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ORGANIZATIONAL AND ECONOMIC ASPECTS OF IMPLEMENTING GENDER VERIFICATION METHODS IN HIGH-LEVEL SPORTS

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Abstract: Organizational and economic aspects of implementing gender verification methods in high-level sports belong to controversial issues since they are concerned with the selection of methods for identifying the corresponding genetic characteristics of the human body. From the perspective of geneticists, endocrinologists and other medical workers, their implementation has long been criticized. To determine the prospects of using genetic achievements for gender verification in high-level sports, the authors of the article have considered the role of genetic information in the sports of the highest achievements and possible correction of borderline conditions; analyzed the methods used from the viewpoint of their reliability; assessed the costs of such genetic studies and examined their organization in the context of determining a competent subject and standardizing techniques and procedures. In contrast to the previous practice of gender verification, the current studies focus on changing testosterone levels and utilize different methods, some of which determine the level of total testosterone and the others define the level of free testosterone. Based on expert estimates, the authors have concluded that the method of tandem mass spectrometry is the most

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effective. Since the International Association of Athletics Federations allows the medical treatment of testosterone levels as a condition for admission to international competitions, the ongoing studies cannot be limited to identifying its quantitative indicators. An additional objective is to reveal the causes of hyperandrogenism, i.e. to expand the list of the methods used whose application should be unified with due regard to modern medical advances. From the economic viewpoint, measuring testosterone levels is not expensive but the costs will inevitably increase 10-15 times for identifying the causes of hormonal imbalances.

Keywords: gender verification, high-level sports, hyperandrogenism, tandem mass spectrometry, total testosterone, free testosterone.

1. Introduction

The gender verification of female athletes in international sports is among the most debatable issues that has legal, ethical and medical aspects. Due to the achievements of modern science, the latter becomes especially acute and raises the question of selecting proper methods for identifying the corresponding genetic characteristics of the human body. According to geneticists, endocrinologists and other medical workers, the implementation of such methods has long been criticized. The problem is not only the reliability of genetic tests but also the neglect of intersexuality, which is believed to entail discrimination against women based on laboratory results. The supporters of such tests provide the following argument: men hold more world records in different sports than women (by 9-18%), which stipulates the tradition of holding separate competitions and ensure relatively equal opportunities for both genders. In this regard, female hyperandrogenism is considered as a threat to fair competition in sports since it is associated with obtaining unreasonable physical advantages. At the same time, ethical aspects of this issue are somewhat blown out of proportion since athletes are already classified according to other biological indicators, i.e. their weight that is crucial in some sports (Stanczyk, F.Z., 2006). We cannot deny that gender verification is more complex and controversial than classifying athletes by weight based on a calibrated scale.

Consequently, the article aims at determining the prospects of using the results of genetic studies for the purposes of gender verification in high-level sports. The achievement of this task will contribute to the following improvements: determining the importance of genetic information for the purposes of gender verification in high-level sports and possible correction of borderline conditions; establishing acceptable genetic research methods and evaluating their effectiveness; estimating the costs of genetic tests.

2. Literature Review

Experts from different countries studied the implementation of gender verification methods in the sports of the highest achievements. For example, A. de la Chapelle examined the use and misuse of sex chromatin screening for the gender identification of female athletes. B.D. Dickinson, M. Genel, C.B. Robinowitz, P.L. Turner and G.L. Woods considered the issue of gender verification of female Olympic athletes. J. Fiet, F. Giton, I. Fidaa, A. Valleix, H. Galons and J.P. Raynaud studied the development of a highly sensitive and specific new testosterone time-resolved fluorimmunoassay in human serum. N.M. Malysheva investigated free and biologically active forms of testosterone as the most appropriate markers for assessing one's androgen status. Other scientists also studied gender verification methods in sports.

3. Methods

The above-mentioned objectives and tasks can be solved only by assessing the existing research methods. We give priority to molecular methods, including genetic screening, and complex interdisciplinary approaches, i.e. an endocrinological, genetic and gynecological examination. In addition, we considered the prospects of their application to address the issue of admission athletes to competitions.

The methodological basis of the study was laid by dialectical, teleological, logical, formal-legal and system-structural methods.

Throughout the study, we implemented the universal dialectical method to consider the use of genetic research for the purposes of gender verification in its connection with the current development of science and technology. In its radical form, the idea

was realized through the teleological method interpreting and studying topical issues through the prism of goal setting, considering objectives and development strategies and ensuring the optimal legal regulation of relations associated with genomic research and the use of its results in high-level sports.

The logical method was used to correlate the variety of gender verification approaches with the expediency of genetic research in conformity with the current international practice. In addition, we referred to the formal-legal method to consider the prospects of their regulation as a means of improving the legal support of high-level sports.

The system-structural method allowed us to consider the relationship between disorders of sex development, their identification through different methods and the results of competitions, whose presence or absence is crucial for determining the feasibility of legal regulation of public relations in this area.

4. Results

Gender verification as a condition for holding sports competitions poses a difficult challenge for sports science and medicine, as well as sports officials of various ranks. In the 1930s, they started to question the ability of female athletes who were genetically closer to male physiological parameters to participate in women's competitions since they gained an unfair competitive advantage based on the larger size of androgen-enhanced skeletal and muscle mass, strength and speed. Since the 1960s, the International Olympic Committee and the International Association of Athletics Federations have been verifying the gender of athletes (initially by a physical and/or direct gynecological examination).

The development of genetics provided new tools to solve this problem, which let the International Olympic Committee officially sanction the gender testing of athletes before international competitions in 1968. Experts used buccal smear to identify the Barr body (X chromatin) that forms in the cell nucleus through the inactivation of the female X chromosome and allows verifying one's gender (Albert de la Chapelle, 1986). Given the direct relationship between chromosomal and anatomical sex in most people, this method was quite effective. Over 20, 13 women have been banned from sports

competitions according to the test results, although the identified genetic differences were not confirmed at the phenotypic level as special physical advantages in sports.

Later it was found that several genetic disorders that hinder normal sexual development do not provide any potential benefits in sports. At the same time, this method did identify athletes with congenital adrenal hyperplasia that can provide competitive advantages, i.e. it conditions high levels of adrenaline, norepinephrine, cortisone and androgens in blood.

Therefore, a conviction was formed that the Barr body was analyzed to unfairly suspend some athlete from competitions rather than to discover those who deliberately deceived the sports committee.

Since 1991, a polymerase chain reaction analysis of the SRY gene locus on Y chromosome has been used for gender verification that was deemed necessary to trace the fetal gonad differentiates into testicles and determine male phenotypic development. The universality of such diagnostics is conditioned by the following advantages: any biological materials can be accepted for testing and it shortens the time to get a diagnosis (automated polymerase chain reaction amplification provides results in 4-5 hours).

However, this method was not irreproachable as the above-mentioned gene did not explain all cases of abnormal sex development. At the very least, many true hermaphrodites do not have the SRY gene and only 15% of women have the Y chromosome due to this gene. Finally, it was proved that the SRY gene could be located on the X chromosome as a result of translocations during meiosis. Thus, the transition to PCR-based methods replaced one diagnostic genetic test with another but did not solve the initial problem since it called into question the participation of women with androgen insensitivity syndrome in sports competitions (Dickinson, B.D., 2011).

Experts emphasize that disorders of sexual development include any body condition when the genitals are atypical of the chromosome and gonads. Thus, they propose to highlight post-puberty transgender transitioning, whose consequences should be evaluated in each specific case (Martínez-Patiño, M.J., 2010). This leads to a logical conclusion that this method is imperfect

because it does not allow one to identify men and women with such a disease as congenital adrenal hyperplasia that can provide certain competitive advantages, i.e. it causes high levels of catecholamines (adrenaline and noradrenaline), glucocorticoids (cortisone and its derivatives) and androgens in blood (Rupert, L., 2002).

Currently, gender verification is associated with the identification of hyperandrogenism symptoms. The priority method of their assessment is the measurement of testosterone, which is supposedly produced as a precursor of androgens: androstenedione from thecal cells and dehydroepiandrosterone from the adrenal cortex that transforms into testosterone, especially in adipose tissue. Testosterone production rates, including direct ovarian secretion and peripheral metabolism by both the ovaries and adrenal glands, maintain circulating testosterone concentrations. On the contrary, metabolic clearance rate defined as the volume of blood purified irreversibly per unit time is the main process that reduces circulating androgen concentrations. We should consider both general testosterone and free testosterone, which leads to the formation of various research approaches. Although clinical implications of hyperandrogenism are well known and their types are extremely diverse and unspecific (Nikonova, L.V., Tishkovskii, S.V., 2018).

The situation is aggravated by many factors affecting testosterone concentrations in human body, from the person's age and physiological state to the course of their disease and the time of day at which the sample was taken. As a result, the measurement of testosterone is more complicated than the analysis of other hormones. In addition, some methods can detect other steroids with a similar structure. According to specialists, the starting point should be the assessment of total testosterone that can be conducted through immunoassay and, if needed, mass spectrometry. If the upper limit of testosterone levels is exceeded twice, it is recommended to conduct a dehydroepiandrosterone sulphate analysis. This hormone is an inactive form of dehydroepiandrosterone synthesized by the adrenal glands that plays an important role in the conversion of estrogen into testosterone. Moreover, the level of dehydroepiandrosterone sulphate above 600 mg/dl indicates androgen-secreting adrenal adenoma. In case this level complies with the norm, it

can imply either ovarian hyperthecosis or androgen-secreting ovarian tumors. In rare cases, high testosterone levels are associated with a marked increase in globulins (Pugeat, M., Dechaud, H., 2010).

5. Discussion

In most cases, clinical studies focus on measuring total testosterone as the starting point for analyzing hyperandrogenism symptoms. Its low concentrations and structural similarities to circulating androgens require the use of accurate and quite sensitive research methods. Their list includes immunoassay based on the innate ability of antibodies to bind small molecules. The accuracy of studies depends on the quality of antibodies capturing testosterone and the method used to detect the antibody-bound testosterone. In addition, we should highlight a labeled probe and the system used to immobilize immune complexes.

This method is easy to use because it requires a small volume of samples and a short analysis time. Therefore it can be utilized for measuring testosterone in clinical and pharmacological conditions (Fiet, J., Giton, F., 2004). It is suitable for automated platforms that reduce not only human errors but also the cost of such an analysis. In addition, it has certain advantages over radioimmunoassay that requires the use of antibodies labeled with a radionuclide to determine the radioactivity of the resulting immune complex in conformity with beta or gamma radiation. In this regard, chemiluminescence and fluorescence are currently the main methods for detecting testosterone, as evidenced by modern scientific proposals for such clinical studies.

At the same time, this method has its drawbacks. In particular, specialists noted its lack of specificity that depends on the quality of the antibodies produced to testosterone. All non-isotopic methods, except for VitrosECi, exaggerate the determined level of total testosterone compared to the standard radioimmunoassay method (Malysheva, N.M., 2009).

In this case, unexpected biotin interference can cause both overestimated and underestimated test results depending on the chosen research method. The latter bears a bigger risk since biotin therapy comprises analytical intervention in many immunoassays

through streptavidin-biotin capturing methods, which can wrongly indicate different endocrine disorders. This circumstance is especially significant for gender verification in sports aimed at detecting high testosterone levels in the blood of athletes since biotin is a water-soluble vitamin (B7) belonging to the group of low-molecular metabolically active organosilicon compounds used in polyvitaminic complexes and sports nutrition. It is part of enzymes regulating protein and fat metabolism, participates in the synthesis of glucokinase and is a coenzyme combining various enzymes, including transcarboxylase.

Excess biotin in blood sample interferes with traces of a biotinylated hormone or specific biotinylated antibody, depending on the chosen system, and connects with streptavidin-coated microparticles, which affects the signal system and leads to overestimated or underestimated test results. Under these conditions, false testosterone data can be obtained. Specialists see the solution to this problem in the adsorption of biotin in magnetic streptavidin-coated microparticles (Piketty, M.P., Prie, D., 2017).

Testosterone levels can also be measured through mass spectrometry that has recently gained particular importance. It is the only method to detect and analyze the superheavy molecules of organic substances (Konenkov, N.V., Makhmudov, M.N., 2007). The development of liquid chromatography along with atmospheric-pressure chemical ionization and electrospray ionization enables to relate liquid chromatography and mass spectrometry, which marked significant scientific progress since the liquid eluent phase makes derivatization unnecessary for measuring most steroids, including testosterone. The achievement of complex objectives for the purposes of steroid analysis is possible due to the improvement of sample preparation technologies, liquid chromatography column technologies and mass spectrometry. The most popular sample processing strategies include protein precipitation, solid phase extraction and liquid-liquid extraction (Keevil, B.G., 2013).

Despite its high effectiveness, this method also has some drawbacks, primarily related to technical aspects of the study. In particular, experts highlight the following risks: high-level variation in the efficiency of atmospheric-pressure chemical ionization, mandatory

standardization, "isotope effects" of internal standards, differential impact of matrix effects on the analyte and internal standard of isotopes, interference in metabolic transformation (Pugeat, M., Plotton, I., 2018). In addition, the human factor remains a source of possible errors in conducting research and interpreting its results.

The study object is free testosterone but the issue of its role is still open. At the same time, there is convincing evidence that the concentration of free hormones reflects a clinical situation more accurately than the total level of hormones in one's plasma.

Accordingly, the key point is the development of research methods, as well as accurate and highly sensitive ways to measure testosterone concentrations. We should keep in mind that the complex of "free testosterone – total testosterone" seems to be a thermodynamic system where the free fraction depends not only on the concentration of total testosterone but also on the characteristics of globulin that binds sex hormones, the association and dissociation of this complex determined by temperature and pH (Goncharov, N.P., Katsiya, G.V., 2008).

For a long time, the main method of separating protein from free testosterone before its measurement had been equilibrium dialysis based on analyzing the testosterone fraction associated with sex hormone-binding globulin and albumin. This method allows measuring the percentage of free testosterone, which is usually 2-3% of its total amount circulating in blood.

This study is often considered the simplest method for determining free testosterone but its results can inadequately reflect the true state of things, as evidenced by significant discrepancies in the data on free testosterone concentrations obtained by different and not always standardized methods (Ivashkina, S.G., 2007). Their reliability is questioned because of matrix effects that demand higher standards of preparing test samples, in particular, the deposition of a fraction not associated with sex hormone-binding globulin with ammonium sulfate.

Some time ago, centrifugal ultrafiltration-dialysis was recognized as an alternative method but it was found that the temperature of ultrafiltration (37°C) influenced the concentration of this hormone in ultrafiltrate (Chen, Y., Yazdanpanah, M., 2010).

Everyday clinical practice can also utilize methods for estimating the concentration of free testosterone that are based on the absence of inter-individual variability in the binding affinity of sex hormone-binding globulin, as well as the constancy of albumin concentrations and the affinity of albumin-binding testosterone (Heinrich-Balard, L., 2015). From the theoretical perspective, free thyroxine index corresponds to free testosterone at the low molar ratio of total testosterone to sex hormone-binding globulin. In general, the calculated values of free testosterone correlate with the results of equilibrium dialysis. This method is imperfect since it aims at obtaining reliable information about the true concentration of total testosterone but it can be challenging due to the possible polymorphism of sex hormone-binding globulin under the influence of drugs and endocrine disorders.

The study of hyperandrogenism symptoms can become a separate area of clinical research in the gender verification of athletes since the International Association of Athletics Federations connects the possibility of participating in international competitions with adjusting the level of testosterone in blood, which cannot be done improperly at risk of harm.

The adrenal cortex producing dehydroepiandrosterone that affects androgen receptors is a source of many problems. A significant portion of dehydroepiandrosterone sulfotransferase is sulfated by the action of dehydroepiandrosterone sulfotransferase.

Dehydroepiandrosterone sulfotransferase is a precursor to active androgens and can be used by ovarian follicles to synthesize testosterone and even converts to dihydrotestosterone in peripheral tissues after conversion to androstenedione, without the mandatory formation of testosterone.

The normal process of hormone production might be impaired due to adrenal hyperandrogenism. In most cases, it is congenital but it can be caused by neoplasms associated with an increase in the number of cells that produce androgens, which inevitably leads to an increase in the production of hormones. To determine the connection between hyperandrogenism and disorders of the adrenal cortex, dehydroepiandrosterone is examined.

In some cases, experts stress the relationship between congenital adrenal

hyperplasia and polycystic ovary syndrome. However, modern studies have concluded that ovarian androgens, especially testosterone, have only a limited effect on adrenocortical functions (Goodarzi, M.O., Carmina, E., 2015).

For the needs of differential diagnosis, samples for adrenocorticotropic hormone are used as a confirmatory test. They are the most important stimulator of the adrenal cortex that enables to identify almost 100% of patients with genetically proven non-classical congenital adrenal hyperplasia, regardless of the type of mutation. In the near future, the development of sequencing platforms should simplify the study of the CYP21A2 gene.

Scientists have many questions about polycystic ovary syndrome that is characterized by adverse hormonal disorders causing metabolic and gynecological problems in women. Nowadays it remains an endocrine mystery due to the fact that genetic factors work in line with environmental signals contributing to its pathogenesis. The studies of genes involved in steroidogenesis that presumably control susceptibility to polycystic ovary syndrome and its phenotypic heterogeneity have not been convincing due to various diagnostic criteria, the likely contribution of several genes to these processes, differences in lifestyle, environmental factors and the size of the samples under investigation (Dadachanji, R., Shaikh, N., 2018).

While assessing the prospects of using the above-mentioned methods for gender verification in high-level sports, we should standardize approaches to their implementation to ensure reliable results. At first glance, it seems effective to use automated methods for determining steroid hormones. Their advantages include is reduced risks of unauthorized intervention and low costs of testing. However, they cannot provide satisfactory results for several reasons. Thus, immunoassay without preliminary extraction or purification of the material, as well as the insufficient accuracy of the devices used, cause significant deviations from the real indicators. The interpretation of the results obtained is no less difficult since it requires the knowledge of normal concentrations and deviations in the female population who do not have diseases that provoke hyperandrogenism.

One of the problems requiring solution is the definition of entities authorized to conduct such studies. Two possible solutions are as follows: to establish a unified center operating under the auspices of the international sports association interested in assessing hyperandrogenism symptoms, which is currently the International Association of Athletics Federations, or to transfer appropriate authorities to national federations. In both cases, it is necessary to develop a standardized decision-making scheme for assessing the level of testosterone and identifying the initial cause of excess androgen excess, as well as agreeing on the methods used for achieving this goal. A group of French scientists proposed one of such methods.

In particular, they noted that testosterone twice the upper limit of normal suggests an androgen-secreting tumor. In addition, dexamethasone samples can be used to identify ovarian androgen-secreting tumors and hypertosis.

If testosterone is slightly above the upper limit, the most likely diagnosis is polycystic ovary syndrome. To exclude Cushing's disease, a non-classical type of 21-hydroxylase deficiency should be screened depending on clinical conditions. The study subject might be gonadamandrostenedione, whose increased level indicates diseases causing hyperandrogenism (Pugeat, M., Plotton, I., 2018).

5. Conclusion

In contrast to the previous practice of gender verification, the current studies focus on changing testosterone levels and utilize different methods, some of which determine the level of total testosterone and the others define the level of free testosterone. Based on expert estimates, we have concluded that the method of tandem mass spectrometry is the most effective. Since the International Association of Athletics Federations allows the medical treatment of testosterone levels as a condition for admission to international competitions, the ongoing studies cannot be limited to identifying its quantitative indicators. An additional objective is to reveal the causes of hyperandrogenism, i.e. to expand the list of the methods used whose application should be unified with due regard to modern medical advances.

From the economic viewpoint, modern tests measuring the level of total testosterone are not expensive (which is proved by a wide range of private

medical centers) but the costs will inevitably increase 10-15 times for identifying the causes of hormonal imbalances. The key point is to harmonize the methods used and standardize them for all national sports federations.

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