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Review

Androgen deficiency in men with chronic obstructive pulmonary disease

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Abstract: Hypogonadism is a clinical condition comprising symptoms and laboratory evidence of testosterone deficiency and low androgen receptor sensitivity. The importance of hypogonadism in clinical practice is often underestimated. Androgen deficiency habitually occurs in various conditions causing abnormal functioning of many organs and systems, as well as impairing the quality of life in patients. Androgen deficiency often occurs with various somatic diseases. Chronic obstructive pulmonary disease (COPD) is one of the most important medical and social problems of modern medicine, in which severe systemic (including hormonal) disorders occur. This review presents data on androgen deficiency in men with COPD and its potential impact on the patients. We have analyzed literary sources in the eLIBRARY and PubMed databases.

Keywords: chronic obstructive pulmonary disease, hypogonadism, androgen deficiency.

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Introduction

In the modern world, chronic obstructive pulmonary disease (COPD) is a noteworthy social and economic problem. Its prevalence among the population is about 12%, and the incidence progressively increases. In most countries, COPD is recognized among major causes of death [1]. As the severity of COPD increases, the likelihood of achieving control with basic inhalation therapy declines. Most patients with severe bronchial obstruction have an uncontrolled, progressive course of the disease, whereas the control is achieved in about quarter of patients [2].

It is well known that with a long course of the disease, along with pronounced pathological remodeling of the airways and lungs, the following systemic changes develop: body weight deficiency, sarcopenia (hypotrophy of skeletal muscles), osteoporosis, cardiovascular disorders, depression, chronic kidney disease, the risk of developing diabetes mellitus and metabolic syndrome. All of these lead to a rapid and substantial reduction in the patient quality of life. Thus, with the progression of the disease, changes in other organs and systems become of great clinical importance rather than solely the pathology of the bronchopulmonary system [1, 3, 4, 5]. In this regard, the issues of studying the mechanisms of forming systemic manifestations, a more accurate assessment of the disease course, and methods for correcting developing pathological changes in patients with COPD are still relevant.

The approach to studying COPD, as an ailment with severe systemic disorders, has revealed the relationship between changes in the respiratory system and significant disorders of the endocrine system. It was established that, in patients with COPD, the blood levels of testosterone, dehydroepiandrosterone (DHEA), thyroid hormones, thyroid stimulating hormone (TSH) and leptin undergo changes [6,7]. Of great interest, in our opinion, is the study of changes in the functioning of the hypothalamic-pituitary-gonadal axis, which can play an important role in the development of other systemic manifestations in patients with COPD. Our review analyzes and summarizes a wide range of studies dedicated to the problems of diagnosis, mechanisms of development and clinical significance of androgen deficiency in COPD patients.

Androgen deficiency

A number of interrelated hormones are involved in the functioning of the hypothalamic-pituitary-gonadal axis. Of these, first of all, we should mention testosterone, over 95% of which is synthesized by Leydig cells. In blood serum free testosterone, that is, not bound to proteins (approximately 2% of its total amount), penetrates cells causing metabolic effects. The remaining testosterone (98%) is bound to sex steroid-binding globulin (SSBG) and albumins. Some of the testosterone bound to proteins can be released and easily penetrate the cells; and, therefore, the amount of bioactive testosterone exceeds the level of free testosterone. Anabolic properties, along with testosterone, are also attributed to dihydrotestosterone, dehydroepiandrosterone, androstenedione. The synthesis of androgens by Leydig cells is stimulated by luteinizing hormone (LH), produced by the anterior pituitary gland, the activity of which is regulated by gonadotropin-releasing hormone (GnRH) of the hypothalamus [8, 9, 10].

Low serum testosterone levels in men, as well as reduced sensitivity of receptors to androgens, in combination with the

development of characteristic symptoms and/or features are called hypogonadism [11]. Thus, the term *hypogonadism* describes the clinical and biochemical syndrome associated with low testosterone levels or reduced sensitivity of the receptor apparatus to androgens. It could have a negative impact on the function of many organs and systems, reducing the quality of life and life prognosis [11, 12].

Sensu the level of disturbances in the hypothalamic-pituitary-gonadal axis functioning, primary and secondary hypogonadism are distinguished. The former presumes a decrease in the testosterone concentration as a result of direct damage to the testicular tissue, with overproduction of LH and follicle-stimulating hormone (FSH). The causes of its development are Klinefelter syndrome, cryptorchidism, some types of antitumor chemotherapy, testicular trauma and irradiation, infection-caused orchitis, HIV infection, and myotonic dystrophy [13]. In secondary hypogonadism, a reduction of testosterone levels is associated with a decrease in LH production. Secondary hypogonadism can be observed in hyperprolactinemia, obesity, iron overload syndrome; in the course of taking opioid drugs and glucocorticosteroids (GCS); androgen deprivation; anabolic-androgenic steroid withdrawal syndrome; hypogonadotropic hypogonadism; hypothalamus and pituitary gland disorders; head trauma; after surgery or irradiation of the pituitary gland. The simultaneous development of primary and secondary hypogonadism is also possible, in which case the testosterone concentration declines, and the change in LH and FSH levels varies depending on the prevalence of the first or second form of the hypogonadism [13, 14].

There are also organic and functional types of hypogonadism. Organic type causes a persistent dysfunction of the testicles, hypothalamus, or pituitary gland due to congenital or acquired disorders. Functional hypogonadism is manifested by a reversible decrease in the content of testosterone, LH and FSH as a result of various potentially eliminable ailments [13, 15].

From the age of 30-35 years old, the amount of total testosterone begins declining by about 0.8-2% annually, whereas the content of free testosterone and testosterone bound with globulin diminishes by 2% per year. At the same time, the SSBG concentration grows by about 1.6% per annum [8,16]. The age-related decrease in testosterone concentration in men is associated with degenerative changes in the testes, their hypoxia as a result of microcirculatory insufficiency, as well as with a reduction in the number of Leydig cells. At the same time, with age, the disorder of the circadian rhythm of LH synthesis and, consequently, of testosterone, occurs [8, 17]. According to a number of studies, the prevalence of age-related androgen deficiency among men in the age group of 40-49 years old is 0.1% –16.5%; in the age group of 50-59 years old, it is 0.6% – 31.8%; and, for the age group of 60-69 years old, tan incidence of androgen deficiency is 3.2% – 30.1% [18].

Clinical manifestations of androgen deficiency are reduced libido, erectile dysfunction, depression, fatigue, irritability, sleep disorders; decreased muscle mass and muscle strength; reduced body hair; diminished bone mineral density; osteoporosis; visceral obesity, and gynecomastia. However, the severity of these symptoms does not always correlate with the degree of decrease in biochemical parameters [17, 19]. In clinical screening, since the symptoms arising from testosterone reduction are varied and nonspecific, one should focus on a decrease in libido and sexual activity, decline in the number of morning erections and adequate erections [11]. It is important to take into account the possibility of developing these disorders due to somatic diseases (such as diabetes mellitus, vasculopathy, etc.), or due to taking medications (spironolactone, beta-blockers) [11].

A reduction in the level of total serum testosterone under 12.1 nmol/l is considered the deficiency [17]. When the concentration of total testosterone is from 8 to 12 nmol/l, it is recommended to investigate the content of both SSBG and free testosterone [11, 19]. To detect subclinical hypogonadism, determine the primary and secondary forms of hypogonadism, it is recommended to assess the concentration of LH in the blood serum [12, 19]. Blood sampling for the analysis of total testosterone and LH is performed on an empty stomach twice (on different days), in the mornings (from 7 to 11 am); this is due to fluctuations in testosterone levels throughout the day and its reduced levels after meals [11, 12].

Currently, there is an understanding of the relationship between the reduction in testosterone levels and diseases of various organs and systems [14]. The development of hypogonadism can be caused by both the disease itself and the prescribed therapy. Thus, the prevalence of hypogonadism among middle-aged men with decompensated diabetes mellitus and obesity may exceed 50% [19]. It should be noted that a number of researchers consider reversible hypogonadism as an adaptive response of the body that develops in acute severe somatic pathology. A decrease in testosterone levels determines a decline in physical activity, energy expenditure, and reproductive behavior, thus protecting the patient's body from behavioral actions that could increase the risk of cardiovascular diseases [20]. Hence, in clinical practice, the question may arise, "What happens first: a disease that causes hypogonadism, which aggravates the course of that disease – or these two problems occur simultaneously; and, therefore, the development of hypogonadism is not initially associated with somatic pathology?". It is difficult to answer this question unequivocally and, obviously, it is necessary to analyze all the factors in each specific case.

Hypogonadism in COPD patients

Currently, a decrease in testosterone levels has been proven in coronary artery disease, arterial hypertension, stroke and atherosclerotic lesions of peripheral blood vessels, chronic kidney disease, non-alcoholic fatty liver disease, chronic viral hepatitis, liver cirrhosis, and HIV infection [14]. A relationship has been demonstrated between a decrease in testosterone concentration and mortality from cardiovascular diseases [21]. Along with this finding, a high prevalence of androgen deficiency has been described in patients with respiratory pathologies (COPD, sarcoidosis, sleep apnea) [14].

In the population of patients with COPD, a fairly high prevalence of androgen deficiency was revealed, which, according to various authors, ranges from 22 to 69% [22]. According to research by S.A. Mousavi, et al, secondary hypogonadism was detected in 58.6% of 140 examined men with COPD at the age of 67.4±10.1 years [23]. Similar data were presented in the publication by M. van Vliet, et al: in 58% of the examined patients with COPD, a decrease in testosterone concentration was detected [24]. R. Rubinsztajn, et al. revealed hypogonadism in 33% of patients with severe course of the disease [25]. The most large-scale study to examine the prevalence of hypogonadism in the general population versus the patients with COPD was conducted

by T. Mulligan, et al. The study included 2,162 patients, among them 220 men with established bronchial obstruction, of which 43.5% had androgen deficiency [26].

Currently, the questions, whether such hormonal changes are clinically significant and what are the consequences of developing a deficiency of sex steroids in patients with COPD, remain controversial. A number of authors consider hypogonadism in patients with COPD as one of the major causes of developing such systemic manifestations of the disease, as weight loss, muscle weakness, and a reduction in bone mineral density [6, 27].

In the emphysematous phenotype of COPD, the progression of the disease, along with a deterioration in the ventilation function of the lungs, is characterized by the body weight loss and decrease in muscle mass, which are predictors of a poor prognosis [28]. The pathogenetic mechanisms underlying the development of this process are associated with both systemic inflammatory effects and changes in the function of the endocrine system, including the development of androgen deficiency [3, 6, 14]. This justifies the search for the relationship between the presence and severity of changes in the level of sex hormones and the development of systemic manifestations in COPD patients.

The study of the energy balance in patients with stage III-IV COPD (GOLD) showed that the processes of catabolism prevail over the processes of anabolism. In particular, this was described in the publication by R. Debigaré, et al. [29]. The authors evaluated the indicators characterizing catabolic (blood cortisol, IL-6) and anabolic processes. They examined 45 men with COPD, whose average age was 65 years old, and the forced expiratory volume in the first second (FEV_1) was 40%. The study revealed a decrease in the levels of testosterone, dehydroepiandrosterone (DHEA), insulin-like growth factor responsible for anabolic processes in the body, as well as a higher percentage of androgen deficiency development compared with the control group of healthy men of comparable age.

In the study by Van Vliet, et al. [24], which included 78 men with COPD with an average FEV_1 rate of 44% and average age of 66 years old, and 21 healthy men (control group) of an average age of 63 years and FEV1 rate of 108%, a higher prevalence of androgen deficiency was found as well in patients with COPD. Along with this, during the study, exercise tolerance was examined (a test for a six-minute walk was used), along with the strength of the quadriceps femoris muscle, and the levels of FSH and LH were determined. It was shown that patients with COPD, as compared with healthy individuals, had a higher concentration of FSH and LH, while the content of total and free testosterone was reduced even in conditions of normal blood gas parameters and absence of systemic GCS therapy. An inverse relationship was established between body mass index and the levels of total testosterone, free testosterone and SSBG. A direct relationship was discovered between the distance covered in the 6-minute walk test, the strength of the quadriceps muscle, and the concentration of circulating testosterone. The authors showed the dependence of hormonal disorders on the smoking experience: the higher the value of the smoking index, the lower was the level of free testosterone in blood. It was noted that at lower levels of total testosterone, free testosterone and SSBG, the content of C-reactive protein was significantly higher, which cud imply a relationship between changes in hormonal status and the severity of systemic inflammation [24].

As mentioned above, androgenic status may change when taking certain medications. Therefore, it is important to contemplate the issue of the effect of taking systemic glucocorticosteroids (SGCS) on the change in hormonal status in patients with COPD. E.g., the study by Kamischke, et al. [30] demonstrated that in men over 60 years of age with stage III COPD (GOLD) who did not take SGS, the concentration of free testosterone in serum was reduced in 45% of cases, while in the group of patients taking SGS, the concentration of free testosterone was reduced in 100% of cases, and the degree of reduction was in a direct proportion to the SGCS dose.

Reduction in the concentrations of a total and free testosterone, SSBG, and DHEA in men over 50 years of age was observed by Karakou, et al. [31] as associated with a decrease in FEV_1 below 50% of the norm. Also, in this group of patients, a significant increase in the LH level and the absence of changes in the FSH level were found, compared with healthy individuals in the control group.

Testosterone content in COPD patients goes down to a greater extent with more severe course of the disease. The presence of a relationship between changes in the concentration of sex hormones in blood and the severity of bronchial obstruction in patients COPD was demonstrated in the study by S.A. Mousavi, et al. [23]. The authors studied the prevalence of secondary hypogonadism among patients with COPD and revealed a relationship between the blood level of a total testosterone and FEV_1 indicator (direct correlation), which indicated that the degree of decrease in the concentration of sex hormones correlated with the stage of COPD. A study of the LH and prolactin levels in blood showed that their content remained within the normal ranges in all patients with COPD; however, LH concentration was the lowest in patients with stage IV (GOLD).

Changes in androgenic status in men with COPD could also be detected at an earlier COPD stage, which was demonstrated in the study by V.I. Podzolkov, et al. The study included 12 male patients with a moderate COPD (mean age 50 years old; pack/year rate 33.0; FEV_1 81.0%, FEV_1/FVC [forced vital capacity] 68.0%), and 16 men with a moderate COPD (average age 54.5 years; packs/years rate 38.0; FEV_1 61.5%, FEV_1/FVC 67.5). It was established that in the group of patients with a moderate COPD, the levels of a total and free testosterone in their blood were below normal values, while in patients with a moderate severity, they were within the normal range. It was also shown that the lowest dehydroepiandrosterone sulfate (DHEAS) level was observed in patients with a moderate COPD (smokers who did not cough, patients with a moderate COPD and subjects with a chronic bronchitis associated with smoking), compared with the comparison groups. There were no changes in serum concentrations of FSH, LH and progesterone. When analyzing the obtained data, a positive correlation was established between FEV_1 and the concentration of a total testosterone, as well as between FEV_1 and the concentration of a free testosterone and DHEAS. Besides, in the group of patients with COPD stage II (sensu GOLD), an inverse correlation was discovered between the number of packs per year and the levels of free and total testosterone in the blood serum [32].

With exacerbation of COPD, even more pronounced reduction in the level of DHEAS in the blood serum is observed, which was shown in the study of F. Karadag, et al [33].

According to published sources, in patients with COPD, secondary hypogonadism with a reduced level of gonadotropic hormones is detected most often [22, 23, 34, 35]. It is believed that the progression of COPD leads to hypothalamic-pituitary dysfunction, which entails a decrease in the level of a total and free testosterone [25, 34]. At the same time, there is an evidence of an increase in the levels of LH and FSH with a decrease in the levels of androgens in patients with COPD, which was discovered in the study by Van Vliet, et al. [24].

It should be noted that the question of the clinical significance of hormonal changes in patients with COPD remains controversial. For example, the study performed by F. Laghi, et al. [36] did not reveal a greater prevalence of androgen deficiency in patients with COPD and its effect on quality of life, respiratory muscle dysfunction, osteoporosis and exercise tolerance, compared with healthy individuals.

However, back in the 1980s, on the basis of autopsy data in subjects with chronic obstructive bronchitis, a decrease in Leydig cells and testicular size was described, which, according to the authors of the study, may have been a direct consequence of exposure to hypoxia [37].

The lack of a certain well-established concept on the development of hormonal disorders in COPD patients can be explained by relatively small number of studies in this field. The conflicting data may be due to different age composition of participants, different criteria used to define hypogonadism, and different ethnic composition of subjects. Nevertheless, the available results of conducted studies allow considering the development of hypogonadism in COPD an important problem that must be paid attention to when studying the pathogenesis of this disease and developing approaches to its treatment.

Summarizing the above, the probable causes of hypogonadism development in COPD patients include smoking, age, concomitant comorbid pathology, hypoxia and hypercapnia, SGCS intake, and persistent systemic inflammation. It should be emphasized that the severity of COPD correlates with the severity of hypogonadism [6, 14].

Separately, we should emphasize an effect of smoking on the development of androgenic disorders in men, since smoking is a major etiological factor in COPD. It is well known that tobacco smoke has a systemic effect on the human body, causing pathological changes in various organs and systems. Studying the effect of smoking on the level of sex steroids in men resulted in somewhat controversial data. In smokers with COPD, there is a decrease in testosterone concentration, while in the absence of COPD, its relative increase was observed. This was demonstrated in the study by K. English, et al. [38]: the content of total testosterone, free testosterone and SSBG in the blood serum in smokers was higher than in nonsmokers. However, despite an increase in the concentrations of total and free testosterone, the amount of bioactive testosterone did not change. That is, an increase in the concentration of hormones does not necessarily lead to an increase in their effect on the human body. This was also confirmed in the research conducted by A.E. Makarevich, et al. [39], who surveyed 197 smoking men, among whom there were identified groups of patients with chronic non-obstructive bronchitis associated with smoking and COPD of varying severity. A relative increase in the blood testosterone content was revealed in the patients with chronic bronchitis, while its reduction by 1.4 and 1.6 times was established in patients with severe COPD with compensated and decompensated cor pulmonale, respectively. It was also shown that smokers increased the level of DHEAS in their blood [40]. The cause of the relative increase in the concentration of sex steroids in blood of smokers without COPD remains unknown to date.

Systemic inflammation developing in patients with COPD is characterized by an increase in the number of proinflammatory mediators. An increase in TNF-α, IL-1 and IL-6 may lead to reduction in testosterone concentration due to increase in the aromatase (an enzyme that converts testosterone to estradiol) expression, which probably is indicative of the relationship between the development of androgen deficiency and systemic inflammation in COPD [6].

Regardless of the causes of hypogonadism development in COPD patients, it is obvious that it increases the severity of the disease course via leading to a disturbance of the energy balance by shifting the balance towards energy deficit, and also to depression, sarcopenia, muscle weakness, a feeling of weakness in the legs, and later to the development of a motor activity deficiency. Other consequences of hypogonadism are osteoporosis and reduction in the quality of life in general [6, 22, 41, 42].

The effectiveness of replacement therapy

Considering the significant impact of hypogonadism on the course of somatic pathology and the risk of death in patients with COPD, it can be assumed that its correction should lead to positive outcomes. There are few studies examining the effect of testosterone replacement therapy (TRT) on the course of COPD, and placebo-controlled studies are scarce as well. Consequently, there is no consensus on the advisability of using TRT, as well as there are few clearly formulated indications for its use in patients with COPD. However, in conducted studies, it was shown that in patients with COPD, the addition of TRT to treatment leads to an increase in muscle mass and an improvement in respiratory mechanics, which helps eliminating shortness of breath and increasing physical activity, thus reducing the risk of exacerbations [6, 14, 42, 43, 44, 45]. Androgen therapy leads to an improvement in the quality of life in general, eliminates erectile dysfunction, and is able to prevent the development of osteoporosis [13]. In our opinion, these results should be taken into account when developing rehabilitation programs for patients with COPD, despite the lack of data confirming the effect of androgen replacement therapy on the course of the inflammatory process and respiratory function improvement of the lungs. On the other hand, the limitation of TRT use may be associated with the development of side effects, such as erythrocytosis, sleep apnea, and stimulation of prostate cancer growth [13]. In addition, when prescribing TRT, we should bear in mind that the decrease in testosterone levels may be transient, for example, with aggravation of COPD or short-term intake of SGCS, which dictates the need to reinvestigate the level of androgens during the treatment [6]. Hence, the treatment of androgen deficiency with testosterone preparations in patients with COPD should be carried out solely in conditions of clinical manifestations of androgen deficiency, confirmed by laboratory data. In that case, positive effects could be achieved in the form of increased physical activity, muscle mass and quality of life.

Conclusion

Androgen deficiency is a common disorder, the role of which is habitually underestimated. Various somatic pathologies can contribute to the development of secondary hypogonadism. Hypoxia, hypercapnia, the use of systemic glucocorticosteroids and a pronounced inflammatory process in patients with COPD cause testosterone deficiency, which, in turn, could worsen the course of COPD. Thus, for a deeper understanding of the formation mechanisms of hormonal disorders in the population of patients with COPD, further studies with larger samples are needed, taking into account an influence of various factors on the development of androgen deficiency. A deeper understanding of endocrine disorders, their impact on the course and progression of the disease would help developing new treatment strategies and finding personalized approaches to the treatment of patients with such socially significant pathology.

In presented review, we have analyzed and summarized the available research data on the prevalence, mechanisms of development, manifestations, and approaches to the diagnosis and treatment of androgen deficiency in patients with COPD, which were offered in domestic and foreign literary sources in scientific libraries eLIBRARY and PubMed.

Conflict of interest

The authors declare no conflicts of interest pertaining to this project.

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