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## Aging and the endocrine system

### Starzenie i układ endokryny

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#### INTRODUCTION

Biological aging is characterized by the progressive deterioration of the function of all tissues and organs, leading to the loss of ability to restore homeostasis under stressful conditions and, consequently, to the increased risk of development of aging-related diseases. This phenomenon also affects the neuroendocrine function of hypothalamus-pituitary axis, as well as influ-

#### S u m m a r y

Biological aging is characterized by the progressive deterioration of the function of all tissues and organs. As a consequence of aging, rhythm, sequence, and amount of majority of the hormones secreted by the hypothalamus, pituitary, as well as by the peripheral endocrine cells and organs significantly change. For example, the secretion of melatonin, growth hormone, sex hormones, dehydroepiandrosterone and of other numerous hormones decreases, while the secretion of TSH and cortisol may increase in aging individuals, including those who age successfully (without disease). This in turn results in worsening of the adverse effects of aging. Some aging-related hormonal changes however might play a protective role in aging; for example, low-normal or slightly decreased activity of the pituitary-thyroid axis in the elderly seems to be associated with longer survival and better health.

Notably, since in the elderly signs and symptoms can be atypical and similar regardless of their etiology, it is sometimes difficult to distinguish the effects of aging *per se* from these caused by diseases.

#### S t r e s z c z e n i e

Starzenie charakteryzuje się stopniowym pogarszaniem funkcji wszystkich tkanek i narządów. Wskutek starzenia znacząco zmieniają się rytm i sekwencja wydzielania oraz ilość większości hormonów produkowanych przez podwzgórze, przysadkę oraz obwodowe komórki i narządy endokryne. Na przykład, znamienne zmniejszeniu ulega wydzielanie melatoniny, hormonu wzrostu, hormonów płciowych, dehydroepiandrosteronu oraz licznych innych hormonów, podczas gdy wydzielanie TSH i kortyzolu może się z wiekiem zwiększyć, również u osób, które starzeją się pomyślnie (bez chorób). To z kolei zwykle pogarsza niekorzystne skutki starzenia. Niektóre związane ze starzeniem zmiany hormonalne mogą jednak odgrywać rolę ochronną, np. niska (prawidłowa) lub nieznacznie obniżona aktywność osi przysadkowo-tarczycowej u osób starszych wydaje się być powiązana z dłuższym przeżyciem i lepszym stanem zdrowia.

Co istotne, ponieważ u osób starszych objawy mogą być nietypowe i do siebie podobne mimo różnej etiologii, niekiedy trudno jest odróżnić skutki starzenia jako takiego od skutków spowodowanych występowaniem chorób.

ences the structure and function of peripheral endocrine organs. Aging is also accompanied by changes in the number and sensitivity of receptors that may change the responsiveness of target tissues to hormones and neurotransmitters. However, it is sometimes difficult to distinguish the effects of aging *per se* on endocrine physiology from these caused by diseases since their signs and symptoms might overlap. In addition, signs

and symptoms of endocrine disorders in the elderly can be poorly expressed and atypical (1). In this review we present basic concepts regarding pathophysiology of some endocrine dysfunctions in elderly patients, as well as brief guidelines regarding diagnosis and treatment of these conditions.

## MELATONIN

**In the second decade of life nocturnal peak of melatonin secretion starts to decline, and in the eighth decade of life it is usually less than a quarter of this observed in young adults; moreover, in some individuals peak secretion might be completely absent. This phenomenon may reflect the progressive, aging-related calcification of the pineal gland causing loss of secretory tissue; however, there is no direct relationship between the extent of gland calcification and hormone secretion (2).** Loss of nocturnal secretory pulse most possibly contributes to the high prevalence of disturbances of the circadian rhythm and other physiological rhythms. Melatonin supplementation is therefore considered an efficient treatment for individuals with serious age-related sleep disturbances; it is usually inefficient however in patients with mild sleep problems. A starting dose for most elderly adults is as low as 0.3 mg taken 1 hour before or at bedtime. If after a week of treatment situation does not change, the dose should be doubled or increased further; in some patients the effective daily dose can be as high as 5 mg. Alternatively, the patient can take a second dose if he/she is still not asleep 10-15 minutes after waking up at night (3). The data regarding the use of melatonin as a treatment in elderly patients with cognitive impairment associated with dementia are not consistent; nevertheless, in some patients suffering from Alzheimer's disease, administration of melatonin may reduce hyperactivity in the evening and at night (4).

## GROWTH HORMONE

**Aging is accompanied by a gradual impairment of growth hormone (GH) secretion and a parallel decrease in serum levels of insulin-like growth factor-1 (IGF-1); daily GH secretion in old individuals might be only 5-10% of its secretion in young adults. This is a consequence of the aging-associated decrease in hypothalamic GH-releasing hormone (GHRH) baseline secretion and subsequent decrease of pituitary responsiveness to GHRH, as well as of age-related changes in somatotrope secretory function, and of the lifestyle (lower physical activity and sleep disturbances) (5).**

The clinical picture of "physiological", aging-associated GH deficiency includes the decrease of lean body mass and bone mineral density and the increase of adipose tissue mass (especially within abdominal cavity), all leading to the increased rate of metabolic disturbances, cardiovascular disease, fractures, and mortality. Encouraging results of GH replacement therapy in children suffering from GH axis insufficiency lend sup-

port to the concept of its use in the elderly to combat aging-related changes in body composition, muscle strength, bone mineral density, as well as to increase the quality of life. Indeed, it was shown in randomized trials, that the recombinant human GH (rhGH) replacement therapy in the elderly resulted in the increase in lean body mass and in quality of life; however, such beneficial effect was accompanied by a number of significant side effects such as glucose intolerance or diabetes, edema, carpal tunnel syndrome and arthralgias. In addition, genetic and functional studies performed in animal models, as well as association studies in humans, strongly suggest that lower activity of the IGF-1 axis is associated with longer life, while IGF-1 excess might promote neogenesis (6). Therefore, nowadays the rhGH treatment is recommended only for patients with GH deficiency that is not associated with aging, and should not be used as an element of anti-aging treatment, unless aging is accompanied by diseases such as sarcopenia, in which the administration of GH can provide therapeutic benefits (7).

## THYROID HORMONES

**Aging per se is not associated with a significant change in the size of the thyroid, but the density of this gland increases. The uptake of iodine remains unchanged or slightly decreases. Healthy aging is characterized by the increase of thyroid stimulating hormone (TSH) secretion and serum concentration, a slight decrease of triiodothyronine (T3) and free T3 (fT3) concentrations and an increase of reverse T3 (rT3) levels. Thyroxin (T4) synthesis also decreases with age; however, since its half-life time in circulation is increased, the levels of T4 and free T4 (fT4) remain unchanged. The lowest activity of the thyroid hormone axis was observed in centenarians, which is consistent with numerous data indicating that low-normal or subclinical thyroid insufficiency in elderly and long-lived individuals is associated with a longer survival and with a better health (8).**

The percentage of individuals with anti-thyroperoxidase and anti-thyroglobulin antibodies significantly increases with age until the ninth decade of life and decreases thereafter. Aging is also associated with the increasing incidence of thyroid diseases. Notably, their clinical manifestations are less pronounced compared to younger individuals and the symptoms are frequently incorrectly attributed to aging. Elderly patients are often treated with drugs that disrupt the function of the thyroid axis. Therefore, in case of biochemical abnormalities but without clear symptoms, blood analysis should be repeated, and patient's health status and treatment should be reviewed (9).

It is estimated that after the age of 60, subclinical hypothyroidism may affect up to 20% of women and up to 8% men (it should be remembered though, as mentioned above, that it might be only a sign of natural thyroid aging), while clinically overt symptoms: fatigue, cognitive impairment, depression and metabolic

complications, are present only in approximately 5% of elderly individuals. Overt hypothyroidism or subclinical hypothyroidism with TSH levels  $> 10 \mu\text{IU/ml}$  should be treated according to the generally accepted protocols, initially with  $12.5 \mu\text{g}$  of levothyroxine per day, a dose that can be doubled after 2 weeks and further increased every 2-4 weeks until the target TSH level is achieved. This varies depending on age: for individuals under the age of 70 years, the recommended TSH concentration is  $2.5\text{-}3.5 \mu\text{IU/ml}$ , while for those over 70 years –  $4\text{-}5 \mu\text{IU/ml}$ . Treatment of elderly individuals with subclinical hypothyroidism and TSH level below  $10 \mu\text{IU/ml}$  is a subject to individual decision. Since epidemiological studies have not confirmed its association with cognitive impairment, depression, or increased overall mortality, it is suggested that in individuals free of hypothyroidism symptoms and in relatively good health, hormone supplementation is not necessary but the patient should be monitored so as not to miss the appearance of the symptoms indicating the need for treatment (10).

Both subclinical and overt hyperthyroidism are also more common in the elderly, affecting up to 6% and to 0.5-3% of the population over 60 years, respectively; however, the diagnosis is less apparent due to lack of the characteristic hypermetabolic symptoms which are usually replaced by fatigue, muscle weakness, atrial arrhythmias, weight loss, or accelerated bone loss. It was shown in most epidemiological studies that both subclinical and overt hyperthyroidism may lead to the increased risk of total and cardiovascular mortality in patients over 65 years old and, therefore, should be treated in each case. The etiology of hyperthyroidism in the elderly does not differ significantly compared to younger individuals and is usually associated with Graves' disease (GD). On the other hand, toxic adenoma, toxic multinodular goiter and iodine-induced hyperthyroidism (after administration of contrast agents or iodine-rich drugs such as amiodarone) are more common in the elderly than in young patients. The diagnostics of hyperthyroidism in the elderly is the same as in younger age groups, but the treatment might be slightly different. In elderly patients with GD there is a good chance of achieving remission with prolonged (up to 24 months) pharmacological treatment. The initial dose of methimazole should not exceed  $30 \text{ mg/day}$  (notably, due to its hepatotoxicity, propylthiouracil is not routinely recommended for treatment of hyperthyroidism). In patients with thyroid autonomy, surgery and radioiodine administration are the most effective treatment options. In these patients, methimazole is often used to treat hyperthyroidism before implementation of radical therapy and one should remember that it does not induce permanent remission and discontinuation leads to relapse of the disease. However, in elderly patients with increased surgical risk and/or inability to comply with radiation safety guidelines, long-term treatment with thionamides is an option to consider (11).

**The prevalence of thyroid nodules and of all types of thyroid neoplasms increases with age. Although both papillary and follicular thyroid carcinomas are more common in women, the female-to-male ratio declines in the elderly and males are at higher risk of more aggressive forms of thyroid cancer. In older patients, sporadic medullary thyroid carcinoma is also more frequent.** Age is a strong negative predictor in prognosis of the anaplastic (undifferentiated) thyroid carcinoma, and by the time of diagnosis most patients have widespread local invasion and distant metastases. The diagnosis and treatment of thyroid cancers in the elderly are typical and the only difference is the rate of TSH suppression after radical treatment: in the elderly suppression can be less strict (12).

### VITAMIN D AND PARATHORMONE

**Calcium dysregulation observed in the elderly of both sexes results from the decreased dietary intake of this ion due to poorly balanced diet, reduced absorption in the intestine, as well as its impaired renal reuptake. Age-related hypocalcaemia is severely aggravated by the commonly co-existing vitamin D deficiency. This in turn results from insufficient dietary intake, decreased synthesis of vitamin D precursor in the skin, impaired renal metabolism leading to a decreased conversion of the precursor to the active form of vitamin, and, most likely, from age-related receptor resistance. Vitamin D deficiency in the elderly contributes to osteoporosis, falls and to the increased low-energy fracture risk. It is also associated with higher prevalence of metabolic syndrome, cardiovascular disease, declining muscle strength and sarcopenia, lower physical function and, possibly, with the increased risk of several cancers** (13). Therefore, vitamin D supplementation is recommended to all elderly individuals regardless of the season at the dose of at least 1000 IU per day and up to 4000 IU (temporarily even higher) depending on the level of insufficiency, time of the year, coexisting diseases, etc.). Target 25-hydroxycholecalciferol ( $25\text{OH-D}_3$ ) level in serum of elderly person should be  $80\text{-}100 \text{ nmol/l}$ . The prescribed medication should contain only vitamin D; medications containing both vitamin D and calcium are not recommended since the vitamin content is commonly lower than declared or bioavailability of the vitamin is reduced. Dietary intake of calcium should be  $1000\text{-}2000 \text{ mg}$ . **Age-related hypocalcaemia leads to the compensatory increase of parathormone release and, subsequently, to the secondary hyperparathyroidism with its clinical consequences. Proper supplementation of both vitamin D and calcium can significantly decrease PTH level** (14).

### CORTISOL

Aging is associated with a variable changes in corticotropin (ACTH) and cortisol secretion and their mutual relationship. Some epidemiological studies suggest that the mean 24-hour serum cortisol concentrations are 20 to 50% higher in the elderly compared to young

individuals; however, such a view is not unanimous since others suggest that cortisol levels remain stable during aging. The response to stress measured by cortisol levels is prolonged. All these changes may hinder the diagnosis of hypercortisolism. It is believed that age-related changes in cortisol secretion do not impair the response of pituitary-adrenal axis in acute stress (e.g. illness); however, prolonged age-related hypercortisolism may effect in insomnia, impaired cognitive function, lower bone density, as well as an increased number of fractures and unfavorable changes in body composition (15, 16).

### ALDOSTERONE

Aldosterone secretion declines with age as a result of decreased rennin synthesis, and its concentrations in the eighth decade of life may constitute only 50% of this observed in young individuals. It can result in the increased urinary sodium wasting and hyponatremia. These changes can be also aggravated by co-existing increased serum concentrations of the atrial natriuretic peptide and hinder the diagnosis of primary aldosteronism in the elderly. Severe symptoms should be adequately treated (17).

### DEHYDROEPIANDROSTERONE

**Dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) are precursors of active androgens and estrogens. Their secretion and serum concentrations reach their maximum in the third decade of life and decrease significantly thereafter, so that in the eight decade of life they constitute only 5-20% of those observed in the young. Since a higher serum concentrations of DHEA and DHEA-S seem to be associated with better health and with longevity, it was speculated that administration of DHEA might reverse some age-related changes in body composition and function (18).** However, a placebo-controlled trial in which DHEA was administered for 2 years to healthy elderly men and women in dosages sufficient to increase its serum levels to these typical for young subjects, showed no improvement in body composition, oxygen consumption, muscle strength, or insulin sensitivity. Similarly, systematic reviews of the literature revealed that DHEA or DHEA-S supplementation does not improve cognitive performance in older adults (19, 20). In conclusion, even though DHEA and DHEA-S concentrations can be considered as markers of biological aging, the current view is that their administration to the elderly has no proven benefits and may result in signs of hyperandrogenism in women.

### ESTROGEN

The age-dependent decline in ovarian function may be partly caused by changes in the quantity, quality or in the secretion pattern of the hypothalamic and pituitary hormones, and/or a primary loss of ovarian responsiveness to these hormones. Other researchers claim that menopause is primarily a result of aging

of the ovary itself. The final menstrual period is determined retrospectively; twelve months of amenorrhea in women above 45 years old is equivalent to clinical menopause and reflects ovarian follicular depletion. Early serum markers of menopause include anti-müllerian hormone (AMH) and inhibin B, which concentrations decline with age (and reflect follicular decline) causing the rise of follicle-stimulating hormone (FSH) concentration (21). **It should be remembered that although ovarian function declines after the menopause, they remain hormonally active producing small amounts of estradiol (E2), estrone (E1) and DHEA.**

The average age of the last menstrual period in Poland is 51 years (22). The timing of menopause is affected by a number of factors including genetics, ethnicity, smoking and reproductive history. **Family history of early menopause represents a risk factor, and genome-wide association studies identified a number of regions associated with the age of menopause. Smoking accelerates the occurrence of menopause by about two years.**

The early phase of menopause is characterized by irregular menses with normal or high E2 levels, but with low luteal phase progesterone concentrations. Over time menstruation irregularity increases and FSH and E2 serum levels fluctuate strikingly. The serum FSH concentrations increase to about 70-100 IU/l over several postmenopausal years, to finally decline by 40% during the last 30 years of life. In postmenopausal women, E2 serum levels remain low, about 5-20 pg/ml. A predominant estrogen after menopause transition is estrone.

**Menopause is characterized by several symptoms affecting women's quality of life and include hot flashes, sleep and mood disorders, as well as urogenital complains (23).** In addition, hormone-dependent changes in lipid metabolism and bone loss have implications for long-term health. The hallmark symptom of menopause are hot flashes (also called "vasomotor symptoms"), occurring in up to 80 percent of women. The symptoms begin as a sudden sensation of heat centered in the chest and in the face, rapidly generalized and lasting for 2-4 minutes. Hot flashes are often associated with intense perspiration and occasionally with palpitations, sometimes followed by chills, shivering and anxiety. They occur several times per day, commonly at night. Hot flashes result from the dysfunction of "thermoneutral zone" in hypothalamus due to estrogen withdrawal, and represent inappropriate peripheral vasodilatation. Anxiety, depression and cognitive changes may arise directly from estrogen depletion. Mood changes and vaginal dryness resulting in dyspareunia can lead to sexual dysfunction. Joint aches, breast pain, aggravation of migraines, weight gain or unfavorable skin changes are common ailments of menopausal women. Long-term deficiency of estrogen causes also a number of effects seriously deteriorating health status of postmenopausal women, including osteoporosis and cardiovascular disease (CVD). The onset of bone loss

is closely tied to estrogen deficiency and begins during the menopausal transition. Between the menopause and the age of 75 years, women lose approximately 20% of their bone mass and it has been estimated that about 8% of this is due to estrogen deprivation. CVD after menopause is mainly caused by unfavorable changes in lipid profile (increase in low density lipoproteins concentration) and by the lack of vasodilatory effect of estrogens. Since the prevalence of chronic heart disease is low in premenopausal women and increases rapidly after natural menopause, the postmenopausal state is considered a risk factor of CVD. Recognition of menopause-related estrogen deficiency as a one of CVD risk factors is an important argument in decision-making on hormonal replacement therapy (HRT) in peri/postmenopausal women.

HRT was commonly prescribed in the second half of the 20<sup>th</sup> century. However, results of the Heart and Estrogen/Progestin Replacement Study (HERS) (24) and of the Women's Health Initiative (WHI) study raised doubts about its safety (25). Last 10 years brought about numerous data on this issue and a large part of the research did not confirm the highly alarmist information from these studies. In 2014, the Polish Menopause and Andropause Society Management presented up-to-date recommendations concerning HRT use, based on a core consensus statement prepared in 2013 by international organizations operating in the field of women's health (26). According to these recommendations (27), due to the possible adverse effects, systemic HRT should be used only by women without contraindications, and at the lowest effective doses in order to alleviate vasomotor symptoms, prevent osteoporosis and prevent other systemic disorders associated with estrogen deficiency which prevalence increases in the postmenopausal period. Absolute contraindications to HRT include pregnancy, undiagnosed abnormal uterine bleeding, high risk of venous thromboembolism, inadequate controlled hypertension, history of myocardial infarction or cerebral stroke, unstable coronary disease, liver failure or active liver disease and estrogen-dependent cancer. A contraindication to progestin therapy is meningioma. The dose and duration of HRT should be consistent with treatment goals, patient priorities and safety issues, and should be individualized. The accepted standard systemic dose is 2 mg of E<sub>2</sub> for oral administration and 50 µg for transdermal administration, while 1 mg/25–37.5 µg and 0.5 mg/14 µg represent the low and the ultra-low dosages, respectively. The therapeutic dose depends on efficacy in elimination of menopausal symptoms and is usually higher in younger women. HRT consisting of estrogen and progestin in sequential or continuous regimen, independently of the route of their administration, should be prescribed to women with preserved uterus. HRT in women after hysterectomy/amputation of the uterine corpus consists of the continuous administration of a fixed dose of estrogen alone. The most important difference compared to the previous recom-

mendations is that HRT initiation should take place before the age of 60 years or within the first 10 years after the menopause, because the benefits are then more likely to outweigh the risks. In each case, initiation of HRT is an individual decision, depending on quality of life and health priorities, as well as personal risk factors including the risk of venous thromboembolism, stroke, ischemic heart disease and breast cancer.

Although HRT is the most effective treatment for vasomotor symptoms, it has also a favorable effect on the connective tissue, skin, joints and intervertebral discs, improves mood, decreases depressive symptoms, sleep disorders and increases sexual satisfaction. HRT is the first-line management for the prevention of osteoporosis-related fractures in at-risk women before the age of 60 years or within the first 10 years after the menopause. Low and ultra-low doses of estrogens have beneficial effect on bone mass density, while standard-dose estrogen therapy lowers the risk of fractures in different locations. Estrogen therapy has also beneficial effects on vascular function, cholesterol levels and carbohydrate metabolism. Several studies provide evidence that standard-dose estrogen-alone HRT may decrease the incidence of coronary heart disease and all-cause mortality in women younger than 60 years old and within the first 10 postmenopausal years. Data on estrogen plus progestin HRT in this population show a similar trend for mortality, but in most clinical trials no significant influence on the prevalence of coronary heart disease has been found. Initiation of HRT beyond so-called "therapeutic window" (i.e. > 60 years of age or > 10 years from the last menstrual period) may lead to the increased frequency of coronary incidents, especially during the first two years of treatment. Despite the vascular effect of HRT, the risk of venous thromboembolism and ischemic stroke increases during oral HRT, but the absolute risk below the age of 60 years is low. A higher risk occurs during the first year of therapy and rises with age, in women with high body mass index (a nearly threefold increase when body mass index (BMI) exceeds 30 kg/m<sup>3</sup>), and accompanies higher estrogen dose. Some observational studies suggest that transdermal therapy with ≤ 50 µg/day of estrogen may minimize this threat. One of the most important and complex issues is a relationship between the HRT and a risk of breast cancer in women over 50 years old. The increased risk of breast cancer in this population is primarily associated with the addition of a progestin and related to the duration of the therapy. The risk of breast cancer attributable to HRT is small (less than 1 case per 1000 women per 1 year) and decreases after cessation of the treatment. Available data do not support the use of HRT in breast cancer survivors. The duration of systemic HRT is still under discussion, however the safety margin for estrogen therapy seems to be up to about a dozen years.

Local low-dose estrogen therapy is preferred for women whose symptoms are limited to vaginal dryness or associated with discomfort during sexual activity.

Low-dose local estrogen therapy is more effective than systemic treatment and requires no supplementation with progestin. This kind of therapy is no subject to mentioned above temporal constraints regarding the time-point of treatment initiation.

## TESTOSTERONE

**The syndrome of man aging, associated with a decrease in serum testosterone concentration and, to the greater extent, with a decrease in free testosterone level, is called late-onset hypogonadism (28).** The decline in testosterone secretion in aging man is modest and has entirely individual course. Its clinical consequences have not been well established, because it is often difficult to distinguish between the testosterone deficiency and the results of aging itself. Together with declining testosterone, sex hormone binding globulin (SHBG) concentration increases; therefore, less of the total testosterone is in a free form (i.e., biologically active). Man aging is accompanied by the increase in serum gonadotropin concentrations (FSH > luteinizing hormone – LH), but the rise is not proportional to the fall in testosterone levels. It suggests that the decline of testosterone levels that occurs with aging is due to both secondary and primary hypogonadism. Testicular size, which reflects primarily the volume occupied by the seminiferous tubules, is smaller in older men than in young men (mean volume 20.6 ml and 29.7 ml, respectively), but sperm production does not appear to change dramatically with increasing age.

Some features of aging in men may be assigned to the decline in serum testosterone levels and include: loss of bone mineral density with an increased risk of fractures, decline in muscle mass and strength, and increase in fat mass and development of central obesity. Testosterone deficiency-related changes in body composition are associated with hyperinsulinemia, higher risk of diabetes and unfavorable changes in lipid profile (increased triglycerides, total cholesterol and LDL, decreased high density lipoprotein levels). These metabolic disturbances lead to the increased risk of arterial hypertension, cardiovascular disease, transient ischemic attacks and strokes and, consequently, to the increased mortality. The age-related decrease in serum testosterone concentrations in men may be also associated with a decline in neuropsychological function and can cause unfavorable mood changes. All these conditions may lead to the impaired sexual activity. The biochemical diagnosis of testosterone deficiency is based on three measurements showing decreased morning testosterone serum levels. LH and prolactin should be checked to rule out the secondary reasons of low testosterone level.

The question of whether or not testosterone should be administered to older, healthy men is still a matter of debate (29). Currently, the Endocrine Society recommends (30) testosterone administration only to patients who meet the laboratory criteria, show symptoms of hypogonadism and do not have contraindications to

such treatment. In general, testosterone treatment in these men has not been associated with increased cardiovascular risk. The beneficial effects of testosterone in these men are clear, and there is no reason to suspect that increasing the serum testosterone to normal would increase the risk of any condition above normal for a given age group. Although epidemiological studies show that normalized concentration of testosterone does not increase the risk of prostate cancer *de-novo*, the prostate-specific antigen concentrations should be monitored during the replacement therapy. An absolute contraindication for testosterone supplementation is a history of prostate cancer. It is also contraindicated in patients with severe lower urine tract symptoms (it may increase the volume of prostate), sleep apnea, increased hematocrit (> 54%).

Oral testosterone is available, but not recommended, because these preparations seems to be not fully effective in producing virilization and may have unfavorable hepatic side effects (cholestatic jaundice, hepatic cystic disease called *peliosis hepatis* and hepatoma). Transdermal testosterone delivery is the most desirable, because maintains relatively stable serum concentrations of the hormone, resulting in a stable physical strength, mood and libido. 1% testosterone gel is supplied in 5 and 10 g tubes (not available in Poland). Alternative form of testosterone administration is an intramuscular injection of its esters resulting in gradual release. 100 mg of testosterone enanthate might be administered once a week or every two weeks. After a single injection, the mean serum testosterone concentration increases up to the upper limit of normal values for one to two days and gradually decreases to the mid-normal range by the time of next injection.

The benefits of the proper testosterone supplementation include: decrease of fat mass and of total cholesterol levels, increase of lean mass, muscle strength and of the bone mineral density, improved insulin sensitivity and sexual activity.

## CONCLUSIONS

When assessing the function of the endocrine system in elderly patients, it is important to distinguish between the effects of aging *per se* on endocrine physiology from those caused by disease-related changes. Notably, diagnosis of endocrine dysfunction in the elderly not always requires therapeutic intervention (e.g. in some cases of subclinical hypothyroidism). The age-related hypothalamic-pituitary-gonadal axis insufficiency in women is well defined and studied, and guidelines for HRT after menopause are well defined. On the other hand, the function of GH-IGF-1 system, of the male hypothalamic-pituitary-gonadal axis, and of zona reticularis (the layer of adrenal cortex synthesizing DHEA) decline progressively with age in most people and age-adjusted ranges of normal values for serum IGF-1, testosterone and DHEA concentrations can be defined. However, a routine

replacement therapy with GH, testosterone and DHEA in the elderly remains a matter of debate and administration of such therapy is still not evidence-based. The secretion of other hormones is also

influenced by physiological aging but since these changes are much less predictable and still insufficiently investigated, recommendations for routine supplementation cannot be formulated.

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