Continuing Medical Education

Hormones in rejuvenation: a review of their true effectiveness

Hormônios no rejuvenescimento: revisão de sua real eficácia

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Received on: 15 June 2012
Approved on: 2 August 2012

This study was carried out at the Faculdade de Medicina de São José do Rio Preto (Famerp) – São José do Rio Preto (SP), Brazil.

Financial support: None
Conflict of interest: None

ABSTRACT

Hormones are very important in the aging process because some of their levels decrease. Therefore it can be hypothesized that hormone replacement therapy might slow aging. In light of the increasing interest in rejuvenating treatments that can yield good results, hormone replacement therapy has dawned in scientific circles. This review examines the roles of growth hormones melatonin and dehydroepiandrosterone, as well as those of bioidentical hormones in rejuvenation. The authors have also sought to evaluate the results of studies on hormone replacement therapy, considering the risks and benefits of using those hormones, which are seen as the "fountain of youth."

Keywords: hormones; rejuvenation; growth hormone; melatonin; dehydroepiandrosterone.

RESUMO

Os hormônios possuem grande importância no envelhecimento devido à diminuição de alguns durante esse processo. Dessa forma, existe a hipótese de que a reposição hormonal possa retardar o envelhecimento. Diante do crescente interesse em tratamentos rejuvenescedores que apresentem bons resultados, a terapia de reposição hormonal tem-se destacado no meio científico. Esta revisão analisa o papel do hormônio do crescimento, da melatonina, da desidroepiandrosterona e dos hormônios bioidênticos no rejuvenescimento. Buscamos, também, avaliar resultados de estudos de terapia de reposição hormonal, observando riscos e benefícios do uso desses hormônios considerados "fonte da juventude".

Palavras-chave: *hormônios; rejuvenescimento; hormônio do crescimento; melatonina; desidroepiandrosterona.*

INTRODUCTION

Aging is a natural biological process that leads to the decline of physical and mental abilities over the years. The effects of aging occur in different body systems, including the endocrine system, which suffers the decline of several hormones, known for endocrine senescence.[1] Hormones play an important role when it comes to aging because there is decrease in production, efficacy and clearance effect of some hormones during that process. Hence, the hypothesis that hormones may delay the aging process has existed for thousands of years.[2]

Due to the increase in human life expectancy over the last century and the resulting increase in the elderly population, interest in anti-aging treatments (or therapies aimed at ensuring a healthier aging process) has increased. In this way, hormone replacement therapy has brought enthusiasm to the scientific community as an anti-aging alternative.[3]

The present review aims at examining the role of four types of hormones – GH, melatonin, dehydroepiandrosterone and bioidentical hormones – in rejuvenation. It also seeks to evaluate the results of studies involving hormone replacement therapy, noting risks and benefits of using those hormones, which are deemed as the "fountain of youth".

GROWTH HORMONE (GH)

GH is a peptide produced by the anterior hypophysis in a pulsatile way, with peaks of greater amplitude in phases three and four of deep sleep. Its pulsatile characteristic is controlled mainly by two hypothalamic proteins: the GH releasing hormone (GHRH), which acts by stimulating the secretion, and the inhibitory action somatostatin. GHRH and somatostatin, in turn are influenced by many factors, such as physical activity, nutrition, sleep, stress, sex steroids and thyroid hormones.

The action of GH takes place both directly – through binding to its receptor in the growth plate – and indirectly –through stimulating liver and tissular production of the insulin-like growth factor-1 (IGF-1). GH and IGF-1 are involved in the regulation of somatic growth in children. In adults, they have the role of maintaining normal body composition, skeletal mass, cardiovascular risk factors and physical and physiological functioning.

The secretion of GH decreases, concurrently to the decline of IGF,at around the age of 30. This decrease reaches roughly 14% per decade in normal adults, due to neurological disorders correlated to the individual's age. After the age of 60, many normal individuals have 24-hour GH secretion that is indistinguishable from that of adult patients with GH deficiency due to pituitary-hypothalamic lesions (DHGA).

Some of the clinical features of aging – alterations in body composition, such as increased total fat mass, decreased lean body mass and decreased bone mass, as well as a higher prevalence of cardiovascular risk factors and decreased cardiac function – resemble pathological manifestations of GH deficiency.4As a result, it is hypothesised that some signs of aging maybe due, at least partially, to low GH and IGF-1 levels, condition also described as somatopause. [5]

Since recombinant human GH replacement has been shown useful in reversing the symptoms of DHGA deficiency, several studies have directed the use of GH to "healthy" elderly patients, aiming at verifying whether the same benefits could be achieved.

GH REPLACEMENT

GH was first used in patients in 1958 and during the ensuing 25 years it was only available from corpse sources. In 1985, GH production through recombinant DNA techniques became available. Since then, there have been U.S. Food and Drug Administration (FDA) approved indications for use in some states of GH deficiency. In 2003, the FDA approved the use of GH for idiopathic short stature. Nonetheless, GH therapy coverageis currently more frequently used for other indications, such as to treat chondrodystrophy syndrome, and to heal wounds and burns. Other uses that have been studied include aging and physical performance,the latter due to the interest shown by athletes in using GH.[5]

Observations on attenuation of GH/IGF associated with age induced clinical trials to seek to answer the question of how physiological alterations, such as reduced muscle mass, reduced strength and aerobic capacity, central adiposity, reduction of bone mass and slow wave sleep, could be reversed through supplementation of GH/GHRH.[1]

In one of the pioneering studies, Rudman et al. used a dose of GH which brought IGF-1 levels found in 60 year-old men to the average found in 20 year-old men. That paper described the effect on body composition of administering human GH for six months to older men and to a group of 12 healthy men between 61 and 81 years old who had IGF1 serum concentrations lower than those found in normal young men. Administration of GH resulted in an increase of 4.7 kg of lean body mass, a decrease of 3.5 kg in fat mass and an increase of 0.02 g/cm2 in muscle density in the lumbar spine, in addition to a significant increase in blood pressure and fasting glucose. The study, however, had drawbacks: it was not double blind, and only 12 individuals were studied.The weekly GH dose used was approximately twice higher than that used in patients with GH deficiency, leading to adverse effects typical of excessive GH action, such as hypertension and arthralgia. Moreover, there was no assessment of muscle strength, endurance exercises or quality of life. Notwithstanding, the study served as the basis for the claims that GH reverses aging.[6]

A study by Blackman et al. (double-blind, placebo-controlled) involving 27 women and 34 men between 68 and 88 years old, who received GH or placebo for 6.5 months, confirmed the effects of GH in body composition. Those effects, however, did not lead to a change in muscle strength or maximal oxygen uptake during exercise in both groups. 7 Similarly, Papadakis et al. showed that administration of GH in elderly over 70 years old for six months led to a small increase in lean mass, not accompanied by an increase in muscle strength. 8 In the study by Taaffe et al., physical training of patients led to increased muscle strength and endurance, which was not higher, however, in those who used hormonal teraphy. 9 Thus, the effects caused by GH on body composition do not translate clinically into increased muscle strength or endurance. Nevertheless, although several studies have demonstrated an increase in lean body mass with GH therapy, the increase of muscle mass and strength was not greater than that that could be achieved with exercise. That finding reaffirms that exercise is an inducer of physiological secretion of GH.[1]

Another important point to be taken into account in connection to hormone replacement is its various possible side

effects. Bronstein et al. listedthe major adverse effects of GHRH replacement in the elderly: fluid retention, arthralgia, carpal tunnel syndrome, glucose intolerance and possibly tumorigenesis and hypertension.

Several clinical studies have evaluated whether there is a risk for GH triggering neoplasia. Though, the mitogenic effects of GH and IGF1 are still debatable. So far some studies have linked elevated IGF-1 with increased risk of ovarian, breast, prostate, colorectal and other cancers.[1] Chan et al. showed that the risk of developing prostate cancer was 4.3 times greater in men with higher serum concentration of IGF1, highlighting a GH replacement GH in older men.

In this manner, the use of GH as an antiaging agent in patients who do not have deficit of GH provides evidence that suggest no real benefit. 10For that reason, studies using GH replacement in somatopause have been disappointing.[11] Davidson Pet al.'s meta-analysis (involving 15 studies in the period between 1985 and 2004), observed no evidence that GH treatment improves the patients' quality of life and well-being.

There is no definitive evidence that older individuals actually benefit from treatment with GH. Strategies aimed at increasing spontaneous GH secretion, such as sleeping and exercising, are safer and certainly less expensive than the GH supplementation scheme.[12] The high cost of the treatment (roughly US$ 1,300 per month for three weekly injections), and the lack of consistent scientific evidence on the actual or potential benefits of that therapy in the elderly are the main limitations for its clinical use.

In this manner, the adoption of a lifelong healthy style, guided by simple measures, such as a balanced and varied diet, weight control, regular physical activity, leisure and entertainment, among others, can promote aging with fewer health problems and better quality of life.

DEHYDROEPIANDROSTERONE

Dehydroepiandrosterone (DHEA) and its sulfated derivative DHEAS are the most abundant steroid hormones, being derived from the adrenal cortex's reticular zone.[13] The adrenal secretion of DHEA has a pulsatile pattern and follows a diurnal rhythm similar to that of cortisol, being under the stimulus of the corticotropin releasing hormone (CRH) and the adrenocorticotropic hormone (ACTH).[14] Nevertheless, in contrast to cortisol levels that have linear increase with increasing age, DHEA levels persistently decline. The fetal adrenal gland synthesizes great amounts of DHEA, but the production of that steroid declines in the post-natal.Theadrenarche (it takes place at between 6 and 8 years of age) is characterized by increased biosynthesis of DHEA and circulating levels of DHEAS, peaking at the age of 30.[13] The maximum DHEA concentration in the third decade of life is followed by a subsequent decline of about 2% per year. That continuous decline ends between the age of 70 and 80, when DHEA levels remain between 10-15% - the normal concentration for that age group.[15] That continuos decrease in serum DHEA and DHEAS levels over the years has been linked to the cognitive decrease typical of aging. Thus, epidemiological studies suggest an association between low levels of DHEA concentration and certain effects of aging.

Although that hormone's physiological and pathophysiological rolesare not yet fully identified, several features are atributed to it. Both DHEA and DHEAS are biotransformed into biologically active androgens and estrogens in peripheral tissues. Thus, in addition to being precursors of sex hormones, they are important in the production of all other hormones secreted by the adrenal gland. They are linked to increased insulin's sensitivity, helping to improve glucose capture, acting mainly throughthe skeletal muscle, liver and adipose tissue. In addition, several studies have documented the association between the decline of DHEA and various adverse effects of aging. [13]

DHEA REPLACEMENT

Several studies have demonstrated the beneficial effects of DHEA on dementia, obesity, lipid metabolism, diabetes mellitus, atherosclerosis, and osteoporosis.[16] Sunderland et al. were the first to report that DHEA concentration in Alzheimer's disease is lower as compared to controls.[16] Barret-Connor et al. showed an inverse relationship between DHEA levels, and cardiovascular disease and mortality in men.[17] Low levels of DHEA were also found in patients with osteoporosis and breast tumors.

Due to DHEA's anti-aging and pro-cognitive effects observed in rodents, attempts have been made to evaluate this hormone replacement in humans. There is consensus on the fact that DHEA replacement can have effects on mood and well-being of people with adrenal insufficiency, suggesting that its replacement could improve the cognitive function in the elderly. To date, however, studies have failed to promote evidence supporting that hypothesis.

Despite low levels of DHEA being related to the impairment of memory,[18] a study conducted by Kritz-Silverstein et al. showed a negative effect of DHEA replacement for the memmory.[19] Wolkowitz et al. concluded that there was no benefit in Parkinson's disease. A review conducted by Maninger et al. concludes that in spite of the positive expectations for DHEA, no beneficial neurobiological and neuropsychiatric effects were found in healthy patients, including those at advanced age and/orwith low concentrations of DHEA. Some studies have demonstrated increased muscle mass and decreased fat mass with a 50mg/day DHEA supplementation.[20] However, according to the study carried out by Nair et al., although there was an increase in lean body mass and a decrease in fat mass in patients receiving treatment with DHEA, there was no difference in endurance and muscular strength between the actual experiment and the placebo groups.[21] Another placebo-controlled study that evaluated the DHEA's effect on muscle strength in the elderly showed no benefit with the use of 50mg/day of DHEA for 12 months, as compared to the placebo.[22] Thus, in spite of thefact that low levels of DHEA are related to low muscle mass and strength, there is little evidence that DHEA replacement improves the signs of aging.

Regarding atherosclerosis, although administration of DHEA has demonstrated a decrease in the atherogenic process

in rats,[23] clinical studies have not found difference in the values of DHEA when comparing patients with and without atherosclerosis.[24] More recently, Boxer et al. carried out DHEA replacement, using 50mg/day for six months in elderly women, with no significant change found regarding cardiovascular risk factors, such as lipid profile, body or abdominal fat, fasting glucose or blood pressure.[25]

Baulieu et al. conducted a study with 280 healthy individuals (men and womens between 60 and 79 years old) who received 50 mg of DHEA or placebo for one year. Results included increased libido in women, and improvements in bone density,skin hydration, sebum production and pigmentation.[26] Labrie et al. also observed an improvement in bone density in postmenopausal women treated with DHEA for one year.[27]

In the study by Morales, 50mg DHEA replacement for six months in both men and women above 50 years showed significant increase in well being in both genders.[28] In a study by Arlt et al., replacement of 50mg of DHEA for four months showed little improvement in mood and no alteration in the well being of patients. Nair et al.[29] showed that there had been no improvement in the quality of life of elderly patients receiving DHEA for two years, when compared to the placebo group.[21]

It is important to highlight that DHEA in elderly men leads to increased testosterone, which in transforming desidrotestosterona can induce growth of prostate cells, both normal and tumoral, being hormone replacement therapy therefore completely contraindicated in prostatic hypertrophy. In women, on the other hand, attention should be given to the fact that DHEA is transformed into estrogen, which required strict control of the hormone and evaluation of risk factors for breast cancer.

In the 90's, the Journal of Clinical Endocrinology and Metabolism has called the DHEA hormone the youth hormone. Although many studies have shown positive effects of DHEA replacement in elderly, others do not offer evidence of that benefit, with its use being still controversial in rejuvenation. 21In this way, there is insufficient evidence to recommend routine treatment with DHEA.

MELATONIN

Melatonin is a hormone that is synthesized from tryptophan by the pineal gland, located in the human brain. It is also produced in the retina, thymus, bone marrow, respiratory epithelia, skin, intestine and other locations. It is secreted in a circadian rhythm according to the light and dark cycle. The maximal secretion occurs during the night and the exposure of the retina to light leads to the fast collapse of melatonin to very low levels. Melatonin takes place in the regulation of important physiological and pathological processes and is considered the hormone that regulates circadian rhythm and seasonal biorhythms through the biological clock. Moreover, it has recognized action in the immune response's modulation, body weight, reproduction, tumor inhibition and anti-jet lag effects.[30]

The night peak amplitude of melatonin secretion reaches the highest levels between the ages of four and seven. After that peak, the melatonin concentration declines up until puberty, when values remain stable up until the age of 35 to 40. After that age, melatonin levels decrease gradually, reaching nightime levels equivalent to daytime concentration by the age of 70. Thus, with increasing age, many individuals do not show differences in melatonin secretion between day and night. As a result, it is proposed that melatonin would have an important role during the life cycle – i.e.duringthe growth, development and maturation phases, as well as during the aging process.

The cause of the decline in melatonin production is unknown, however it has been assumed that the variation in the concentration of that hormone during the life signals the aging of the human body. Some studies have shown that pinealectomy leads to the acceleration of many aspects of aging, which can be partially reversed or reduced through treatment with melatonin. 31In this manner, some evidence suggests that that hormone can act to prevent aging. Based on that knowledge, melatonin replacement therapy has been proposed and practiced worldwide by many people.[32]

MELATONIN REPLACEMENT

The melatonin's antioxidant effect has been described in several studies.[33] Not only melatonin itself, but also several of its metabolites can detoxify free radicals and their derivatives.[34] Due to the melatonin's antioxidant capacity, it can be an effective medicamentemployed to reduce aging, prolong life and contain age-related disorders. Some benefits of the antioxidant property of melatonin were observed in the treatment of rheumatoid arthritis in infertile women, elderly patients with essential hypertension,[35] neurodegenerative diseases,[36] and for reducing cholesterol levels.[37] Nevertheless, some studies have challenged the antioxidant benefit of melatonin-based therapies.[38]

Another role of melatonin is its immunomodulating action, already described in several studies. Guerrero and Reiter suggested that the immunomodulatory properties are mediated via nuclear and membrane receptors.[39] It was also demonstrated the role of melatonin in the activation of B and T lymphocytes, Natural Killer cells (NK), monocytes and cytokines. Aligned with that, studies in rats were able to demonstrate that melatonin injections recovered the immune function in elderly or immunocompromised rats, in addition to antagonising the effects of immunosuppression generated by stress.[40] The immunomodulatory effects – both prophylactic and therapeutic – of melatonin were also observed in patients with asthma and rheumatoid arthritis, inhibiting the inflammatory response. Other studies, however, have demonstrated that melatonin is able to promote rheumatoid arthritis by acting as an immunomodulating agent, stimulating pro-inflammatory cytokines.[41] It follows that the effects of melatonin in the immune system are complex, sometimes contradictory, and depend on several factors, such as the prescribed dose, the patient's immune system, the immunity's circadian rhythm, and the state of the pineal gland.[42]

There is some evidence showing that melatonin is involved in preventing the emergence, development and progression of tumors.[43] The increased incidence of breast, endometrial and colorectal cancers noted in nurses and other shift workers sug-

gest the possibility of connection between the decrease in melatonin secretion and increased exposure to light at night.[44] Ansimov et al. demonstrated that continuous treatment with melatonin in rats decreased the incidence and the size of breast tumors, as well as the incidence of lung metastasis.[45] In patients with prostate cancer, melatonin levels are reduced by two-thirds as compared with thosein patients with benign prostatic disease.[46] The presence of binding sites for melatonin in human colonic tissue suggests that melatonin may play a role in colorectal cancer.[43] However, there are studies describing some questuonson the effects of melatonin on cancer that still need to be answered,[47] and the necessity to conduct clinical trials before this hormone can be accepted as an anticancer drug.[48]

It is known that sleep disorders occur with aging. Due to its effect on the circadian regulation, melatonin is linked to the maintenance of sleeping, hence, many studies have shown decreased levels of melatonin in elderly patients with insomnia.[49]

In addition to those effects, melatonin has anticonvulsant activity and appears to be involved in the modulation of brain function. While patients with Alzheimer's disease have reduced levels of melatonin,[50] thathormone was demonstrated to have cognitive benefits in such patients.[51]

In light of those facts, melatonin has a reputation as miracle drug, and many elderly and middle-aged people have been using it daily.[32] Although there are many theories linking melatonin to aging, its role in that process remains unclear. In brief, the reasons why melatonin could participate in aging process are the following: decreased production during life, a powerful antioxidant activity, reduced sleep efficiency associated with the decrease of its production, circadian rhythm deterioration with increasing age, and immunomodulatory properties.

Notwithstanding, more clinical evidence must become available before any precise recommendation regarding melatonin can be made.[48] Furher studies and clinical trials are necessary to evaluate both the effectiveness and the safety of using this hormone in humans.

BIOIDENTICAL HORMONES

Menopause is the permanent cessation of menstruation, resulting from the loss of ovarian function, which stops the production of estrogens. It can occur naturally or as a result of surgery or medical intervention. The alteration in the hormonal medium, associated with perimenopause and menopause can lead to a variety of symptoms that could negatively affect the quality of life of women. The most common symptoms include hot flashes, night sweats, emotional lability, poor concentration and sleep disorders, which can range from mild to severe.[52] Other symptoms that menopause can cause are vaginal atrophy and accelerated bone loss due to the fast decline of estrogen, the latter being associated with more serious risk of vertebral and hip fractures.

The postmenopausal therapy is an effective and well-tolerated treatment for menopausal symptoms. Various FDA approved hormonal preparations are available for the treatment of women with menopausal symptoms. Nonetheless, despite hormone therapy has proved effective, the use of estrogen-based therapies has fallen significantly since the publication of the findings of the clinical trial Women's Health Initiative (WHI). 53Between 1993 and 1998, over 160 thousand women took part in that trial, which involved the combined hormone replacement therapy (estrogen and progesterone) and showed that the treatment's benefits did not outweigh its deleterious effects. In 2002, the WHI's results suggested an increased risk of breast cancer, cardiovascular disease and thromboembolic events in women using conjugated estrogen and medroxyprogesterone acetate as compared to a placebo group.[54]

Those findings led many women to discontinue hormone therapy and look for a safer alternative for the treatment of menopausal symptoms. In that sense, the search for complementary and alternative therapies included natural hormones, also known as bioidentical compounds.[52] Those compounds have a chemical and molecular structure exactly equal to that of the hormones produced by the human body. More recently, those substances have attracted great interest due to the possibility of relieving menopausal symptoms and offeringincreased safety when compared to conventional therapy.

REPLACEMENT OF BIOIDENTICAL HORMONES (ALTERNATIVE HORMONE REPLACEMENT THERAPY)

The alternative hormone replacement therapy has been widely discussed and disseminated, as in the U.S. alone conventional hormone replacement therapy decreased by 91 million in 2001 to 57 million in 2003, and continues to fall since the publication of the Women's Health Initiative (WHI) study in 2002. In Brazil, there was a 25.2% reduction in indications of synthetic hormones, and approximately 46% of gynecologists began prescribing other medications to fight natural menopausal symptoms.[55] In this line, many studies have been intensified for scientific investigation of the action of natural hormones against the effects of menopause.

Bioidentical hormones have been known for over 20 years, through the extraction and manipulation of hormones contained in plants. Phyto-hormones are found in different parts (leaves, fruits, roots and seeds) of plants such as Cimicifuga racemosa, Mexican yam, licorice, flax, red clover, nonetheless soy is their best known source. Whilst only the chemical precursor of those hormones is natural, they are characterized as natural hormones due to their identical structure to that of endogenous hormones, although produced by recombinant genetic engineering. 56In this manner, the use of those substances assumes that the human body tends to better accept substances similar to those it produces naturally.

Salgado et al. point out that soy offers vast benefits for the human body, since studies comparing Eastern populations – who eat soy daily – with Western groups –who consume very little of that grain – showed that Asian women suffer less from the effects of menopause and are less likely to have breast cancer, osteoporosis and heart disease.[56] Clapauch et al., and Nahas et al. highlighted that only 20% of Eastern women – who consume between 20 and 150mg of isoflavone, a substance present

in soy – have hot flashes during menopause. On the other hand, 80% of Western women – who consume1 to 3mg per day of that substance- have that symptom.[57]

In the study by Fonseca, 78 and symptomatic postmenopausal women were divided into two groups:the first was treated with 60g of soy/day, and the second received a conventional hormone replacement therapy. After four months of treatment, it was concluded that the group which had received soy-had controledthe menopausal symptoms in the same way that the group treated with synthetic hormone did, however the adverse reactions observed in the conventional treatment, such as mastodynia, thrombophlebitis and other,did not occurrin the group treated with soy.[58] Carmignani also concluded that the soy-based food showed good acceptability and few side effects, with an efficacy comparable to conventional HRT and greater than that of the placebo in relieving hot flashes, joint and muscle pain, and vaginal dryness in postmenopausal women.[55] Sousa et al. showed that the ingestion of isoflavone capsules reduced menopausal symptoms in 45% of women.[59]

In an observational study, a decrease in breast cancer was observed in patients who underwent treatment with estrogen and progesterone's bioidentical hormones, when compared to those treated with synthetic hormone.[60] Other studies using doses of natural estrogen and testosterone showed benefits in postmenopausal bone loss, however, despite the claims made in favor of that therapy, none of those assertions was proved, because they were not directly fundamented on bioidentical hormones in addition to requiring clinical studies for its proof.[52]

The most common bioidentical hormones are estradiol, estriol, progesterone and testosterone, which can be present in various formulations, allowing individualized hormone therapy according to the patients' needs to relieve menopausal symptoms.[52] Although the use of bioidentical hormones is theoretically interesting due to their similarity to endogenous hormones and the practicality of pharmaceutical dispensing, there is lack of publications that present randomized controlled clinical trials, proving its superiority over the conventional therapy based on more concrete evidence.[56] The benefits of the therapy should therefore be discussed for each patient, who should use only products that have been thoroughly tested and offer increased safety.

CONCLUSION

The hormone replacement therapy in the elderly is the subject of increasing interest in medicine, due to the decline in hormone production and function with aging. In this manner, many people have bet on hormone replacement as a current source of youth. That correlation is however still uncertain, with controversial study results so far. In line with that, only a few randomized, placebo-controlled trials have been carried out, and most studies do not cover a large number of patients or an extended period of time. As a result, the safety of hormone replacement therapy, the benefit/risk ratio and side effects have not been established yet. The use of alternative antiaging tools that have proven beneficial effects to the organism and can assist in hormone production – such as good sleep, correct eating, and the practice of physical exercises, lead to more accurate results and do not present risks when the it comes to aging and quality of life. ●

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