

## Late-onset hypogonadism

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### Abstract

In Poland, the number of men over the age of 50 years exceeds 6 million. It is estimated that about 2-6% of this population develops symptoms of late-onset hypogonadism (LOH). In men, testosterone deficiency increases slightly with age. LOH is a clinically and biochemically defined disease of older men with serum testosterone level below the reference parameters of younger healthy men and with symptoms of testosterone deficiency, manifested by pronounced disturbances of quality of life and harmful effects on multiple organ systems. Testosterone replacement therapy may give several benefits regarding body composition, metabolic control, and psychological and sexual parameters.

**Key words:** the aging male, testosterone, late-onset hypogonadism.

### The aging male

According to United Nations (UN) estimates, the population on Earth will have increased fourfold from two and a half billion in 1950 to almost ten billion by 2050 [1]. Nowadays in Europe we live twice as long as 100 years ago [2]. This long lifespan is largely due to improved hygiene, reduction of newborn mortality, and more effective prevention and therapy of diseases in adult age. In 2014 in Poland women lived on average 81.6 years, while men lived only 73.8 years [2, 3]. The consequence of this phenomenon is a systematically growing population of older people and the emergence of age-related health problems that have not been seen before. These changes have caused a focus on the health and quality of life of older people.

Aging is a slow physiological process. During the process of aging, the human organism undergoes a series of morphological and functional modifications within all organs, tissues, and cells, characterised by a general tendency towards reduced physiological efficiency and atrophy of various organs and systems [4, 5]. Involutional processes occur in both peripheral glandular secretions as well as in the hypothalamus and pituitary gland. Thus, during the aging process, there is a fundamental change in the secretion of most hormones.

The World Health Organisation found that in 2000 the population of men aged over 65 years amounted to 520 million. It is expected that by 2050 it will increase almost threefold and exceed 1.5 billion men.

It is estimated that between 2 and 6% of these men will develop symptoms associated with late-onset hypogonadism [6].

### The role of testosterone

Androgens play an important role in male reproductive and sexual function. Androgens are crucial for the development of male reproductive organs, such as the epididymis, seminal vesicle, prostate, and penis. In addition, androgens are needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions [7].

Testosterone is a steroid hormone, which acts as the main androgen in men. In 1935 Adolf Butenandt and Leopold Ruizka, independently of each other, described a method of synthesising testosterone from cholesterol. These activities are considered to be the beginning of modern clinical pharmacology and endocrinology. For their achievements, they were honoured with the Nobel Prize in Chemistry in 1939 [8-10].

In men testosterone is synthesised 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 [11, 12]. The substrate for testosterone production is cholesterol, synthesised *de novo* in Leydig cells or derived from plasma lipoproteins [13].

Testosterone production is regulated by the hypothalamic-pituitary-gonadal axis. Gonadotropin-releas-

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ing hormone (GnRH) is produced by neurons of the arcuate nucleus in the hypothalamus [14]. GnRH is secreted into the circulation of the pituitary gland and causes luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release from the anterior pituitary cells. LH stimulates Leydig cells to produce testosterone. Testosterone inhibits LH secretion by negative feedback [15].

During transport in plasma, testosterone is mainly bound to albumin or to sex hormone binding globulin (SHBG), which is produced by hepatocytes. A similar protein, androgen binding protein (ABP), with similar steroid-binding characteristics, was found to be produced in the testis.

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 (three to six-fold compared to testosterone) hormone  $5\alpha$ -dihydrotestosterone (DHT), and through aromatisation to oestradiol.

Both testosterone and its active metabolites are catabolised in the liver and excreted mainly in the urine.

## Hypogonadism

Male hypogonadism is a clinical syndrome caused by androgen deficiency, which can adversely affect multiple organ functions and quality of life [1].

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 defects of the hypothalamus or pituitary cause secondary testicular failure,
- the hypothalamus or pituitary and gonads (hypogonadism in adult men); combined primary and secondary testicular failure results in low testosterone level and variable gonadotrophins levels,
- androgen target organs (androgen insensitivity or resistance) [16, 17].

## Late-onset hypogonadism

This form of hypogonadism is known as late-onset hypogonadism (LOH), age-related hypogonadism, andropause, PADAM (Partial Androgen Deficiency in

Aging Male), ADAM (Androgen Decline in the Aging Male), or TDS (Testosterone Deficiency Syndrome) [16].

Three different factors are responsible for changes in serum testosterone levels in older men.

LOH is a consequence of the aging process, deterioration of hypothalamic-pituitary function, and Leydig cell function in the testes [17]. The aging of males leads to disorders of pulsed secretion of GnRH by dysregulation of the hypothalamic pulse generator and reduction of the frequency and amplitude of LH pulses. The amount and activity of Leydig cells decreases mainly by progression of atherosclerosis and degenerative changes in Leydig cells. Only the free, unbound testosterone is biologically active. SHBG levels increase with age, so the proportion of bioactive free testosterone decreases. In older men, it often leads to an increase in aromatase activity, which metabolises testosterone to oestradiol. This phenomenon is compounded by the co-occurrence of obesity, diabetes mellitus, cardiovascular disease, and cancer [18].

Age-related hypogonadism is a clinically and biochemically defined disease of older men with serum testosterone level below the reference parameters of younger healthy men and with symptoms of testosterone deficiency, manifested by pronounced disturbances of the quality of life and harmful effects on multiple organ systems [19].

In middle-aged men, the incidence of biochemical hypogonadism varies from 2.1% to 12.8% [20]. The incidence of low testosterone and symptoms of hypogonadism in men aged 40-79 years varies from 2% to 6% [20, 21]. Hypogonadism is more prevalent in older men, in obesity, in those with co-morbidities, and in men with a poor health status [22].

Acute illness like head trauma, stroke, myocardial infarction, gall bladder surgery, or acute colitis can also reduce testosterone synthesis. This effect can last for a few days to several weeks. Acute severe burns can result in lower testosterone levels for eight or more weeks. For this reason, caution is necessary in making a diagnosis of testosterone deficiency during, or in the weeks immediately following, an episode of acute illness [23].

Several drugs can interfere with testosterone. Up to 70% of men who regularly take opioid drugs, including methadone and tramadol, have suppressed testosterone levels. Long-term glucocorticoid therapy can also suppress the hypothalamic-pituitary-testicular axis. Some drugs used to treat anxiety and depression, either directly or through their provocation of hyperprolactinaemia, may cause testosterone deficiency. Sexual dysfunction can be associated with use of  $5\alpha$ -reductase inhibitors [24].

There is no universally-accepted lower limit of "normal range" for total testosterone. Based on the

consensus reached in 2009 by representatives of leading societies concerned with the problem of hypogonadism in men: the American Society of Andrology (ASA), the International Society of Andrology (ISA), the International Society for the Study of Aging Male (ISSAM), the European Association of Urology (EAU), and the European Academy of Andrology (EAA), the lowest norm for total testosterone levels in older men could not be clearly defined [19]. In the diagnosis of LOH we use the norms adopted for healthy young men. 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 range from 2.5 to 4.0 ng/ml [25, 26].

There are no pathognomonic symptoms of LOH. However, the most characteristic symptoms are erectile dysfunction, decreased sexual activity and loss of libido, decreased muscle strength, decreased vital energy, hot flashes, gynaecomastia and decreased testicular volume, and low-energy fractures. Non-specific symptoms include: decreased self-confidence, motivation, depression and irritability, memory and concentration impairment, sleep disorders or insomnia, and decreased psychomotor activity. There is a higher prevalence of type 2 diabetes, obesity, cardiovascular disease, osteoporosis, and anaemia in men with decreased testosterone levels [27]. The clinical consequences of hypogonadism are determined by the age of onset and the severity of hypogonadism. In LOH, the severity of many clinical symptoms is much lower than in pre-pubertal onset of androgen deficiency. The mortality of patients with testosterone deficiency is significantly higher than among men with normal serum testosterone level [28]. Pye *et al.* estimated that severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the testosterone level and the presence of sexual symptoms contribute independently. Compared with eugonadal men, the multivariable-adjusted risk of mortality was twofold higher in those with testosterone level less than 2.5 ng/ml (irrespective of symptoms; HR 2.3; 95% CI: 1.2-4.2) and threefold higher in those with three sexual symptoms (irrespective of serum testosterone; compared with asymptomatic men; HR 3.2; 95% CI: 1.8-5.8). Similar risks were observed for cardiovascular mortality [29].

Hypogonadism is a generally acknowledged risk factor for osteoporosis, and testosterone substitution is an accepted therapeutic measure for prevention of osteoporosis as well as for improving bone mass in patients with manifest hypogonadism. According to the latest guidelines on osteoporosis from the Endocrine Society, total testosterone measurement is suggested in all men evaluated for osteo-

porosis or considered for pharmacological treatment with bone-active agents [30].

Testosterone deficiency is associated with reduced lean body mass (LM; primarily muscle mass), bone mineral density (BMD), and increased fat mass (FM) with concomitant changes in body composition.

The Massachusetts Male Aging study (15-year follow-up) of 950 healthy, aging men revealed that lower concentrations of total testosterone and SHBG were predictive of the development of metabolic syndrome [31]. In 2009, a new definition of metabolic syndrome was established, with at least three or more criteria required for diagnosis: central obesity, hyperglycaemia (including T2DM), hypertension, hypertriglyceridaemia, and low HDL-cholesterol (HDL-C) [32].

The accumulation of visceral fat as a highly active endocrine organ represents a specific problem, which manifests itself as a complex pathological entity with increased blood pressure as well as disturbed fat metabolism and glucose tolerance, which is known as metabolic syndrome. Visceral fat secretes inflammatory cytokines (adipokines), pro-coagulative substances, and substances which activate the angiotensin-aldosterone system. That is why persons with metabolic syndrome have a threefold increased risk for clinically manifested cardiovascular events and stroke. The risk of developing type 2 diabetes mellitus is increased fivefold [5]. A strong correlation between decreased testosterone levels and increased cardiovascular mortality has been reported in meta-analyses showing that testosterone in the normal range is related moreover to reduced all-cause mortality [33, 34].

In older men with LOH, testosterone replacement therapy (TRT) may present several benefits regarding body composition, metabolic control, and psychological and sexual parameters.

TRT has a beneficial effect on health, manifested by improvement in mood, concentration, sleep quality, physical and mental fitness, increased libido, increased frequency of morning erections and erotic dreams, and improvement of erectile dysfunction and satisfaction with sex life. Randomised trials show a correlation between restored physiological testosterone levels, muscle mass, and strength measured as leg-press strength and quadriceps muscle volume [16, 35]. TRT improves bone mineral density at the lumbar spine and femoral neck [36]. Body composition is influenced by TRT in hypogonadal men, with a consequent decrease of fat mass and an increase in lean body mass [37]. TRT has positive effects on glycaemia and lipid profile, and it decreases insulin resistance and visceral adiposity in hypogonadal men with impaired glucose tolerance and lipid profile, with a consequent decrease of mortality [38].

## Conclusions

With larger numbers of people reaching advanced age, the health problems as well as social and psychological problems of older men play an increasingly important role in clinical medicine and research. It should be remembered that testosterone therapy may improve their lives.

## Disclosure

Authors report no conflict of interest.

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