PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B, Vol. 64 (2010), No. 3/4 (668/669), pp. 93–97.
DOI: 10.2478/v10046-010-0028-3

Review

LATE-ONSET HYPOGONADISM: REVIEW OF THE PROBLEM

Anatolijs Požarskis and Juris Ērenpreiss

Rīga Stradiņš University, Dzirciema iela 16, Rīga, LV-1007, LATVIA
E-mail: drpozarskis@inbox.lv

Communicated by Viesturs Baumanis

The study investigates late-onset hypogonadism (LOH), its influence on male joint system, build, cardiovascular system, haematopoesis, cognitive functions, and sexual function. LOH is a clinical and biochemical syndrome, which is related to aging and characterised by typical symptoms and a decreased serum testosterone level. It causes a worsened life quality, and the functions of various organs are badly affected. LOH is diagnosed when the testosterone level is below 8 nmol/l (230 ng/dl) or it is at the border-line (from 8 and 12 nmol/l) and there are LOH clinical symptoms such as a decreased libido, erectile dysfunction, reduced muscular mass and strength, increased obesity, reduced bone mineral density, osteoporosis, and depression. All patients with LOH are indicated testosterone replacement therapy (TRT). TRT is contra-indicated to patients suffering from prostate or thoracic gland carcinoma. In case of erythrocytosis (haematocrit > 52%), severe heart failure, marked prostate benign hyperplasia with the obstruction of urine pathways, and obstructive sleep apnoe syndrome, TRT is relatively contra-indicated and should not be started unless these dysfunctions are cured. The treatment of LOH requires thorough patient monitoring, which includes digital rectal examination and Prostate Specific Antigen conducted after 3–6 months and 12 months in the first treatment year. It is necessary to determine the total blood count after 3–4 and 12 months in the first treatment year and afterwards once a year.

Key words: *late-onset hypogonadism, testosterone deficiency, testosterone replacement, contra-indications.*

INTRODUCTION

The number of elderly people is constantly growing world wide and it will grow in the future. In 2006, 10% of the population was over 60 years old, and in 2050, the proportion will reach 21%. The male longevity is less than of a female. In Latvia the human longevity is one of the lowest in Europe — 67 years (Anonymous, 2007). In recent years, there have been a lot of investigations on age-related sexual hormone changes in men. Women are known to have a menopause sooner or later when the ovaries stop producing estrogens. In men when they get older the secretion of testosterone reduces, but the level of changes is very individual and not all men fall below the physiological norm. If, however, testosterone is deficient, pathological changes in men cause the development of various chronic diseases and also lower the quality of life.

The problem we are investigating is closely related to the necessity to improve the quality of life in men after the age of 40.

PATHOLOGICAL PHYSIOLOGY, DEFINITION

During aging, the number of Leyding cells that secrete testosterone is reduced in the testicles. Men aged 50–70 have 40% less Leyding cells than men at the age of 20–30 and its volume also falls to 40% (Neaves *et al*., 1984). Experiments on animals prove that the enzyme secretion that takes part in testosterone synthesis was reduced in aging rats (Gooren, 2009). Pathological changes are seen in the hypothalamic-hypophyseal axis: the normal release of free gonadotrope hormone and its supply to the hypothalumus is affected. As a result, secretion of this luteinizing hormone (LH) also changes, characterised by a higher frequency but lower amplitude, which influences testosterone synthesis in the testicles. With age, the synthesis of other kinds of hormones is also affected. Melatonin secretion is reduced, which causes sleep disorders in elderly men. Somatotropic hormone secretion is also reduced. Although the secretion of insulin is not affected, the tissue susceptibility to insulin is reduced with age. However, the cortisol level is not reduced (Gooren, 2009).

Testosterone includes free testosterone (1–3%), albumin-bound testosterone (40–50%) and sex hormone binding globulin (SHBG) bound testosterone (50–60%). The former testosterone fractions are active (bio-accessible), and the latter is inactive. After the age of 40, the level of free testosterone declines by 2.8% on average every year. The total testosterone level reduces by 1.6%, the level of albumin-bound testosterone by 2.5%, but the level of SHBG in-

creases by 1.3% a year (Feldman *et al*., 2002). In general, this level of physiological testosterone does not cause any problems. The problems appear when the testosterone level falls below the physiological norm. Pathologic reduction of testosterone level occurs due to chronic diseases (such as coronary heart disease, diabetes mellitus, metabolic syndrome, etc.) and/or inappropriate lifestyle (sedentary lifestyle, adiposity). A complex of symptoms, which develop in these cases is termed 'late-onset hypogonadism' (LOH). Actually, this is accelerated, but not physiological, aging.

Thus collectively, LOH is an age-related clinical and biochemical syndrome, which can be characterised by typical symptoms and a reduced level of serum testosterone. As a result, the LOH causes life quality to worsen and negatively affects functions of various organs (Morales and Lunenfeld, 2002).

Regarding pathogenesis, LOH is considered as mixed origin hypogonadism, and includes mechanisms of both primary and secondary hypogonadism. Primary mechanisms include the decrease of the testosterone production in testes due to the involution of Leidig cells. Secondary mechanisms include decreased secretion of the gonadotrophin releasing hormone by the hypothalamus, and more frequent but irregular luteinizing hormone pulses with lower amplitude. Therefore, the assessment of the gonadotropic hormones is recommended to determine the effect on to pituitary function in LOH males.

Testosterone-related organs are brain, cardiovascular system, muscles, adrenals, liver, penis and prostate. LOH symptoms are non-specific and depend on the male's age, disease history as well as the degree and length of testosterone deficiency. Nevertheless, LOH is known to cause changes in most male organism systems.

LOH AND BONE DENSITY

Androgens regulate muscle mass and body build by affecting bone mineral density. Most investigations have indicated the presence of androgen receptors in osteoblasts, osteoclasts, osteocytes, and chondrocytes. Experimental *in vitro* studies show that androgen influences osteoblast proliferation, differentiation and mineralisation, as well as production of various cytokins, such as IGF-1, an autocrine-paracrine regulator of sexual steroid anabolic effect. Androgens inhibit osteoclastogenesis and bone resorption and stimulate bone formation by increasing periostal synthesis (Isidori *et al*., 2005). Due to LOH, bone mineral density decreases leading to osteoporosis. The reduction of bone mineral density increases risk of bone fractures. Hypogonadism in elderly men is related to increased fracture risk (Boonen *et al*., 1997; Stanley *et al*., 1991). In a study performed in USA, which included 78 men with femoral fractures at the age over 65 years, who received medical care at home, it was found that femoral fractures were four times more frequent in men suffering from hypogonadism (Boonen *et al*., 1997; Stanley *et al*., 1991). Also, vice versa, analysing 110 men with osteoporosis and 106 with normal bone mineral density, Brazilian researchers observed that 25% men with osteoporosis and only 12.2 % men with normal bone mineral density had hypogonadism (Clapauch *et al*., 2008). Testosterone replacement therapy (TRT) is effective in men with hypogonadism: it increases bone mineral density especially in the vertebrae lumbale, where fractures are most frerquent in cases of osteoporosis (Isidori *et al*., 2005).

LOH AND BODY BUILD

LOH causes changes in male body build by decreased muscular mass and strength (Morley *et al.*, 2001). This makes elderly people dependent on others: when muscular strength decreases, it is difficult for the people to carry out daily activities. Muscular regression occurs in 13.5% of people aged over 70, and reaches 29% incidence at the age over 80 (Morley *et al.*, 2001). Testosterone, dihydrotestosterone and somatotropic hormone play an important part in the development of muscle deficiency. TRT in elderly men increases muscular mass and decreases adiposity.

Visceral adiposity tends to increase in patients with LOH, and is an independent risk factor for insulin resistance and cardiovascular disease. Adiposity is one of the most wide spread chronic diseases today affecting 9–30% of adults globally (Butrova, 1999). Adiposity not only increases fat amount in the organism, but also influences its distribution in different body parts. It is considered that increased fat accumulation in the abdominal region is an independent risk factor for insulin resistance and type-2 diabetes. In clinical practice abdominal obesity is diagnosed when the waist is over 94 cm in males and over 80 cm in females. Computer tomography and magnetic resonance methods have demonstrated two kinds of obesity: subcutaneous abdominal and visceral (in organs). Visceral-type adiposity is associated with the highest risk of complications. Etiology of visceral adiposity leads to genetically predisposed inactive lifestyles. Sedentary lifestyle as well as the excessive use of fats and carbohydrates in the diet leads to the excessive fat accumulation in the abdomen region, which in turn causes insulin resistance and hyperinsulinemia, the predictor of type-2 diabetes. In addition, excessive visceral adipose tissue accumulation is related to the atherogenic lipid profile: hypertriglycerydemia and increased level of apolipoprotein B. Changes in the thrombolytic system occur, increasing the risk of thrombosis (Butrova, 1999). The factors mentioned above lead to increased incidence of cardiovascular disorders (Fox *et al*., 2009; Ho *et al*., 2009).

In the case of abdominal adiposity, the insulin resistance is associated with compensatory hyperinsulinemia (Butrova, 1999). In recent years, it was discovered that adipose tissues, which carry out endocrine and paracrine functions, produce biologically active substances that influence tissue susceptibility to insulin. Enlarged adipocytes manufacture a great amount of cytokines, particularly TNF-α and leptin. TNF-α affects insulin interaction with receptors and also increases intercellular glucose transport. In liver leptin re-

duces the action of insulin and also possesses autocrine action increasing transport of glucose by insulin stimulation. Intensive lipolysis in visceral adipocytes releases free lipoic acid (FLA) into the portal system and liver, where under the influence of FLA binding of insulin with hepatocytes becomes disrupted. The clearance of metabolic insulin in liver becomes affected, causing systemic hyperinsulinemia. In turn, hyperinsulinemia strengthens insulin resistance in muscles due to impairment of the autoregulation of insulin receptor. FLA is also a substrate for triglyceride secretion and its increased concentration causes triglycerydemia. As a result, the so-called metabolic syndrome develops, which includes insulin resistance, abdominal obesity, and arterial hypertension (Butrova, 1999). Its development considerably increases risk of cardiovascular diseases and their complications. The use of testosterone medicine reduces the amount of fats in the organism and adiposity in men with hypogonadism (Kapoor *et al*., 2006). Therefore, the risk of cardiovascular disease should be also reduced (Morales and Lunenfeld, 2002; Kapoor *et al*., 2006). The use of testosterone for 12 month in men with hypogonadism and angina pectoris was shown to increase time to ischemia, decreased body mass index and triglyceride level (Mathur *et al*., 2009). The underlying mechanism has been investigated in various small-range studies but large-range research is still required (Morales and Lunenfeld, 2002; Sarkar, 2009)

LOH AND THE CARDIOVASCULAR SYSTEM

In recent years, there has been increased interest in the action of androgens on the cardiovascular system (CVS) and atherosclerosis development. Androgen receptors are found in the endothelial and smooth muscular cells of blood vessels. Endothelial cells become activated if the blood-vessels are damaged and this favours the formation of atherosclerotic plaque. However, androgens have impact on this process. Testosterone affects vasoconstriction and vasodilatation and nitric oxide (NO) synthesis. Generally, testosterone reduces endothelial dysfunction and promotes the decrease of vasospasm of coronary blood vessels, rupture of atherosclerotic plaque and thrombosis (Isidori *et al*., 2005). Studies show that there is negative correlation between the level of endogenous androgen and development of atherosclerosis (Manolakou *et al*., 2009). Castrated animals fed by cholesterol had faster atherosclerosis progression, which was reduced with the onset of testosterone replacement therapy (Netteship *et al*., 2009) The testosterone level is inversely proportional to atherosclerosis risk in elderly men (Hak *et al*., 2002). Men with stenosis of at least 75% of one coronary artery had a lower testosterone level than men without coronary stenosis. 50% of men with stenosis have a hypogonadal bioactive testosterone level (Phillips *et al*., 1994). Several studies have investigated the effect of TRT on CVS and cardiovascular risk. Jaffe (1977) observed that testosterone therapy reduced ST depression, shown on an electrocardiogram, by 32% after four weeks and by 51% after eight weeks of treatment, compared with placebo controlo. Webb and his co-authors (1999) showed that infusion of a supraphysiological dose of testosterone into the coronary artery significantly increased the diameter of the coronary and brachial arteries and increased blood flow. Various studies with placebo controls have shown that TRT improves subjective state of the patients with cardiovascular disease and objective criteria as well. Therefore, the TRT is recommended to patients with testosterone deficiency and cardiovascular diseases if there are no contraindications.

LOH AND THE COGNITIVE FUNCTION

As a consequence of LOH, male cognitive function worsens: poor memory, concentration power and dementia signs. The level of plasma testosterone is lower in patients with Alzheimer disease than in healthy men. The number of depressive cases increases in elderly men. Although cases of major depression are not observed very often, one of the most common diseases at that age is dysthimia. Men with dysthimia have a lower testosterone level than healthy men (Schweiger *et al*., 1999). In studies on men who underwent chemical castration to prostate cancer, concentration and memory worsened. Studies examining the correlation between the level of testosterone in serum and cognitive functions are contradictory, but they do tend to suggest that a decrease of the level of endogenous testosterone causes reduction of cognitive ability in the elderly men (Beauchet, 2006). Randomised placebo controlled studies show that TRT tends to be fairly effective in relation to different cognitive functions both in hypogonadal and eigonodal elderly men. Similar results were obtained in men with Alzheimer disease and mild cognitive impairment. However, these studies involved small cohorts of patients and possessed different structure and methodology. Therefore, to make more definite conclusions on the TRT action on the cognitive functions, further research in larger populations is necessary (Beauchet, 2006).

LOH AND HAEMATOPOESIS

LOH causes changes in haematopoesis. The haemoglobin level is known to decrease with age. In elderly men the level of endogenous testosterone is correlated with the level of haemoglobin. In a study on elderly men, haematokrit was observed to have 39.9% incidence in hypogonadal and 45.6% in eigonadal men (Ellegala *et al*., 2003). Grossman with co-authors (2009) investigated 464 men with type-2 diabetes and found a lower testosterone level to be associated with anaemia. Similarly, in the investigation of 492 healthy men testosterone concentration was found to affect the haemoglobin level in men of different age groups (Yeap *et al.,* 2008). There is little data in the literature on the effect of TRT on the haemoglobin level in hypogonadal men. In a study on 40 patients with kidney insufficiency, who underwent haemodialysis, interaction of TRT with erythropoetin (a medicine for treating anaemia) was not found (Brockenbrough *et al*., 2006). Further thorough studies are necessary to investigate the action of TRT on haematopoesis.

LOH AND THE SEXUAL FUNCTION

LOH reduces the male sexual function. Adequate sexual function has an important role in an elderly male's life. The longer his sexual life is, the longer he feels glad, perfect and optimistic. An adequate sexual life is known to maintain both physical and mental health in a good state. When a person gets older, his libido decreases, while the frequency of erectile dysfunction increases. A reduced testosterone level is associated with a reduced libido. To restore normal libido, it is necessary to obtain a normal testosterone level (Davidson *et al*., 1983). There is no precise data on the influence of the testosterone level on erectile function. Some publications mention that LOH influences only libido (Zitzman and Nieschlag, 2003). Other publications suggest that, as a result of TAT, erectile function decreases in more than 50% of cases (Yassin and Saad, 2007). It was also shown that almost all men have increased libido. In guidelines on the treatment of LOH, it is mentioned that men, both with decreased libido and/or erectile dysfunction and reduced testosterone level, are recommended to undergo TRT.

LOH TREATMENT

Taking into account the negative influence of LOH on different organs and system functions, it is important to know in which cases and how this syndrome should be treated.

According to the International Society for the Study of the Aging Males, the published guidelines of the year 2009 (Wang *et al*., 2009) recommend LOH diagnosis that should be based on clinical symptoms (such as decreased libido, erectile dysfunction, reduced muscular mass and strength, increased fat accumulation in the body, reduced bone mineral density, osteoporosis, depression) and confirmed by laboratory tests showing deficiency of the total or free testosterone. Testosterone deficiency needs to be confirmed by laboratory studies repeatedly.

Serum samples for the testosterone indication must be used from 7 to 11 a.m. If the total testosterone level is over 12 nmol/l (350 ng/dl), testosterone replacement therapy is not necessary. If the testosterone level is below 8 nmol/l (230 ng/dl), TRT is indicated. If the testosterone level is at a border-line level (from 8 to 12 nmol/l), individual solution is necessary considering both clinical symptoms and possible treatment outcome and risks. For TRT indication, the level of free testosterone is not precisely defined. It is considered that if the free testosterone concentration is < 225 pmol/l (65 pg/ml), TRT indication can be considered.

TRT is absolutely contra-indicated if a man suffers from prostate or thoracic gland carcinoma. In cases of erythrocytosis (haematocrit > 52%), severe heart failure, marked prostate benign hyperplasia with the obstruction of urine pathways, obstructive sleep apnoe syndrome, TRT is relatively contra-indicated and can be started after treatment. When LOH is being treated, thorough patient monitoring is required, including digital rectal examination (DRE) and prostate-specific antigen (PSA), which should be performed at 3–6 months and 12 months in the first treatment year. If treatment is being continued, PSA should be estimated once a year. TRT is not considered to cause development of prostate cancer, but it can promote growth of an existing carcinoma. As prostate carcinoma has a high metastasis risk already at the first stage of disease, it is necessary to perform DRE and determine the PSA level in blood at least once every six months.

Erythrocytosis is described as a side-effect of the TRT. Therefore, it is necessary to measure total blood count at 3–4 and 12 months in the first treatment year, and subsequently, once a year.

CONCLUSION

LOH is a syndrome that causes serious impairment in the male organism. To diagnose LOH, confirmation of clinical symptoms and laboratory studies is needed. Before starting testosterone replacement therapy, it is necessary to consider possible outcome and risk and to inform the patient about the advantages of the TRT and its possible side-effects. If the TRT course has no regression of the symptoms, the cause of the existing symptoms should be considered. As male's average lifespan is very low in Latvia, it is necessary to develop and introduce into clinical practice a screening diagnostic algorithm of LOH for males after the age of 40.

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Received 22 October 2009

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VĒLĪNI SĀCIES HIPOGONĀDISMS: PROBLĒMAS APSKATS

Rakstā aplūkota vēlīni sākuša hipogonādisma (VSH) problēma. VSH ir klīnisks un bioķīmisks sindroms, kas saistīts ar novecošanos un raksturojas ar tipiskiem simptomiem un samazinātu seruma testosterona līmeni. Tā rezultātā pasliktinās dzīves kvalitāte un tiek negatīvi ietekmētas dažādu orgānu funkcijas. VSH diagnosticē, ja testosterona līmenis ir zem 8 nmol/l (230 ng/dl) vai testosterons atrodas robežlīmenī (no 8 līdz 12 nmol/l) un ir VSH kīniskie simptomi (samazināts libido, erektilā disfunkcija, samazināta muskuļu masa un spēks, paaugstināts tauku uzkrājums ķermenī, pazemināts kaulu minerālblīvums, osteoporoze, depresija). VSH pacientiem indicēta testosteronaizvietojošā terapija.