

Features of diagnostics and treatment of partial androgen deficiency of aging men

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Introduction Decreasing of testosterone level is an important part of a male elderly.

Material and methods To describe this phenomenon a PubMed and national databases were searched for 17 β -dehydrotestosterone, common testosterone, free testosterone, 17 β -estradiol, luteinizing hormone, partial androgen deficiency of aging men.

Results The reduction in intensity of the processes of tissue renewal of the testicles results in a partial androgen deficiency of aging men. A decrease in the levels of total and free testosterone and an increase in the levels of 5 α -dihydrotestosterone, 17 β -estradiol, sex hormone binding globulin, LH and FSH, along with a decrease in the amplitude of the rhythm of incretion of LH, FSH and total testosterone will testify to a deficiency of testosterone.

Conclusions It is very important to make an individualized selection of the dose of testosterone preparation which enters the blood plasma.

Key Words: 5 α -dehydrotestosterone \leftrightarrow common testosterone \leftrightarrow free testosterone \leftrightarrow 17 β -estradiol \leftrightarrow luteinizing hormone \leftrightarrow partial androgen deficiency of aging men

INTRODUCTION

A decrease in the pool of pluripotent stem cells among men after 40 years of age [1] leads to a reduction in the intensity of processes for renewing tissues, including tissues of endocrinal organs. This reduction in intensity of processes of tissue renewal of endocrinal organs has a negative effect on these organs' function [2].

The systemic character of the changes taking place in people of older age groups is proven by the development of atrophy and fibrous changes in other tissues and organs. In particular, among men, one can note atrophy of the testicles, which shows itself through the development of fibrosis of the basal membrane of tubular testicles, the reduction in the quantity of Leydig cells and other changes. Atrophy develops in other endocrine organs as well, for example one can see a reduction in the size of the hypophysis [3]. Involution changes of the aging kidney are expressed by a reduction in its mass and volume and by progression of the accretion of connective-tissue compo-

nents. After 40 years, there is sclerosis of about 10% of the nephrons every ten years (1% per year) [4]. The overall mechanisms of regeneration, which depend on the quantity of the pool of pluripotent stem cells and the speed at which this pool decreases with age, determine the equal intensity of sclerosis of the majority of tissues among people of older age groups. The rate at which the general testosterone level decreases among aging men is 1% per year in accord to these values of the intensity of sclerosis of tissues.

Men show a reduction in the amount of testosterone circulating in their blood. The latter phenomenon received the name partial androgen deficiency of aging men (PADAM) [5]. PADAM triggers abnormalities in the mechanisms of regulation in the system of the gonads-hypophysis-hypothalamus, and in particular, an increase in the activity of the hypophysis [6].

A whole series of compensatory-adaptive reactions is formed in order to compensate for the lack of testosterone. This series of reactions affects endocrine, paracrine and autocrine levels [7].

Particularities of adenohipophysial regulation under partial androgen deficiency of aging men

As a result of the interaction of neurohumoral regulatory processes, the age-related decrease in testosterone production among aging men is reflected in the entire system of hypothalamic-pituitary regulation. The violation of regulatory mechanisms in the presence of PADAM is a particular case of a compensatory reaction made by the structures of the central nervous system and endocrine glands, which is characteristic of hypoproduction of one or several hormones.

A decreased testosterone level stimulates not only the incretion of LH but the incretion of gonadotropin-releasing hormone [8], and, secondarily, of FSH. Among some patients with partial androgen deficiency of aging men, the levels of LH and FSH do not exceed normal values despite the low level of testosterone. In the presence of PADAM, one can observe an increase in the activity of 5 α -reductase and aromatase, and, accordingly, an increase in the levels of 5 α -dihydrotestosterone and 17 β -estradiol [9, 10]. The increased levels of 5 α -dihydrotestosterone and 17 β -estradiol suppress the incretion of LH, FSH and gonadotropin-releasing hormone by the principle of negative feedback [8]. Testosterone and 5 α -dihydrotestosterone connect with one and the same receptor. The affinity of binding of the androgen receptor for 5 α -dihydrotestosterone is higher than for that of testosterone [8]. For this reason, the reduction in testosterone production among patients with PADAM and the responsive increase in 5 α -dihydrotestosterone and 17 β -estradiol can be unaccompanied by an increase in LH and FSH among some patients. The expressed increase in LH and FSH levels can be seen when there is a significant reduction in testosterone and, consequently, in a significant decrease in 5 α -dihydrotestosterone and 17 β -estradiol (such as, for example, after orchidectomy) [7].

The incretion of LH and FSH using the negative feedback mechanism can be assisted by extragonadal testosterone production [11].

Loss of the rhythm of gonadotropin-releasing incretion by the hormone among patients with PADAM, as well as its long and constant (in tonic regime) effect, leads to de-synthesis of the according receptors on gonadotropin cells and to suppression of the incretion of LH and FSH, despite the deficit in testosterone [8, 12].

When the level of testosterone is decreased, one can observe an increase in the level of prolactin [7]. An increase in the production of 17 β -estradiol leads to a reduction in the content of prolactin-inhibiting

factor – dopamine, in the hypothalamus. Thus, estrogens have a direct activating influence on the incretion of prolactin by the hypophysis [8, 13].

An increase in 17 β -estradiol leads to an increase in the concentration of thyroxin-connected globulin. The reciprocal decrease in free T₃ and T₄ promotes intensification of the formation of thyrotropin-releasing hormone and TTH. The incretion of common T₃ and T₄ is intensified. The production of thyrotropin-releasing hormone and TTH keeps increasing until the normal concentration of free T₃ and T₄ is restored. Thyrotropin-releasing hormone stimulates the incretion of lactotropic cells of the adenohipophysis, which leads to an increase in prolactin [8].

An increase in the level of STH is also connected to an increase in 17 β -estradiol. This is proven by the results of functional trials with estrogens. In these trials, one can observe an intensification of the incretion of STH [8]. An increase in the level of STH causes an increase in the formation of IGF-1. An increase in the level of IGF-1 accompanies insulin resistance and a growth of tolerance to glucose [8].

PADAM leads to the development of insulin resistance [7, 14, 15]. Hyperglycemia develops in response and this leads to growth in the level of insulin. This insulin together with a decrease in sensitivity of hypothalamic centers to the slowdown of glucose leads to an incretion of growth hormone-releasing factor and corticoliberin by neurons of the hypothalamus into the portal system of the hypophysis, as well as suppresses incretion of somatostatin. Growth hormone-releasing factor stimulates the incretion of somatotrophic hormone – the contrinsular hormone.

An increase in stimulation of the formation of growth hormone, as well as a decrease in the amplitudes of its impulse incretion under PADAM, is accompanied by an increase in mitotic activity (despite the decrease in absolute values of growth hormone among men of older age groups as compared to younger men). Thus, prescribing preparations of growth hormone which have an expressed mitogenic effect will additionally stimulate mitotic activity, increasing the risk of cancerogenesis.

An increase in the production of glucocorticoids suppresses the formation of dopamine and reduces the inhibiting effect of dopamine on the synthesis of prolactin [8].

Extra-gonadal testosterone production among men with partial androgen deficiency of aging men

A whole series of compensatory-adaptive reactions aimed at increasing mitotic cell activity take place

in order to make up for the PADAM. The given compensatory changes are expressed both by intensification of the incretion of various mitogenic factors, and by an increase in the production of testosterone itself. The increase in testosterone production is achieved both thanks to hypophysial stimulation of Leydig cells and to the process of testosterone synthesis by other tissues, for which such a function should be abnormal [7, 11]. Extragonadal synthesis of steroid hormones is caused by hormonal and autocrinal–paracrinal factors which have mitogenic activity [16].

Each of the eukaryotic cells (with minor exceptions) is a carrier of the individual's entire genetic information. While the genome is almost identical for all cells in the organism, their proteom and metabolom are determined by inner and outer physiological factors. The fact that cells are included in compensatory reactions means that this process is capable of modulating their metabolom, which is proven by the hormonal activity of a significant number of non–endocrinic cells in the organism. Potentially any cell in the organism can have hormonal activity. For example, patients with PADAM have extra–gonadal testosterone production [11], analogues of hypophysial hormones can be formed by cells of cancerous tumors of the prostate gland [17], extragonadal production of estrogens is done by fatty tissue and several other types of tissues among women [16] in the menopause period, rennin is synthesized by myocytes of the wall that brings arterioles of the kidney when there is an expressed and long–term ischemia of its tissues [4] and other examples.

Hormonal activity among tissues which are neither endocrinal nor neuroendocrinal by nature is a result of either a lack of the corresponding endocrine factor (for example, extragonadal production of androgens among men with PADAM [11] and of estrogens among women [16] during the menopause period) or by the hormone formed taking part in the chain of compensatory–adaptive reactions. An example of the latter is the synthesis of prolactin by tissue of cancerous tumors in the prostate gland [17], which leads to an increase in aromatase activity.

Apparently, the situational expression of compensatory hormonal activity by the majority of cells and tissues (including tumorous ones) forms a diffuse endocrine system (APUD–system) [11].

The strongest expression of extragonadal production of testosterone among men in the andropause period is achieved when there is a significant increase in mitotic activity of cells; as in when there is a malignant transformation [11]. The malignant transformation of cells is the most expressed manifestation of com-

pensatory changes as PADAM develops. This given effect, apparently, has an influence on the pathophysiological role of the cancerous tumor.

Extragonadal testosterone production is directed at compensating for partial androgen deficiency of aging men. Among some patients with PADAM, extragonadal testosterone production allows men to support their total testosterone level within the range of a normal referent interval despite the fact that these patients belong to older age groups. In some cases among older men, the level of total testosterone is significantly higher than the upper level of the norm. Extragonadal testosterone production makes it more difficult to diagnose PADAM.

The compensatory incretion of hormones by non–endocrinal cells and tissues is not a regulated process, however [4, 8, 13], and is not adequate. This is proved by the signs of a lack of testosterone regulation among patients with PADAM in the form of atrophy of androgen–dependent tissues and the high expression of AR in these tissues [11].

Endocrinal tissues have a whole series of unique enzymes for synthesis of the according hormones. For example, a series of peptide hormones from the hypophysis have oligosaccharide chains with a high amount of mannose. These chains end both with sialic acid and sulphates. Analogous hormones which aren't made by the hypophysis, and for which transferase of the hypophysis doesn't play a role in development, have only sialic acid at the end of their oligosaccharide chains. Biological activity is determined, for the most part, by the speed at which the hormone is taken out of the body, rather than by the hormone's quantitative amounts. Peptide hormones with oligosaccharide chains that end with sulfate have a shorter period of half–breaking. This allows them to support the physiological impulse regime of regulation and to support the necessary sensitivity of their receptors. The forms of hormones that hold sialic acid or free mannose for the most part have a longer period of half–breaking. This doesn't give them the chance to support the regulatory process in full; the biological activity of the given isoforms of hormones is much lower in these cases [18]. A breakdown in the defense of ending carbohydrate remainders of a whole series of chemical structures together with the appearance of free mannose on their surface [19] is characteristic of men of older age groups [14].

Prescribing androgen–replacement therapy using testosterone preparations leads to the reverse development of the above–mentioned compensatory–adaptive reactions and to a decrease in extragonadal testosterone production.

Influence of partial androgen deficiency of aging men on the impulse regime of incretion of several hormones

The endocrine and nervous systems function in a coordinated way, thereby supporting the consistency of the body's inner environment. Although there is an obvious difference in the mechanisms by which these two systems pass along information, each of the two systems features the release of chemical substances as a way of making communication between cells. The endocrine system is a continuation of the central nervous system. Neuroincretorial cells of the hypothalamus combine characteristics of both systems: they get information from higher-lying parts of the central nervous system through synaptic transfers and, at the same time, synthesize hormones which are transported along with the current of axoplasma to the hypophysis. The sensory stimulus is transformed into hormone incretion; such a transformation is called a neuroendocrinal response [20].

Sending information to the central nervous system is done with the help of a frequency pulse code. This code uses both the frequency of the transfer of nerve impulses, as well as the quantity of nerve impulses in "formed packages" [21]. J. Furth was one of the first researchers to use methods of analysis from cybernetics for evaluating the function of the hypophysis (1967) [22]. Regulation of the rhythm of incretion of hormones of the hypothalamus is done by the suprachiasmatic core of the middle brain [13]. The suprachiasmatic core serves not only as a pacemaker for rhythms, but is also one of the most important centers for integration of the brain. Axons of afferent neurons end in the suprachiasmatic core. These afferent neurons are located in more than 20 sections of the brain [23].

The system of regulation of rhythms includes three components: neuron-pacemakers, an afferent regulation unit which adapts the work of the pacemaker, and an efferent unit which transfers commands of the pacemaker to the functional target [24].

The success of the transfer of the biological signal depends not only on the level of the hormone but also on the frequency of the incretion of the hormone. This conclusion is confirmed by the dependency of the correlation of formation of LH and FSH levels on the frequency of incretion of gonadotropin-releasing of the hormone [8]. The pulse of the rhythm of the formation of hormones from the point of view of cybernetics is related to "discrete messages", which are capable of sending a significantly large volume of information, unlike "non-stop messages", which have a constantly changing size [21].

Information from the central nervous system, which is transferred in the form of nerve impulses which follow one after another at regular intervals and are united into packets, is transformed into an impulse rhythm of formation of hormones [12]. The ability of neurons of the suprachiasmatic core (unlike neurons of other sections of the brain, which have endogenic rhythm) to transform a series of rhythms into single impulses [25] allows this to be achieved.

Incretion of gonadotropin-releasing hormone by the hypothalamus, of other hormones by the adenohypophysis (besides prolactin), and of testosterone by the testicles is done impulsively which complies with the short period of their decomposition, and takes place on average once every 60–90 minutes. Unlike other hormones of the front part of the hypophysis, prolactin is formed in tonic mode [8]. This type of incretion is made up of a "continuous message" and, accordingly, carries less information. The incretion mode of prolactin is determined by regulation by dopamine (DA), which is also formed in tonic mode [13]. Prolactin is a phylogenetically older hormone and its incretion mode is less complete as compared to that of other hormones of the adenohypophysis, which have an impulse incretion mode. As a result, the volume of information carried through incretion of prolactin is significantly inferior to the analogous value for the majority of other hormones which formed at later stage of evolution [12]. The development of PADAM is accompanied by a break-down in the impulse regime of hormone incretion by the adenohypophysis. These changes lead to limitation and distortion of the information being transferred, which regulates a whole series of physiological processes including proliferate activity [12]. For example, LH is the stimulator of synthesis of IGF-1 in Sertoli cells. IGF-1 strengthens the expression of LH receptors on Leydig cells and thereby activates steroidogenesis. FSH has a slowing-down influence on the creation of transformation growth factors in Sertoli cells. Transformation growth factors reject steroidogenesis in Leydig cells [8]. In relation to this, the frequency of the rhythm of formation of gonadotropin-releasing hormone, which determines the correlation between LH and FSH, has a direct influence on the level of cell growth factors, and, accordingly, on cell proliferation [12].

As testosterone production goes down as men age, the agreement between the central and peripheral core of the hypothalamus-hypophysis-gonad system is broken down. When changes in the testes take place as men get older (smaller quantity of Leydig cells), those patients who have PADAM demonstrate that the impulse incretion of gonadotropin-releasing hormone and LH isn't accompanied by an adequate

impulse incretion of testosterone. The central nervous system understands this state to be an even deeper manifestation of androgen deficit. There is thus a compensatory increase in the levels of gonadotropin-releasing hormone, LH, and FSH, using a mechanism of inverse feedback [8]. Despite the increase in the level of testosterone, the mode for testosterone incretion becomes non-physiological and gradually becomes tonic.

The reaction of Leydig cells in tonic mode to the impulse formation of gonadotropin-releasing hormone and LH among men with PADAM is accompanied by a gradual transition to a tonic regime of hormone incretion by the hypophysis and hypothalamus.

Apparently, a decrease in impulse incretion of hypothalamus-hypophysis hormones is additionally determined by the suppression of activity of neuron-pacemakers of the suprachiasmatic core due to the transition to tonic regime of the periphery endocrine organs (testosterone) and, accordingly, changes in the characteristics of the afferent signal which is received as part of the mechanism for negative inverse feedback.

The long and continuous (in the tonic mode) influence of gonadotropin-releasing hormone leads to de-synthesization of this hormone's receptors on gonadotropin cells and to suppression of the incretion of LH and FSH, despite the remaining deficit of testosterone [8]. Thus, among those patients studied with PADAM, the original levels of LH and FSH don't exceed the normal referential interval.

The use of analogues of gonadotropin-releasing hormone, which have a suppressing influence on gonadotropin cells of the hypophysis as well as on Leydig cells [8], is based on this effect.

Suppression of the impulse incretion of gonadotropin-releasing hormone, in turn, is reflected in the correlation of LH and FSH, and in the formation of cell growth factors. A vicious circle is formed.

Melatonin together with a change in the expression of its receptors in the suprachiasmatic core has a significant influence on the regulation of neuron-pacemakers [24].

Hormonal regulation of mitotic activity of normocytes is discreet and impulsive. The change from the impulse formation of hormones to a tonic incretion regime inhibits the onset of the physiologically necessary dephosphorylation phase. The signal chain, which carries the mitogenic signal, takes on a continually active state ("the pressed button effect"). The cell is thereby held in a regime of constant mitotic activity [26].

In this way, the physiological rhythm of incretion of hormones helps the neuroendocrine system to complete its main function, which is integration

of various biological processes into a single organism. These processes take place on the molecular, cell, tissue, organ, and system levels. An age-related decrease in the production of peripheral hormones (especially during PADAM) leads to a loss of impulse rhythm and the establishment of a tonic incretion mode for a whole series of hormones, as well as to an increase in mitotic activity. The reverse development of these changes can be observed in men of older age groups with PADAM who are given androgen-replacement therapy. The restoration of the physiological regime of incretion of testosterone, in turn, is the main criteria by which the success of androgen-replacement therapy can be judged.

Diagnostics of partial androgen deficiency of aging men

A decrease in common testosterone production of 1% per year takes place in men older than 40. Most often, there is a decrease in the free testosterone level (by 1.2–2.5% per year) which can begin from 30–35 years of age. By 80 years of age, the average level of common testosterone decreases in men by 40% from the according level at 25 years old, while free testosterone is 60% lower. Thus, one can speak of a partial rather than an absolute deficit of androgens.

Extra-gonadal testosterone production, aimed at compensation of PADAM, makes diagnostics more difficult [11].

The level of testosterone depends on the formation of luteinizing hormone (LH) of the hypophysis. When the level of testosterone in the blood plasma is either raised or decreased using the mechanism of negative feedback, the level of LH is changed accordingly. Analogously, the level of thyrotropic hormone is used in diagnostics of the euthyroid state and when evaluating the use of replacement therapy [27].

Testosterone inhibits production of sex hormone binding globulin (SHBG) by the liver. The decrease in testosterone level leads to an increase in the level of SHBG in the plasma [3] and an analogous effect can be seen during an increase in estrogens [8]. After 40 years of age, the level of SHBG increases in men by about 1.3% per year [3]. As a result, the quantity of testosterone which is available for cell targets (free and connected with albumen) decreases even more. At the same time, the content of common testosterone in the blood serum can remain close to normal [8].

5 α -Dihydrotestosterone, 17 β -estradiol, total testosterone, free testosterone, globulin (which connects sex hormones), LH, and FSH are a united inter-dependent system. The age-related decrease in the

incretion of testosterone concerns all levels of this system. The given values and the estimate of the rhythm of incretion of part of them objectively reflect PADAM. They can be used both in primary diagnostics of partial androgen deficiency of aging men and in evaluating the effectiveness of using androgen-replacement therapy.

In order to make diagnostics of the breakdown in the rhythm of incretion, one should measure hormone levels by taking five samples in the blood serum taken at an interval of 20 minutes each [12] – a period of time that covers the whole average period of impulse incretion [8].

A decrease in the levels of common and free testosterone, and an increase in the levels of 5α -dihydrotestosterone, 17β -estradiol, globulin (which connects sex hormones), LH and FSH, and a decrease in the amplitude of the rhythm of incretion of LH, FSH and total testosterone will testify to a lack of testosterone. Conversely, a normalization of the given values will point to the adequacy of the androgen-replacement therapy provided [12].

Methods of correction of partial androgen deficiency of aging men

The reverse development of these changes is observed when conducting androgen-replacement therapy among men of older age groups with PADAM. Recovery of the physiological regime of testosterone incretion is one of the main criteria of the adequacy of conducting androgen-replacement therapy. The daily dose of testosterone which enters the blood plasma when conducting androgen-replacement therapy among patients with PADAM should not exceed the average daily production of testosterone which, according to data collected by a number of authors [8, 28], equals 5–7 mg/day. Prescribing a large daily dose of the preparation leads to suppressing the body's own testosterone production while losing the incretion rhythm; renewal of regulation, which is done by method of testosterone, therefore doesn't take place.

Partial androgen-replacement therapy should be aimed at managing the imbalance of the hormonal system, which develops as a result of a decrease in testosterone production by the peripheral endocrine organ – the testes.

Discovering, treating, and monitoring partial androgen deficiency of aging men, as well as conducting differential diagnostics of PADAM *vs.* other forms of hypogonadism, are recommended by the EAU (2013). In order to exclude prostate cancer, all patients are recommended to receive preliminary digital and ultrasound rectal examination of the prostate gland,

as well as measuring the level of PSA and, if necessary, conducting a biopsy of the prostate.

An exogenous introduction of testosterone in patients with PADAM leads to a decrease in the level of LH and a decrease in the levels of hormonal and autocrine-paracrine factors that stimulate both gonadal and extragonadal synthesis of steroid hormones. A decrease in the level of the given factors leads to a reverse development of compensatory-adaptive reactions that are directed at hyperstimulation of the production of testosterone. Therefore, the prescription of small doses of preparations of testosterone may not be accompanied by a significant increase in the level of common testosterone, which is proven by the results of ten years of use of testosterone undecanoate [29].

It is very important to make an individualized selection of the dose of testosterone preparation which enters the blood plasma. Exceeding the level of the age-related decrease in testosterone production with the prescribed dose of the preparation can lead to blocking the organism's own production of the hormone, and to losing the rhythm impulse incretion of testosterone. In this case, androgen-replacement therapy will no longer fulfill its main task – reinstating regulation conducted by means of testosterone.

When conducting androgen-replacement therapy in patients with PADAM, one must take into account the average daily production of testosterone upon calculating the daily dose of testosterone which enters the blood stream: 5–7 mg/day (apparently the level of 7 mg/day is closer to the average statistical value) [8, 28]. It's also necessary to take into account the age-related reduction in testosterone production after 35–40 years of age of 1% per year on average for common testosterone [2].

Optimal androgen-replacement therapy should bring the newly-formed level of exogenous testosterone as close as possible to its physiological daily fluctuations, with a maximum level in the morning hours and a gradual decrease through the course of the day.

The optimal dose for dermal gel preparations of testosterone, considering losses when being absorbed (about 90%), can apparently be calculated based on the patient's age while making corrections for anthropometric data. For example, for a man 50 years old (with 1% loss of incretion of the hormone after 35–40 years of age), the likely decrease in testosterone production will be 10%, while the absolute figure (with production of 7 mg/day of testosterone as the norm) will be 0.7 mg/day. Thus, the average man of 50 years old will need to replace 0.7 mg of testosterone per day. Considering the 90% loss of the preparation when being absorbed, the patient

needs to receive 0.7 ml 1% dermal gel testosterone per day. For some patients, calculation should be started from 35 years old. The stomach area is optimal for applying the gel thanks to its primary deponation in fatty tissue and its ensuing gradually weakening entry into the blood stream. Considering the greatest need for testosterone in morning hours, the gel must be applied in the morning hours as well. One can calculate the dose of the injected preparation depot in a likewise way (but without accounting for absorption, which doesn't occur). When using testosterone undecanoate one must keep in mind that about half of its dose is made up of undecanoate. Thus, in comparison to the dose calculated for testosterone, the dose of testosterone undecanoate should be doubled. It is necessary to repeat measurements of common testosterone and other above-recommended diagnostic indicators after 1 month in order to control the adequacy of the dose prescribed. If necessary, the testosterone dose preparation is corrected with repeat control examination. Apparently, considering the decrease in intensity of the majority of biological processes in man with age, the optimal level of testosterone after the beginning of androgen-replacement therapy can be considered to be a level of the hormone which slightly exceeds its lower normal value in the blood (12 nmol/l).

Before the appearance of special dosimeters, the daily dose of the dermal gel can be measured using two needles (10 ml and 1 ml (2 ml)), connected by a rubber coupler. The gel is put into the large needle through the heel, and then is collected in the necessary amount from the large needle through the

rubber connector into the small needle. The necessary daily dose of the gel is administered from the small needle on the stomach skin in the morning.

Normalization of the level of luteinizing hormone and other hormonal and autocrinal-paracrinal factors when conducting androgen-replacement therapy creates optimal conditions for the functioning of Leydig cells. That said, one doesn't observe either the depletion of these cells due to hyperstimulation nor a reduction of their function due to hypostimulation. Considering the inevitable increase of irreversible changes in the testes as age increases, patients with PADAM need constant monitoring and, if necessary, an increase in the dose of the testosterone preparation.

Thus, replacement therapy using testosterone preparations in patients with partial androgen deficiency of aging men can lead to a decrease in the levels of 5 α -dehydrotestosterone, 17 β -estradiol, and a series of cell growth factors and to recovery of neurohumoral regulation in the gonads-hypophysis-hypothalamus system. Androgen-replacement therapy can be used for lowering the risk of development of both benign hyperplasia and prostate cancer and can also help in prevention of such diseases and pathological states such as type II diabetes, obesity, atherosclerosis, osteoporosis, atrophic changes in the skin, a reduction in sexual activity, and psycho-emotional and vegetal abnormalities. Replacement therapy should be conducted consistently, since stopping the treatment or prescribing separate courses of treatment leads to reactivation of the above-described pathological processes [14, 30].

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