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# Testosterone supplementation in men

## Suplementacja testosteronu u mężczyzn

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None  
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### Summary

Androgens are important in every phase of human life and play an important role in male reproductive and sexual function. Male hypogonadism is a clinical syndrome caused by androgen deficiency which can adversely affect multiple organ functions and quality of life.

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis. Male hypogonadism is the main indication for testosterone supplementation. Several preparations are available, which differ in the route of administration, pharmacokinetics and adverse events. The selection should be a joint decision by both the patient and the physician. Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed. Nowadays, in Poland the available agents are intramuscular injections or transdermal gel.

Testosterone therapy may present several benefits regarding body composition, metabolic control, psychological and sexual parameters.

### Streszczenie

Androgeny odgrywają istotną rolę na każdym etapie życia mężczyzny i pełnią ważną funkcję w jego czynnościach rozrodczych i seksualnych. Hipogonadyzm u mężczyzn jest zespołem klinicznym spowodowanym niedoborem androgenów, który może niekorzystnie wpływać na funkcje wielu narządów i jakość życia.

Hipogonadyzm spowodowany jest niewydolnością jąder lub zaburzeniami na jednym lub kilku poziomach osi podwzgórze – przysadka – gonady. Hipogonadyzm u mężczyzn jest głównym wskazaniem do suplementacji testosteronem. Na rynku dostępnych jest kilka preparatów, różniących się drogą podawania, farmakokinetyką i mogącymi występować działaniami niepożądanymi. Wybór powinien być wspólną decyzją zarówno pacjenta, jak i lekarza. Preparaty o krótkotrwałym działaniu są preferowane do podawania w początkowej fazie leczenia, a zatem wszelkie działania niepożądane, które mogą wystąpić, obserwowane są wcześniej i leczenie można przerwać w razie potrzeby. Obecnie w Polsce dostępne są preparaty testosteronu podawane domięśniowo oraz w postaci żelu transdermalnego. Uzupełnianie niedoboru testosteronu może przynosić szereg korzyści związanych z zmianą składu ciała, poprawą kontroli metabolicznej oraz parametrów psychologicznych i seksualnych.

### THE ROLE OF ANDROGENS

Androgens are important in every phase of human life and play an important role in male reproductive and sexual function. During the embryonal stage, testosterone determines the differentiation of the sexual organs, during puberty, the further development toward the adult male phenotype which is then maintained along with important anabolic functions such as body composition, muscle formation, bone mineralization and fat metabolism.

The method of synthesizing testosterone from cholesterol was first described in 1935 by Adolf Butenandt and Leopold Ruizka (1, 2). In men testosterone is synthesized mainly in the testes (95%), in Leydig cells. Less than 1% of testosterone is produced in cells of the adrenal cortex and less than 5% comes from the peripheral metabolism of its precursors (3, 4). Testosterone production is regulated by the hypothalamic-pituitary-gonadal axis. Gonadotropin-releasing hor-

mone (GnRH) is produced by neurons of the arcuate nucleus in the hypothalamus (5). GnRH is secreted into the circulation of the pituitary gland and causes LH and FSH release from the anterior pituitary cells. LH stimulates Leydig cells to produce testosterone. Testosterone inhibits LH secretion by negative feedback (6). The biological effect of testosterone is due to the connection of the hormone with the androgen receptor. A small portion of the circulating testosterone (less than 10%) becomes a precursor to the production of two other hormones: through  $5\alpha$ -reduction it gives rise to the highly biologically active hormone  $5\alpha$ -dihydrotestosterone (DHT), and through aromatization to oestradiol.

Male hypogonadism is the main indication for testosterone supplementation. The other possible applications are constitutionally delayed puberty, male hormonal contraception (experimental use) and in anemia (7). Because of its erythropoietic effect testosterone is used to the treatment of aplastic and renal anemia, but lost ground to erythropoietin after the latter was introduced.

## HYPOGONADISM

Male hypogonadism is a clinical syndrome caused by androgen deficiency which can adversely affect multiple organ functions and quality of life (8).

Hypogonadism results from testicular failure, or is due to the disruption of one or several levels of the hypothalamic-pituitary-gonadal axis.

Male hypogonadism can be classified in accordance with disturbances at the level of:

- the testes (primary hypogonadism); primary testicular failure is the most frequent cause of hypogonadism and results in low testosterone levels, impairment of spermatogenesis and elevated gonadotrophins,
- the hypothalamus and pituitary (secondary hypogonadism); central defect of the hypothalamus or pituitary causes secondary testicular failure,
- the hypothalamus or pituitary and gonads (late-onset hypogonadism); combined primary and secondary testicular failure results in low testosterone level and variable gonadotrophins levels,
- the androgen target organs (androgen insensitivity or resistance) (9, 10).

Androgen deficiency increases slightly with age also in healthy men (9). In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1-12.8% (9, 11). The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 varies from 2.1-5.7% (11, 12).

The diagnosis of hypogonadism requires the presence of characteristic symptoms and signs in combination with decreased serum concentration of testosterone.

According to the various recommendations of the scientific societies and the "working groups", the lower values of total testosterone below which substitution therapy is suggested are ranging from 2.5 to 4.0 ng

per ml (8-13.9 mmol per l) (13-15). It is preferred to obtain a serum sample for testosterone determination between 07.00 and 11.00 h in the fasting state. Total testosterone assessment should be repeated at least on two occasions. In addition, in men with total testosterone levels between 2.5 to 4.0 ng per ml, the free testosterone level should be measured to strengthen the laboratory assessment (9, 16).

The clinical manifestation of hypogonadism is determined by the age of onset and the severity of hypogonadism.

The signs and symptoms suggesting prepubertal-onset hypogonadism are small testes, cryptorchidism, gynecomastia, a high-pitched voice, linear growth into adulthood, eunuchoid appearance, sparse body hair, infertility, low bone mass, sarcopenia, reduced sexual activity and desire. The most characteristic symptoms of hypogonadism in adults are loss of libido, erectile dysfunction, decreased sexual activity, decreased muscle strength, decreased vital energy as well as hot flashes, gynecomastia and decreased testicular volume, and low energy bone fractures. Non-specific symptoms include: decreased self-confidence, motivation, depression, irritability, memory, concentration impairment, sleep disorders or insomnia, decreased psychomotor activity. There is a higher prevalence of obesity, type 2 diabetes, cardiovascular disease, osteoporosis and anemia in men with decreased testosterone levels (14, 17).

## TESTOSTERONE SUPPLEMENTATION

Testosterone is one of the oldest hormones in clinical use. It has been available for three quarters of a century. The goal of treatment is to restore testosterone levels to the mid-normal range, approximating the natural, endogenous production, without significant side effects or safety concerns, and alleviating the signs and symptoms associated with testosterone deficiency.

Testosterone therapy (TT) may present several benefits regarding body composition, metabolic control, psychological and sexual parameters. Improvement in hypogonadal signs and symptoms occur at different times for different organ systems (18). TT has a beneficial effect on health, manifested by improvement in mood, concentration, sleep quality, physical and mental fitness, increases of libido, increased frequency of morning erections and erotic dreams and improvement of erectile dysfunction and satisfaction with sex life. Significant improvement in quality of life occurs within 3-4 weeks of starting TT. Significant improvement in libido is usually experienced within 3-6 weeks of supplementation. Up to 12 months of TT may be required before significant improvement in erectile and ejaculatory function is observed. Effects on depressive mood become detectable after 3-6 weeks of starting testosterone supplementation, with maximum improvement occurring after 18-30 weeks (8).

Randomised trials show a correlation between restored physiological testosterone levels, muscle

mass and strength measured as leg press strength and quadriceps muscle volume (9, 19). TT improves bone mineral density at the lumbar spine and femoral neck (20). Body composition is influenced by TT in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass (18). These changes occur within 12-16 weeks of starting TT and stabilize at 6-12 months, but can continue to improve over years.

TT impacts positive effects in glycemia and lipid profile, decreases insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile with a consequent decrease of mortality (17, 21). Effects of testosterone supplementation on lipids appear after 4 weeks, with maximal effects being seen after 6-12 months of treatment. Insulin sensitivity may improve within a few days of starting TT, but effects on glycaemic control become evident only after 3-12 months (8).

Several preparations are available, which differ in the route of administration, pharmacokinetics and adverse events. The selection should be a joint decision by both the patient and the physician (22). Short-acting preparations are preferred to long-acting depot administration in the initial treatment phase, so that any adverse events that may develop can be observed early and treatment can be discontinued if needed (9). In Poland the available agents are intramuscular injections (testosterone undecanoate, enanthate and solution of four testosterone esters: testosterone propionate, phenylpropionate, isocaproate, decanoate) and transdermal gel.

Testosterone enanthate is the oldest form of testosterone that has been used since the 1950s.

Testosterone enanthate is available as short-acting intramuscular delivery systems (with intervals of 1-2 weeks). The standard dose is 100-200 mg testosterone enanthate. Testosterone enanthate represents safe and valid preparation. However, this preparation may cause fluctuations in serum testosterone from high levels to subnormal levels, and it is consequently associated with periods of well-being alternating with periods of unsatisfactory clinical response. Testosterone enanthate is also associated with increased rates of erythrocytes and haematocrit (23).

In Poland testosterone undecanoate is only available as a long-acting intramuscular injection. After the initial injection testosterone undecanoate in dose a 1000 mg, a further injection is given after 6 weeks and is subsequently repeated every 3 months. This long time of action ensures a normal testosterone serum concentration for the entire period, but the relatively long wash-out period may cause problems if complications appear (24).

Transdermal testosterone preparations are available as transdermal 1 or 1.62% gel.

It provides a uniform and normal serum testosterone level for 24 hours (daily interval). Common side-effect consists of risk of interpersonal transfer if appropriate precautions are not taken (25).

In some countries other forms of testosterone are available, for example testosterone undecanoate as an oral preparation, transdermal testosterone as a skin patches, sublingual or buccal tablet and subdermal implant every 5-7 months (9).

Contraindications against testosterone treatment are prostate cancer, male breast cancer, severe sleep apnoea, male infertility-active desire to have children, haematocrit above 54%, severe lower urinary tract symptoms due to benign prostatic hyperplasia and severe chronic cardiac failure (New York Heart Association Class IV) (8, 9).

TT should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency.

The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.

Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above 54%.

Prostate health should be assessed by digital rectal examination and serum PSA level before the start of TT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually. Recommendations regarding what constitutes a concerning rise in PSA include an increase of 1.0 ng/ml over baseline PSA (26) or a PSA velocity greater than 0.4 ng/ml per year (27). If possible, rectal palpation should be supplemented by transrectal ultrasonography (TRUS) as it allows non-invasive evaluation of the entire organ.

Bone mineral density (BMD) should be monitored only in men whose BMD was abnormal before initiation of TT. An increase in lumbar spine BMD may already be detectable after 6 months of TRT and may continue for 3 more years (18).

## CONCLUSIONS

Testosterone deficiency is a relatively common problem that confers a significant health burden upon men that can be ameliorated by appropriate clinical interventions. Testosterone supplementation should restore the serum testosterone level to the mid-normal range of specific age groups of men, which is usually sufficient to alleviate various manifestations of hormone deficiency. Testosterone therapy may present several benefits regarding body composition, metabolic control, psychological and sexual parameters.

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