

POST-CASTRATION SYNDROME: RELEVANCE, IMPACT ON QUALITY OF LIFE, METHODS OF CORRECTION

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ABSTRACT

Aspects of modern medicine cover a huge number of diseases, including post-castration syndrome, which occurs as a result of endocrine testicular dysfunction in men. The relevance of this condition is great, since it is caused by many reasons and is the basis for an inferior life in men. The review shows the impact of this disease on the quality of life and the methods for its treatment. When writing this review, we used data on castration methods and its correction based on materials published in the eLibrary and PubMed databases. The search was carried out using the keywords: "castration", "post-castration syndrome", "prostate cancer". With castration, there is a decrease in serum testosterone levels, as androgens stimulate the growth of prostate cancer. Today, hormone therapy is an alternative to castration in the treatment of prostate cancer. Surgical castration is the gold standard; it can suppress tumor cell proliferation and induce tumor apoptosis, but it causes significant impairment of quality of life. The article presents characteristics of medications, indications, contraindications and side effects of hormone therapy. The quality of life of men with testosterone deficiency is clinically associated with the development of metabolic syndrome, manifested by obesity, hepatic steatosis and type 2 diabetes mellitus. Numerous studies by domestic and foreign scientists confirm the effect of castration in men on their body, which increases the risk of stroke, depression, cognitive disorders and Alzheimer's disease. Thus, despite the significant advances of modern medicine in the treatment of malignant diseases of prostate, post-castration syndrome remains a completely unexplored problem, which indicates the need for further study and the development of effective therapy.

Key words: prostate cancer, testicular cancer, orchiectomy, post-castration syndrome, castration

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ПОСТКАСТРАЦИОННЫЙ СИНДРОМ: АКТУАЛЬНОСТЬ, ВЛИЯНИЕ НА КАЧЕСТВО ЖИЗНИ, МЕТОДЫ КОРРЕКЦИИ

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РЕЗЮМЕ

Аспекты современной медицины охватывают огромное количество заболеваний, в том числе посткастрационный синдром, возникающий в результате эндокринной дисфункции яичек у мужчин. Актуальность данного состояния велика, так как она возникает вследствие многих причин и является основанием для неполноценной жизни у мужчин. В обзоре показано влияние данного заболевания на качество жизни и методы его терапии. При написании данного обзора были использованы данные о методах кастрации и её коррекции по материалам, опубликованным в базах eLibrary и PubMed. Поиск проводился по ключевым словам: «кастрация», «посткастрационный синдром», «рак предстательной железы». При кастрации наблюдается снижение уровня тестостерона в сыворотке, так как андрогены стимулируют рост рака предстательной железы. На сегодня гормональная терапия является альтернативой кастрации при лечении пациентов с раком предстательной железы. Хирургическая кастрация является «золотым стандартом»; с её помощью можно подавить пролиферацию опухолевых клеток и индуцировать апоптоз опухоли, но она вызывает значительные нарушения качества жизни. В материале представлены характеристика лекарственных препаратов, показания, противопоказания и побочные эффекты от проводимой гормональной терапии. Качество жизни мужчин с дефицитом тестостерона клинически связано с развитием метаболического синдрома, проявляющимся ожирением, стеатозом печени и сахарным диабетом 2-го типа. Многочисленные исследования отечественных и зарубежных учёных подтверждают влияние кастрации у мужчин на организм, при котором повышается риск развития инсульта, депрессии, когнитивных расстройств и болезни Альцгеймера. Таким образом, несмотря на значительные успехи современной медицины в терапии злокачественных заболеваний предстательной железы посткастрационный синдром остаётся до конца не изученной проблемой, что свидетельствует о необходимости дальнейшего изучения и разработки эффективных средств терапии.

Ключевые слова: рак предстательной железы, рак яичка, орхизектомия, посткастрационный синдром, кастрация

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INTRODUCTION

Post-castration syndrome (PCS) in men is a symptom complex characterised by endocrine, metabolic and neuropsychiatric disorders that develops as a consequence of endocrine dysfunction of the testicles as a result of surgery, trauma, disease, radiation and tissue destruction after infectious diseases. Cancer ranks second in the mortality structure, behind cardiovascular diseases, and is responsible for up to 11 % of all deaths worldwide. Each year, 18.1 million people get cancer and 9.6 million of them die; thus, 27,000 people die of cancer per day. According to Rosstat (Russian Federal State Statistics Service), in 2018, 41.1 men per 1,000 people aged 16 to 59 years died from malignant neoplasms (96.2 men per 100,000 population); despite a slight decrease in 2019 (respectively to 38.8 and 91.9 men), in general, the number of cases of this pathology does not tend to decrease [1, 2].

All endocrine glands are susceptible to neoplastic growth, but the health effects of these neoplasms are diverse. Pituitary tumors are widespread and the vast majority of cases are benign, but are characterized by a wide range of different effects on the body. Prolactinomas, by causing an increase in prolactin concentration in the blood, exert their influence on the function of the sexual glands through the hypothalamus, contributing to the development of hypogonadotropic hypogonadism. Microprolactinomas are most common in women, causing infertility and menstrual irregularities (secondary amenorrhea), while in men, on the contrary, macroprolactinoma is more frequently observed [3].

The prevalence of urogenital injuries in peacetime is 1–3.5 % of the total number of cases, of which 35–60 % is injuries involving the kidney and 30–41 % involve the scrotum and other parts of the genital organs. A significant proportion of the PCS patient population is prostate cancer (PC), which is the leading cause of death in men. Globally, 1.6 million men are diagnosed with PC each year with 366,000 men (22.88 %) dying. Numerous literature data reveal a significant reduction in the quality of life of men, indicating the need for ongoing rehabilitation in them. In the structure of cancer morbidity in men in the Russian Federation PC occupies the 4th place, and over the last 10 years the incidence has increased more than 2-fold, and its growth rate is currently the highest among all cancer diseases in males [4].

PC has the highest prevalence in developed countries; for example, the probability of diagnosis at age 79 years is 1:47 in countries with a low and/or medium socio-demographic index. In the US, PC is the leading cause of PCS morbidity and mortality; an estimated 180,890 new cases were diagnosed in 2016. The ratio of morbidity to mortality varies considerably around the world, with the highest ratio in North America (10:1), a lower ratio in Australia (2:1), and almost the same in some Caribbean countries and parts of Africa (1.2:1). The ongoing radical treatment of PC can have a negative impact and cause not only disorders of urinary function,

bowel function, sexual dysfunction, but also quality of life, which makes specialists think about the search for new methods of therapy.

Despite its high incidence, prevalence and duration, this type of cancer has the highest 5-year survival rate, accounting for 25 % of all cases.

Other reasons for the development of PCS are testicular trauma caused by sex reassignment surgeries, congenital malformations and anomalies, other oncological, somatic diseases and complications from surgical interventions. The use of Student's criterion is recommended to estimate the incidence and statistical treatment of the injury number in the United States, which allows for the collection of clinical and anamnestic patient data that includes age, gender, and comorbidities at the pre-hospital stage. Pre-hospital comorbidities included cardiovascular insufficiency, arterial hypertension, peripheral vascular disease, myocardial infarction, bad habits (smoking, alcohol), renal failure, pulmonary disease and cerebral circulatory disorders. Injury profile information included a scale to assess the severity and mechanism of injury.

Any injuries to the kidneys, urinary bladder, urethra, ureter, adrenal glands, penis, pelvis, spine and head injuries were also included in the study. An analysis of scrotal and testicular injuries in US patients revealed that among 8030 patients, only 19 (0.23 %) had scrotal/testicular injuries, of which only 8 (44.6 %) cases were due to blunt trauma. In this case, the penetrating mechanism of injury occurred in 50.5 per cent of cases, and the most frequent cause (75.8 %) was assault with a firearm. The mean age of the patients was 31 ± 3.6 years. The majority of patients (74.5 %) had an isolated injury to the scrotum or testis, which required operative treatment to repair the rupture in 48.3 % of cases (37.3 %). One of the causes of testicular injuries was in cases where patients were involved in motorbike accidents; in this group, scrotal/testicular surgery was performed in half of the cases (48.3 %), but the most common surgical procedure was correction of scrotal or testicular rupture (in 37.3 % of cases) followed by unilateral orchiectomy in 23.4 % of cases [5].

Abroad, due to certain psychological and physiological factors, surgeries are often performed for cosmetic purposes: for example, sex reassignment surgery for transgender women. Gender dysphoria is a condition in which a person's sex assigned at birth and the gender with which they identify are not compatible. The American Society of Plastic Surgery's annual report of specialists revealed that 1,759 transfeminine and 1,497 transmasculine surgeries were performed among patients who underwent gender confirmation in 2016, an increase of 27 % and 10 %, respectively, compared to 2015. A recent survey of nearly 28,000 transgender people revealed that among people who were assigned female sex at birth, 21 % had undergone breast reconstruction surgery, 8 % had a hysterectomy, 1 % had a metoidioplasty, and 1 % had a phalloplasty. Among those classified as male at birth, 10 % underwent vaginoplasty

or labioplasty, 9 % underwent orchiectomy, 8 % underwent augmentation mammoplasty, and 6 % underwent facial surgery [6-8].

It is not uncommon to develop PCS with testicular torsion, a situation that is an acute urological emergency affecting 1 in 4,000 men under the age of 25. It results from the rotation of the spermatic cord, where the rotation and subsequent narrowing of the artery leads to ischaemia, causing damage to the testicular tissue, which is also a condition requiring emergency surgical care. Ultrasound testicular sonography in this case is the basis for assessing blood flow and the severity of vascular changes in order to decide whether to preserve the organ [9].

Surgery for congenital anomalies and malformations with undescended testis (ICD-10: Q53.9) is a situation in which orchiectomy may also be required; it occurs when the testicles are located in the abdominal cavity and need to be surgically transferred to the scrotum. If the damage is irreparable, the surgeon may extirpate one or both testicles, so a thorough chiropractic examination is necessary to rule out medical errors. To achieve this, after laying the patient down, warm fingers should be used to palpate the organ from the projection of the inguinal canal to the pubis in the supine position of the patient. The groin, scrotum, inner thigh, femur, perineum and penile region should also be palpated to reveal an ectopic testis. Visualising studies (ultrasound) may influence the treatment tactics and diagnostic laparoscopy is unavoidable to independently evaluate the results [10, 11].

Hormone therapy (HT) has significant advantages over surgical castration (SC) as it can be administered in short or long courses, but it also has adverse effects on the body – it can cause decreased muscle mass, sexual dysfunction, physical weakness, psychological trauma and reduced quality of life (QOL). Adverse metabolic effects of HT are often associated with an increased risk of cardiovascular and neuropsychiatric disease. Immediate symptoms in locally advanced and/or metastatic cancer include: pain, hypercalcaemia, spinal cord compression and pathological bone fractures, which also have a negative impact on general health. Therefore, conservative therapy in patients with PC can improve QOL, preserve and restore urinary, defecation and genital functions [2].

MATERIALS AND METHODS

Data on PCS, methods of its correction published in eLibrary, PubMed databases were used to write this review. The search was performed by keywords: “castration”, “post-castration syndrome”, “prostate cancer”. As a result of detailed source validation, 60 articles included in the review were selected directly for citation to be used for the study.

Castration is defined as “the deprivation of (male animal or human) testicles” and has distant roots.

Surgical castration by orchiectomy (removal of the testicles) was often performed in ancient China. A study of eunuchs in China revealed that castration resulted in 21 of 26 men having little or no prostate gland palpability, suggesting that androgens need to be constantly present throughout of life for the gland to function. Disappearance (reduction in size) of the prostate can be functional (after castration) and age-related, when there is a natural shrinkage of the testicles. Castration today can be performed surgically and chemically [12].

Lack of androgenic stimulation of tumour cells by surgical or pharmacological castration leads to suppression of their proliferation and induces tumour apoptosis. Surgical castration is the «gold standard» against which all other HT methods are compared; removal of the testicles after 24 hours reduces serum testosterone levels to minimal levels. Today orchiectomy is no longer the main method of treatment, mainly because of public opinion, which considers this method barbaric, capable not only of changing the appearance, but also of having a pronounced psychological impact since the procedure is irreversible. The only advantages of this method are simplicity of execution, cheapness and lack of complications, but this method is not popular among patients because of the pronounced negative psychological effect of the operation and irreversibility of the process. Pharmacological castration, therapy with luteinising hormone-releasing hormone (LHRH) agonists – analogues of natural human LHRH that achieve reversible medical castration and antiandrogens, which have the ability to produce maximal androgen blockade and intermittent androgen suppression, are increasingly used for this purpose. However, despite the variety of existing approaches and the vast clinical experience with HT, no «ideal» method of androgen deprivation has yet been found. Recently, new groups of drugs for HT of PC – LHRH antagonists – have appeared on the pharmacological market [13-15]. With this type of castration, there is a decrease in serum testosterone levels, as androgens are known to stimulate prostate cancer growth; therefore, HT can be used to treat patients even with late diagnosed PC [16, 17].

One type of HT is androgen-deprivation therapy (ADT); in men with metastatic PC, it induces an antitumour response and “improves malignancy-associated bone metabolic abnormalities”. ADT can be prescribed for varying lengths of time and can be combined with remote radiation therapy or brachytherapy (interstitial irradiation). The course of HT usually depends on the disease, side effects, complications and contraindications accompanying the therapy, ability to alter testosterone and estrogen levels in men. Several different types of HT exist today, consisting of chemical and surgical means. Chemical castration is performed by three groups of pharmacological agents [18, 19].

The first type includes LHRH agonists or antagonists; LHRH agonists sometimes can cause “testosterone flares” that can be avoided with antagonists. LHRH

agonists include leuprorelin, goserelin, and triptorelin; LHRH antagonists include degarelix, CYP17 inhibitors, and abiraterone [20].

The second group includes antiandrogens, which are involved in blocking the effects of androgens directly on cells, usually through blockade of the androgen receptor itself. These include flutamide, bicalutamide, nilutamide, enzalutamide, apalutamide and darolutamide. These oral medications are divided according to their chemical structure into steroidal (cyproterone, megestrol and medroxyprogesterone) and non-steroidal or pure (nilutamide, flutamide and bicalutamide) [21, 22].

The third group includes preparations of female sex hormones – estrogens. Estrogens act through a feedback mechanism, shutting down the production of androgens and indirectly reducing testosterone levels. The main side effect associated with estrogen administration is that its high activity (due to the presence of estrogen receptors on platelets) can lead to serious or even fatal venous thrombosis (VTE) [21].

The main advantages of ADT are that the therapy results with a reduction in testosterone levels that is rapid and effective, non-surgical, reversible and has the option for oral or subcutaneous administration, unlike current chemotherapy drugs administered intravenously. However, the side effects resulting from HT are significant and can often lead patients to discontinue its use or use it intermittently. The main limitations are hot flashes, loss of libido, fatigue, osteoporosis, erectile dysfunction and more. One of the biggest limitations to the use of HT is the fact that disease recurrence with the development of castration-resistant prostate cancer (CRPC) is often observed after HT [22, 23].

Long-acting LHRH analogues have become the main form of HT in PCS. The drugs are synthetic analogues of LHRH, mainly administered as depot injections once every 1, 2, 3, 6 or 12 months. After a single dose, they stimulate LHRH receptors, causing a transient increase in LH and follicle-stimulating hormone (FSH) release. This in turn causes an increase in testosterone synthesis (“waves” of testosterone or a “flash” effect) that begins 2–3 days after the first injection and lasts for about one week. The “flash” effect can lead to potentially deleterious effects and is manifested by increased bone pain, acutely developing infravesical obstruction, post-renal renal failure, spinal cord compression, and fatal cardiovascular complications associated with a state of hypercoagulability. The risk of developing clinical “flash” events is increased in patients with symptomatic large-volume bone metastases. Concomitant therapy with antiandrogens reduces the frequency of clinical “flashes” but does not completely exclude the possibility of their occurrence [24, 25].

LHRH antagonists are able to bind immediately to LHRH receptors in the anterior lobe of the pituitary gland. This results in a rapid decrease in LH, FSH and testosterone levels without the development of “flashes”, which improves therapy outcomes and compliance on the part of patients. The lack of long-acting depot

forms is considered a disadvantage and a practical limitation to the use of the drugs, as only monthly administration formulations are currently available [26].

One of the drugs in this group is the LHRH antagonist Degarelix, which is administered subcutaneously once a month. The standard dose of Degarelix is 240 mg for the first month, followed by 80 mg monthly thereafter. The indication for this drug is advanced hormone-dependent PC; side effects include decreased libido, headaches, depression, nausea, diarrhoea, muscle pain, increased sweating, increased urination, and anaemia, which should be considered when prescribing the drug [27].

The group of steroid inhibitors of CYP17 enzyme includes the drug Abiraterone, which is used for the treatment of metastatic castration-resistant prostate cancer (in combination with prednisolone). Side effects include urinary tract infections, hepatotoxicity, arterial hypertension, dyspepsia, and peripheral oedema [28].

Steroidal antiandrogens are synthetic derivatives of hydroxyprogesterone. Side effects develop when prescribing drugs of this group develop secondary to a decrease in testosterone levels (gynecomastia is quite rare), and non-pharmacologic include cardiovascular complications (4–40 % for cyproterone) and hepatotoxicity. Cyproterone is usually prescribed in a regimen of two or three times 100 mg; the indication for its prescription is the correction of pathological abnormalities in the field of sexual behavior (if it is necessary to reduce sexual activity), metastasizing or inoperable cancer. Side effects include gynecomastia, weight change, depression, fatigue, cough, and dyspnea [29, 30].

Nonsteroidal antiandrogens do not inhibit testosterone secretion; therefore, libido, general physical well-being, and bone mineral density (BMD) are preserved during antiandrogen therapy [31, 32]. However, nonpharmacologic side effects may be observed when prescribing drugs of this group: visual disturbances (delayed adaptation to darkness), alcohol intolerance, nausea, hepatotoxicity and interstitial pneumonia (sometimes fatal) and headache [33, 34].

Estrogens reduce testosterone levels, but their use causes severe side effects in the form of thromboembolic complications even at the lowest possible doses, so this group is not considered for therapy [35, 36].

The assessment of QOL in men with testosterone deficiency revealed a clinical association with the formation of metabolic syndrome, which is manifested by the development of obesity, liver steatosis and type 2 diabetes mellitus. Evidence for this comes from experimental studies on male rats, confirming the effects of testosterone deficiency caused by castration and the development of body obesity. Numerous studies by domestic and foreign scientists confirm the effect of castration in men on their body, which increases the risk of stroke, depression, cognitive disorders and Alzheimer’s disease. In contrast, men who are castrated before puberty retain prepubertal features

such as a high voice and lack of facial vegetation; when castration is performed after puberty, facial vegetation and a low voice are retained, but men experience physical changes such as loss of body hair, some gynaecomastia and reduced penile size. Side effects of castration can be observed in long-term use of LHRH agonist, when in addition to feminising signs there is weight gain of up to 10 %, mainly due to fat in the abdomen and thighs, loss of muscle mass by 3–4 % on average, mild anaemia, osteoporosis, hot flashes. At the same time, more than 85 % of men with androgen deficiency report decreased libido and erectile dysfunction. In the differential diagnosis, depressive disorders in PC patients who have undergone SC and are deprived of androgen exposure are difficult to distinguish from those with ineffective cancer therapy and aging [37-40].

Depressive disorders in patients with cancer can have a range of negative effects, which include increased risk of suicide, reduced quality of life, reduced life expectancy, poor patient compliance and increased length of stay in oncology hospital. There have been several studies where it is found that single and unmarried men have a 65 % chance of committing suicide. And the probability of suicide is the highest in the group of patients diagnosed earlier, which is probably associated with an increase in the duration of the impact of risk on the patient's psyche. Other important factors influencing the frequency of depressive disorders include: somatic diseases depending on the degree of severity; complications associated with mono- or multi-organ lesions of organs and systems, side effects of drugs (cytostatics, hormonal agents, radiation therapy, etc.).

The stage of cancer has a significant impact on the frequency and severity of depressive disorders. Some of the risk factors for the development of depressive disorders are the severity and traumatic nature of the surgical procedure during surgical treatment. Most often it is represented by polymorphic fears and nosophobia formed against the background of persistent hypothyria (depression, pessimistic assessment of future prospects), which are closely related to the situation of cancer [41, 42].

Different changes in emotional behaviour have been reported in men and transsexuals who have transitioned from male to female. Despite gender reassignment, men have a difficult time dealing with the onset of changes in appearance that are not always appropriate and affect their ability to function sexually. Many studies show that the physical and psychological effects of ADT are severe, leaving patients powerless to cope with depression, cognitive impairment, and dramatically reduced QOL. With reduced libido, many subsequently refuse sex, love and physical contact from their partners. They are embarrassed by the changes in appearance, deeply worried and do not want to discuss this topic, even with doctors, which leads to frustration and depression in partners, and later - to the breakdown of marital relations [43-45].

At the same time, the clinic of PCS development varies significantly depending on age. When comparing patients castrated for PC and voluntary eunuchs, the latter reported higher levels of sexual interest despite being on average two decades younger than the cancer patients. From the perspective of both groups, their self-rated physical health was clearly higher than that of the PC patients, also helped by the fact that they were not burdened by a cancer diagnosis. Nevertheless, these data suggest that the biological factors mentioned - age, health, hormones, and psychological expectations - also affect sexuality in androgen-deprived men. That said, it is worth noting that eunuchs in history have had higher QOL, which depended on cultural norms, time and place of residence.

Voluntary eunuchs had higher levels of mental health and social interaction, with at least 49 % reporting major or minor depression prior to castration, and only 38 % reporting depression after castration, indicating stress. Studies conducted abroad confirm that only 17 % of eunuchs who underwent SC cite their desire to be a woman as the main reason, while 15 % stated that they used this method to give pleasure to their partner. Voluntary eunuchs have one thing in common with PC patients – they hide from prying eyes, and few are able to talk openly about their castrated status in everyday life. However, only 8 % of surgical eunuchs report that they have had this surgery performed against the opinion of their closest friends, relatives and family members. All this suggests that most castrated individuals conceal their morphological and emotional colouration for fear of humiliation in society [46-49].

Thus, despite significant advances in modern medicine in the therapy of malignant prostate cancer, post-castration syndrome remains an understudied problem. The analysis of the material indicates the need for further study and development of new quality drugs that can influence the course of the malignant process and at the same time have little effect on the quality of life. The development of drugs capable of medically correcting androgen deficiency in patients is important in order to eliminate possible physical and psychological changes, to improve the quality of life and health status of patients suffering from malignant disease.

Conflict of interest

The authors declare that the submitted article, its topic, subject and content do not involve competing interests.

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