.

4. *Permanent effects of testosterone on male physiology*

Unlike aerobic capacity, muscle mass and strength, which are modifiable by GAHT, other effects of testosterone on male physiology are hardly modifiable due to the effects of testosterone during intrauterine life and the first years of life. These sex differences concern the nervous system, skeletal structure, and cardiorespiratory system.

Differences in the brain between the sexes begin at birth due to prenatal and postnatal testosterone peaks, resulting in specific behaviors, anatomical differences, and different connections between brain networks. Compared to the female brain, the male brain has greater interconnectivity in those regions attributed to perception-action coordination, auditory/visual-spatial awareness and processing, cognitive processes, reasoning, and complex control¹⁶. The sex-specific connectivity of these subnetworks may underlie the ability of males to exhibit consistently higher levels of motor, visual, and proprioceptive spatial abilities. Regarding the connections between brain networks, the effects of hormone treatment in transgender women remain unclear, with studies generally showing no change or the appearance of an intermediate state between males and females. After 12 months of estrogen therapy, there is a decrease in the propensity to anger and aggression, but male biological dominance in spatial skills, visual memory tasks, and perception does not appear to decrease in transgender women¹⁷. More research is needed to definitively answer how and after how long GAHT can make changes in brain structures.

As mentioned earlier, increasing testosterone levels in boys during puberty result in the formation of larger and longer bones as well as increased bone density, providing more joint surface area which allows for the placement of more skeletal muscles, greater resistance to trauma, and increased fulcrum power¹⁷. Studies in transgender women have shown that long-term estrogen therapy does not cause loss of bone mass¹⁸, due to the stimulation of osteoblastic activity through the binding of 17β -estradiol to the ERs present in bone tissue⁴.

The difficulty in modifying female muscle physiology in transgender female athletes probably stems from long exposure to testosterone and male training programs before hormonal treatment. During training, muscle cells recruit myonuclei from satellite cells resulting in increased protein synthesis leading to muscle hypertrophy. Reduced physical activity and decreased exposure to testosterone affect hypertrophy but do not decrease the number of myonuclei. When these cells with increased number of nuclei are again subjected to an overload of exercise, the cells can rapidly increase protein synthesis and hypertrophy¹⁴. This “muscle memory” mechanism is independent of testosterone levels and its suppression does not completely reverse the effects on muscle fiber density or athletic performance.

Exposure to testosterone during early life in males causes sex differences in the cardiorespiratory system. Compared to women, men have a larger lung volume and a larger rib cage, larger heart size, and therefore a

higher stroke volume¹⁹. These anatomical characteristics, associated with the greater levels of Hb induced by testosterone, give men a greater aerobic capacity, which is essential in athletic performance. While Hb levels respond closely to circulating testosterone levels, the other parameters of the cardiorespiratory system are probably not significantly affected by estrogen therapy.

5. Final considerations and future perspectives

The decrease in serum testosterone levels following GAHT affects Hb levels and, to a lesser extent, muscle mass but does not account for anatomical differences that occurred during fetal development and early years of life. Under current IOC regulations, transgender women can compete in women's categories if serum testosterone levels are below 10 nmol/L for at least 12 months before the competition. However, this target level, in addition to being above the normal testosterone ranges of cisgender women, are difficult for transgender women to achieve on an ongoing basis due to the difficulties encountered during the GAHT. These include side effects, body composition, and adherence to therapy. Furthermore, the IOC does not consider the therapy practiced. Indeed, the use of 5 α -reductase inhibitors leads to an increase in serum testosterone levels but decreases its conversion into DHT. Therefore, the biological effects are blocked by these drugs.

The inclusion of transgender women in sporting competitions only considers serum testosterone levels but no other parameters, such as levels of other hormones and androgens (growth hormone, DHT, DHEAS, androstenedione, etc.) and other non-hormonal factors (Y chromosome, AR) that can play a role in the differences between transgender and cisgender women.

Most of the evidence relates to studies involving non-athletic transgender women. The few studies carried out on female athletes report a reduction in athletic performance, but still with results superior to those of cisgender athletes. Transgender women have advantages, especially in power and endurance sports. However, other sports, such as artistic gymnastics, dancing, and horse riding are disadvantageous. Despite their more compact and resilient skeletal structure, larger heart and lung sizes, and different brain structures, transgender women have to contend with lower muscle mass, reduced hemoglobin levels, and lower aggressiveness due to reduced serum testosterone levels.

More studies on how GAHT may affect the performance of transgender athletes are needed in addition to studies evaluating the effect of lower serum testosterone levels over longer periods of time.

At present, and based on the available evidence, a possible solution to make sports competitions fair and inclusive for all athletes would be to divide the various sports categories not according to gender binarism (male/female), but through an algorithm such as that used in the Paralympics²⁰. The proposed algorithm would be tailored to individual sports and would take into consideration several physiological and social factors affecting athletic function (height, weight, hemoglobin levels, VO₂ max, age of transition, testosterone levels, and presence or absence of testes). The proposed algorithm offers the possibility of creating a new and better space for everyone, instead of trying to fit athletes into the current unsuitable binary structure.

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