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Male hypogonadism – brief review of symptoms, types and ways of treatment

Tywanek Ewa, Trojanowska Paulina, Wronecki Jakub, Wronecki Jakub, Wiśniewska-Ślepaczuk Katarzyna, Robert Jan Łuczyk

1. Tywanek Ewa, ewa.tywanek@gmail.com ORCID: 0000-0002-2311-994X
Chair of Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Chodźki 7, 20-093 Lublin, Poland; Department of Endocrinology with Department of Nuclear Medicine, Center of Oncology of the Lublin Region St. Jana z Dukli in Lublin, Jaczewskiego 7, 20-090 Lublin
2. Trojanowska Paulina, trojanowska_paulina@wp.pl ORCID: 0000-0002-5289-6473,
Department of Pediatric Neurology, Medical University of Lublin, A. Gębali 6, 20-093 Lublin, Poland, Department of Endocrinology, Diabetology and Metabolic Diseases, Medical University of Lublin, Jaczewskiego 8, 20-954 Lublin, Poland
3. Wronecki Jakub, wronecki.jakub@gmail.com ORCID: 0000-0001-8664-7072
Chair and Department of Gastroenterology, Medical University of Lublin, Jaczewskiego 8, 20-954 Lublin, Poland;
4. Wiśniewska-Ślepaczuk Katarzyna, katarzyna.wisniewska@onet.pl ORCID: 0000-0002-1525-2871
Diagnostic Techniques Unit, Faculty of Health Sciences, Medical University of Lublin,
5. Robert Jan Łuczyk, luczykrobert@op.pl ORCID: 0000-0003-0889-6326, Internal Medicine and Department of Internal Medicine in Nursing, Medical University of Lublin, Poland

Abstract:
Appropriate concentration of androgens is necessary for general men's health, especially for development and maintain reproductive and sexual function, as well as metabolic balance. The state of deficiency of testosterone or its inadequate action, as well as inability to produce good quality semen is called hypogonadism. Depending on the function of the testicles, production of androgens and sperm is also conditioned on hypothalamus-pituitary axis, metabolic status and age of the individual. Considering that, hypogonadism of primary, secondary, functional or late-onset origin may be recognised. As it concerns susceptible matter of sexual and reproductive health, it requires special interest of differently clinicians, i.e. endocrinologists, andrologists or urologists.

Key words: hypogonadism; testosterone therapy; Klinefelter Syndrome; metabolic syndrome; obesity

Introduction:

Hypogonadism is the state of deficiency of testosterone or its inadequate action, as well as inability to produce good quality semen, effective in malaise or inability to conceive. Depending on this definition as well as differential pathogenesis and time of onset of androgens deficiency, hipogonadic men will constitute very heterogenous group of patients. Diagnosis of hypogonadism should be maintain with the highest precision and caution. Due to ,,Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline'' a diagnosis of hypogonadism should be made only in men with symptoms and signs concomitant with testosterone deficiency and clearly and consistently low serum testosterone concentrations (Bhasin et al. 2018). As recommended, fasting morning total testosterone concentration should be measured repeatably. In the case, when total testosterone is near to a lower limit or even in normal range, but sex-hormone biding globulin (SHBG) concentration may be altered and affect the measurement, a free testosterone concentration should be assessed. The major aim of treatment, after the completion the diagnostic process, will be however generally similar – whenever it's possible to remove the cause of the disease or dealing with undesirable symptoms. However the ways for realisation thease particular aims may be quite different. Firstly it's necessarily to present efficiently symptoms of testosterone deficiency, as well discuss it's origin.

Symptoms of hypogonadism

In general, clinical presentation of hypogonadism depends on the period, when deficiency of testosterone has appeared. If failure of testicles was present before sexual maturation, the main symptom is the lack or retardation of puberty. Clinical presentation covers the tallness with disproportionately long limbs, small amount of muscle mass, small size of testicles and penis, no male type hair and lack of mutation of the teenager, then. When the cessation of level of androgens appears after the time of puberty, the symptoms may be more discreet. Decreased libido, erection disturbances, infertility, depression or some metabolic abnormalities such as weight gain with reduction of muscle mass and strenght or in the long run reduced bone density may be noted.

Types of hypogonadism

Based on the pathogenesis of hypogonadism, bearing in mind also its receptor action, primary, secondary, peripheral, functional and late-onset or mingled hypogonadism may be diagnosed. As the majority of testosterone is produced in the testicular tissue, due to its damage, primary deficiency or diagnosis of hipergonadotropic hypogonadism is justified. The reasons of testicles damage may vary with coming firstly absence of one or both testicles of congenital or acquired origin. The lack of the gonads may be secondary to injury, inflammation, neoplasm and its medication with radio- or chemotherapy, as well as due to ischemia. In special situations only Leydig cells are damaged, for example due to agenesis. Some genetic syndromes should be mentioned as a cause of primary testicular disfunction, for example Klinefelter or Noonan syndrome, gonads dysgensis or 46, XX syndrome. Besides these detailed clinical situations, undescendent testicles, mumps orchitis or hemochromatosis can also be listed as causes of primary defect of male gonads (Kumar et al. 2010).

According to pituitary or hypothalamus dysfunction, secondary or hypogonadotropic hypogonadism should be recognized and treated. Its isolated genetic form, is called Kalmann syndrome (associated with the impaired development of the ability to smell - anosmia) or non-Kallmann syndrome. Genetically conditioned states, that may lead to central hypogonadism are empty saddle syndrome or underdevelopment of peduncle of hypophysis.

Primary or metastatic neoplasms, as well as their treatment (neurosurgical intervention or radiotherapy) of hypothalamo-pituitary region also may result in testosterone deficiency. Quite seldom, but possible are vascular causes, such as pituitary stroke or aneurysm of internal carotid artery. Interesting are inflammatory or infiltrative diseases concerning this region, such as tuberculosis, syphilis, sarcoidosis, histiocytosis or hemachromatosis (El Osta et al. 2017), as well as lymphocytic inflammation or as a result of meningitis. Human immunodeficiency virus (HIV) or Acquired immunodeficiency syndrome (AIDS) may lead to hypogonadism affecting hypothalamus, pituitary or testes function (Kumar et al. 2010). Special type of medication, such us for example opioids or hormones (Daniell 2002) or spironolactone, corticosteroids, immunosuppressants, ketoconazole, anticonvulsants and psychotropic medications or ethanol may affect pituitary function as well (Kumar et al. 2010). It's widely known, that persistent stress, fasting or exhausting exercises through their action on hypothalamus and pituitary may result in central hypogonadism development. However interesting is, that acute stress or administration of corticosteroids may reduce level of testosterone without accompanying changes in LH or PRL (Cumming et al. 1983).

The next type of hypogonadism, that may be diagnosed mainly due to clinical observation of the patient with potentially adequate levels of androgens measured in the serum, is its peripheral form developing due to androgen, estrogen, FSH or LH receptors disfunction or resistance.

Substantial group of patient with hypogonadism will represent men with functional deficiency of androgens. Diagnosis may be confirmed due to coexistence clinical features of testosterone deficiency with its decreased concentration found in the blood with normal or inadequately low levels of gonadotropins in the absence of tangible organic or hereditary hypothalamo-pituitary axis abnormalities. Obesity is linked to impaired male gonadal function and seems to be the most frequent cause of hypogonadism currently, whereas androgen deficiency predispose to increased fat accumulation and reduced musce mass and bone desity (Carrageta et al. 2019). Due to research of Naifar (Naifar et al. 2015) such antropometric indicators as waist circumference, body mass index and blood pressure were significantly higher in hypogonadal patients compared with controls. Also glycemia, HbA1c, fasting serum insulin and Homeostatic Model Assessment (HOMA-IR) were significantly increased in the testing group. Reduction of body mass may be efficient in improving serum testosterone levels in functional hypogonadism. As one of the treatment options for obesity, bariatric surgery is able to promote a statistically significant improvement in weight, metabolic profiles and total testosterone level in surgical patients (Rigon et al. 2019).

It shouldn't be missed, that one of premises enabling hypogonadism recognition is inability to produce good quality semen. Assesing the importance and clinical leads of semen analysis on men's general health, it's good to take into considerations results of Ferlin discovery: oligospermic men are at a high risk of hypogonadism and have higher body mass index, waist circumference, systolic pressure, low-density lipoprotein cholesterol, triglycerides, lower high-density lipoprotein cholesterol and a higher prevalence of metabolic syndrome - to sum up a low sperm count is associated with a poor metabolic parameters (Ferlin et al. 2021).

Quite controvensial, mainly because of diffuculties in establishing unique cut-of point of serum testosterone level and commonness of hypogonadal symptoms is late-onset hypogonadism (Wu et al. 2010).

Table 1. (Developed on the basis of „Andrologia. Zdrowie mężczyzny od fizjologii do patologii, Słowikowska- Hilczer, J. at al., PZWL, wyd. 1, Warszawa 2021)

TYPE OF HYPOGONADISM	EXAMPLES
hypergonadotropic (primary)	chromosomal abnormalities: - Klinefelter syndrome - Noonan syndrome - dysgensis of gonads - 46, XX syndrome
	congenital lack of testes (anorchia)
	acquired lack of testes (due to: inflammation, injury, neoplasm)
	surgical or farmacological castration
hypogonadotropic (secondary)	isolated hypogonadotropic hypogonadism: (Kallmann syndrome and non- Kallmann syndrome)
	neoplasms of hypothalamus, pituitary, metastases
	vascular origin
	skull injuries, iatrogenic injuries
	inflammatory and infiltrative diseases: tuberculosis, syphilis, sarcoidosis, histiocytosis, hemachromatosis
	genetically conditioned states: empty saddle syndrome underdevelopment of peduncle of hypophysis
	idiopatic
peripheral	androgens and estrogens receptors mutations
	5-alpha reductase deficiency type 2
	FSH and LH receptors mutations
late-onset hypogonadism	ralated with age
functional hypogonadotropic hypogonadism	related mainly with body mass

Treatment of hypogonadism

Because of so various different causes, clinical presentations and goals of therapy of hypogonadism, ways of its treatment may differ. Patients with genetic base of the abnormality, will be most frequently treated in symptomatic way by exogenous testosterone administration.

Oral, intramuscular, subcutaneous or transdermal preparations-gels may be used then(Byrne and Nieschlag 2003).

For secondary congenital hypogonadism, some clinicians recommend starting therapy with gonadotrophins to allow the testicles to reach pubertal size, then until fertility is desired testosterone replacement therapy can be implemented (Corona et al. 2012).

It's good to mention here about contraindications to testosterone therapy. Due to An Endocrine Society Guidelines it isn't recommended in patients who would like to conceive in a near future or present with any of listed conditions: breast or prostate cancer, incorrect morphology of prostate or the concentration of prostate-specific antigen 4ng/mL or 3ng/mL in men with increased risk of prostate cancer without further urological evaluation or severe lower urinary tract symptoms, untreated severe obstructive sleep apnea or such hematological irregularities as elevated hematocrit or trombophilia and medical conditions with cardiological background present within preceding six months like uncontrolled heart failure, myocardial infarction or stroke (Bhasin et al. 2018).

Generally the aim of treatment of any formulations of testosterone is to achive and maintain testosterone concetrations in the mid-normal range (Bhasin et al. 2018). Indispensable element of cure is to monitor symptoms, adverse effects and compliance, as well as hematocrit, serum concentration of testosterone and assessing the risk of prostate cancer occurrence.

As we noted, specific and careful supervision should be performed due to men, who are planning fertility in the near future. Implementation of testosterone treatment results in reduction of gonadotropins secretion – not only luteinizing hormone (LH), which stimulate testosterone production, but also follicle stimulating hormone (FSH), that mobilizes spermatozoa production and maturation. In this specific group of patients, treatment with ability to stimulate own production of testosterone and/or supporting spermatogenesis should be used.

Since gonadotropins regulate function of the testicles, application of exogenous FSH and LH or their analogs, will have similar effect. From the other hand, chemicals, that by their action will increase gonadotropins levels, will have similar effects on gonads; as examples should be listed clomiphene citrate and letrozole.

Treatment with GnRH, basically with the use of pump with pulsatile subcutaneous infusion is possibly most physiological model of medication, especially eligible for hypogonadotropic hypogonadism. Human chorionic gonadotropin (hCG) as an analog of LH, has ability to stimulate its receptor mobilizing endogenous testosterone production. Selective estrogen receptor modulators (SERM) are a class of drugs, that have potency to react with estrogen receptor in stimulating or inhibitory manner. Clomiphene citrate is the representative of mentioned group with mechanism of its action through competitive inhibition of estrogen receptor in hypothalamus and pituitary that prevents circulating estrogen from inducing negative feedback on the gonadotropic action of pituitary. As a result, increase of LH and FSH level is observed, as well as following up rise in testosterone concentration (Carrasquillo et al. 2018). Letrozole, anastrozole and testolactone are examples of aromatase inhibitors. They have great ability to decrease their potency to convert testosterone to estradiol, what reduces the feedack inhibition of estrogens on hypothalamic-pituitary-gonadal axis and due to increase of gonadotropins levels, increase endogenous androgens production. Aromatase inhibitors have an ability to restore a normal testosterone to estrogen (T/E) ratio exceeding 10 (>10) improving subfertility and hypogonadism (Saylam et al. 2011).

Scientific reports present, that clomiphene citrate implemented in hypogonadic males also has an ability to increase of testosterone serum concentration, as well as improving the testosterone/estradiol ratio (Shabsigh et al. 2005)

Not all mentioned methods of treatment are approved by Food and Drug Adminisstration (FDA).

New perspectives

Potentially side effects of treatment mentioned above, mobilizes to develop some new medical perspectives. Testosterone in form of nasal gel, special oral formulations, the anabolic-androgenic steroids (AAS) with its represetative nandrolone and non-steroidal selective androgen receptor modulators (SARM) as well as transisomer of clomiphene citrate, i.e. enclomiphene citrate are tested (Carrasquillo et al. 2018).

Due to constantly and rapidly groving problem of hypogonadism, self-education of clinicians taking care of men is urgently needed.

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