Review Article

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Hormonal therapy for aging process in women

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ABSTRACT

Aging is a natural process that continues over time. This process begins with fertilization and experienced by all living things, with different manifestation between each person. Since time immemorial, mankind has been concerned with the development and maintenance of their youth, slowing the aging process, and prolonging life. Currently, there are major advances for understanding the aging process in an attempt to delay it. Some scientific literature shows that supplementation with hormones such as estrogen, progesterone, testosterone, growth hormone, and thyroid hormones have the potential to improve the quality of life and prevent many symptoms and conditions associated with aging, including fatigue, depression, weight gain, weakness, osteoporosis, loss of libido, and cardiovascular disease. There are doubts about the side effects of long term use of hormonal therapy, including increased risk of cancer. Because hormone levels declines with aging, hormone treatment has been referred to as the "fountain of youth". Many studies were conducted to prove the efficacy of hormonal therapy, but only partial data has shown the expected positive effects of the hormone on aging.

Keywords: Aging process, Hormonal therapy

INTRODUCTION

The aging process

The aging process is a natural process that continues overtime. This process begins with fertilization and commonly experienced by all living things, with different manifestation between each person. The process of birth, growth, puberty and being old are part of the normal aging process, with death as the end result. ¹

Turner et al. stated that the aging process is divided into external and internal aging. External aging process is a process with visible symptoms. Alteration can be observed from the skin, hair, teeth, and posture. Internal aging is aging process which was not visible, such as

degenerative changes that occur in the body. These changes occur in the nervous system, cardiovascular, respiratory, digestive, urinary, and immune system. Aging process may be caused by age factor and may also occur due to psychosocial factors such as stress, socioeconomic, environmental, food (nutrition) and individual health.²

Re-epitheliazation of the stratum corneum after blistering is also diminished, being twice as long for people over 75 than for those aged 25. Injury repair also diminishes with age. Wound healing even begin later is proceed more slowly. For examples a wound area of 40 cm², which in 20 years old subjects took 40 days to heal, required almost twice as long 70 days in those over 80. 4.5

As we get older, our hair will slowly turn white and lose its brilliance. Hair will become thin and gray. Hormonal changes can also lead to hair loss. At 65 years old, approximately 50% of the elderly will also lose their teeth. This change affects the elderly abilities to chew foods and inducing appetite loss. Reduction of bone and body mass may manifest as loss of body height. This process began since adolescent period. Decrease of collagen in the spine resulting in bent spine. It makes the elderly appear shorter. These factors influence each other and affect each individual differently.⁶

HORMONAL THERAPY ON AGING PROCESS IN WOMEN

Since time immemorial, man has been concerned with the development and maintenance of their youth, slowing the passage of age, and prolonging life. Currently there are major advances for understanding the aging process in an attempt to delay it.⁷

Some scientific literature showed that using supplementation containing hormones such as estrogen, progesterone, testosterone, growth hormone, and thyroid hormones have the potential to improve the quality of life and prevents many symptoms and conditions associated with aging, including fatigue, depression, weight gain, weakness, osteoporosis, loss of libido, and cardiovascular disease. There are doubts about the side effects of long term use of hormonal therapy, including increased potential risk of cancer. When trying to find the idea of a balance for each patient, the doctor should be concerned not only about increasing their lifetime, but also their health, including the length of time a person experiences a high quality, strong, and happy life.

Because levels of hormones decline because of aging, hormone treatment has been referred to as "fountain of youth (youth peak)". Many studies were conducted to prove the efficacy of hormonal therapy, but the data has not shown the expected positive impact of hormones on aging (Table 1).⁹

Table 1: Summary of the effect of hormones as antiaging interventions.

Testosterone

Decrease in fat mass and increase in lean mass Mixed data on the effect on cognition

Dehydroepiandrosterone

Inconsistent data on muscle mass, fat mass, and strength Insufficient evidence for improvement in cognition

Growth hormone

Increase in lean body mass; decrease in fat mass Increase in bone mineral density Increase in mortality⁷³

Vitamin D

May improve muscle function

Kamel Nabil S, Julie Gammack, Oscar Cepeda, Joseph H. Faherty. Antioxidants and hormones as antiaging therapies: high hopes, disappointing results. Cleveland Clin J Med. 2006;73(12):1049-56.

Testosterone

The production of testosterone in women is derived from three sources: the ovaries, adrenal glands, and from peripheral conversion of circulating androgens.⁸

Testosterone is used clinically in two different methods, as Androgen Replacement Therapy (ART) and as Pharmacological Androgen Therapy (PAT). For ART, the goal is to replicate, to extend the endogenous androgen exposure by tissues using titration dose of testosterone.

Although there is still no approval from FDA to license the use of testosterone treatment for "testosterone insufficiency" in women, but the use of androgen replacement has been used for more than 70 years. 8

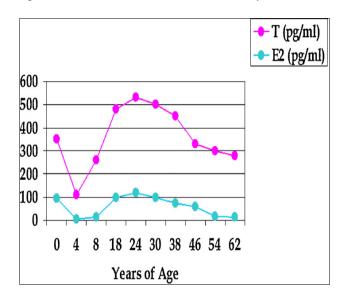


Figure 1: Levels of testosterone (T) and estradiol (E2) on various age.⁸

Schwartz Erika, Kent Holtorf. Hormone replacement therapy in the geriatric patient: current state of the evidence and questions for the future. Estrogen, progesterone, testosterone, and thyroid hormone augmentation in geriatric clinical practice: part 1. Clin Geriatr Med. 2011;4(4):542-59.

There are some reports about testosterone replacement therapy with a variety of benefits that includes increased of libido, bone density, muscle mass, body composition, mood, and erythropoiesis, although their usage is still controversial.⁷

Some potential side effects associated with testosterone therapy in women includes potential adverse effects on the cardiovascular system, hirsutism, acne, and breast cancer. The main concern of testosterone replacement in women is the potential negative effects on lipids. Some studies showed that the use of testosterone may be related with significant adverse effect on levels of lipids, including a slight decrease in High-Density Lipoprotein (HDL).

Dehydroepiandrosterone (DHEA)

DHEA is an intermediate in the metabolic pathway for the synthesis of testosterone, estrone, and estradiol. In men and women, both of DHEA and DHEA sulfate levels (DHEAS, especially circulated as hormone) declined by about 2% per year. At the age of 80, the level is only about 20% of people aged 20 years old. 9

Either DHEA or low-dose testosterone replacement in elderly people has relevant physiologically beneficial effects on body composition, physical performance, insulin sensitivity or quality of life.⁷

Some research concluded that there is little benefit from the recovery of DHEA levels in elderly women and men, where the use of DHEA replacement is an effective treatment in antiaging hormonal therapy. 10-13

Growth hormone

Growth hormone level in the serum is high in early life, according to the period of rapid somatic growth, its level begin to decline after reaching the adulthood and also the maturity of physical and reproductive systems. This decline continues during adulthood and elderly, and consequently GH levels serum in the elderly is significantly lower than in adults. ¹¹

Although the underlying mechanisms are associated with age, variations in GH secretion, include its peripheral effect (ie, gonadal steroids, adiposity), changes in hypothalamic neuropeptides and neurotransmitters may cause decrease of GnRH level and somatostatin hypersecretion absolutely or relatively. In addition, variation in ghrelin, a hormone that is identified as a natural digestive GH Secretagogue (GHS) - plays a role for the decline in GH secretion associated aging. ¹¹

Rudman and colleagues provide the first evidence that GH treatment (30 µg/kg three times a week for six months) in the elderly could reverse some of the changes characterizing a somatopause, such as improvements in body composition and Bone Mineral Density (BMD).¹¹

GHRT is expensive, approximately \$ 12000 - \$ 15000 per year including laboratory screening - because it's not an option for everyone. It is associated with side effects, such as insulin resistance. However, when used properly by a competent physician, GH is safe. GHRT associated with less morbidity and mortality, reduced risk of cardiovascular disease, the reduction of the inflammatory process, as well as improvements in body composition, increased exercise capacity, thus creating a higher quality of life. ¹¹

Basically, treatment with growth hormone can be used to improve body composition parameters, the following is a comparison of the use of growth hormone by some studies. ¹¹

Table 2: Comparison of the use of growth hormone in the aging process. 11

Study	Initial daily GH dose (µg/kg/day)	Duration of treatment (months)	Positive effects	Adverse effects	
Rudman 1990	12.9	6	increase lean mass increase BMD	hypertension hyperglycemia	
Holloway 1994	43	6	decrease fat mass increase lean mass	edema carpal tunnel syndrome	
Papadakis 1996	12.9	6	decrease fat mass increase lean mass	edema arthralgias	
Johannson 1997	9.5	9	decrease fat mass improve insulin sensitivity decrease cholesterol	edema carpal tunnel syndrome arthralgias	
Lange 2002	12.9 (±exercise)	3	decrease fat mass increase lean mass	edema carpal tunnel syndrome	
Franco 2005	7.8	12	decrease fat mass improve insulin sensitivity, decrease cholesterol	edema hyperglycemia	

Giordano Roberta, Lorenza Bonelli, Ellisa Marinazzo, Ezio Ghigo, Emanuella Arvat. Growth hormone treatment in human aging: benefits and risks. Hormones. 2008;7(2):133-9.

A systematic review was done by Liu and colleagues (2007) of 31 articles describing 18 unique study populations who received growth hormone treatment. They conclude that due to small changes in body composition and increased rates of adverse events, GH cannot be recommended as an antiaging therapy.¹⁴

Estrogen

Estrogens are used in HRT:

- 1. Estradiol (E2) are mostly natural and appropriate for therapy, other estrogen such as estrone (E1) and estriol (E3) are weaker than E2, all of these are identical with hormones produced by the ovaries.
- 2. Estradiol valerate: a minor modification of the natural molecule (esterification form).
- Conjugated Equine Estrogen (CEE): a mixture of estrogen derived from pregnant horse urine which mainly consists of estrone sulfate and equilin sulfate.

Synthetic estrogens are synthetic molecules with estrogenic properties such as ethinyl estradiol. Estrogen is mainly used in oral contraceptives, these synthetic hormones have a high potential for adverse effects on the liver and increased risk for hypertension and thromboembolic disease. Potency of synthetic estrogen in the liver is 4-8 times more potent than natural estrogen. ¹⁵

Progestogens/Progestagen/Progestin

All available progestogen appears to be effective in protecting the endometrium from endometrial proliferation effects due to estrogen therapy, given adequate dose and duration of therapy. Progestogen derived from the two chemical clusters namely class 19 - nonprogestogen and C-21 progestogen. The choice of progestogen for hormone replacement therapy depends completely on safety considerations and tolerance. Some of the progestogen available in the market can be seen in Table 3. 16-20

Table 3: Type of progestogen available in Indonesia.

Name	Available brand	Uses	Mechanism of action	Route	Prices*
Levonorgestrel	Postinor-2 , microlut, mirena	Emergency contraceptive	Potent inhibitor ovulation and has androgenic activity	Oral	\$ 1.73
Medroxyprogesterone	Depo-progestin, Deponeo, toriclofem	Systemic contraceptive	Convert the proliferative phase of the endometrium into secretory phase. Parenteral use leads to inhibition of pituitary gonadotropin, thus preventing follicular maturation and ovulation	Oral and intramuscular injection	\$ 11.98 for 20 (1 mL) vial
Norethisterone	Norelut, Primolut N	Systemic contraceptive, abnormal uterine bleeding	Convert the proliferative phase of the endometrium into secretory phase. Parenteral use leads to inhibition of pituitary gonadotropin, thus preventing follicular maturation and ovulation	Oral	\$ 0.38
Progesterone	Cygest, uterogestan	Maintenance of pregnancy, Abnormal Uterine Bleeding	Induce secretory changes in the endometrium, block follicular ovulation and maturation	Oral, intravaginal	\$ 11.06/5 supp
Medrogestone	Prothil, colpro(ne)	Hormone replacement therapy, amenorrhea, treatment of endometrial cancer	Progestogenic effect and oppose the proliferative effect of estrogen	Oral	Not widely available in Indonesia

^{*}Price in US Dollar converted from price in Indonesia with currency exchange rate of 1 USD = Rp. 13.025 (March 2015)

MIMS Indonesia (2015). https://www.mimsonline.com/id/Search/Search.aspx

Symptoms of progestogen side effect are specific and affects the metabolism of carbohydrates and fats in the blood, and is associated primarily with androgenic potency while also depends on the dosage. Potentially high androgenic levo-norgestrel eg, norethisteron, derivatives of 19-nonprogestogen potentially low androgenic or without potential of the C-21 derivatives progestogen, respectively Medroxy Progestorone Acetate (MPA) and progesterone and didrogesterone. ¹⁵

Administration route of hormone replacement therapy is one of the important factors for the success of the treatment. Hormone replacement therapy can be administered in various ways such as: oral, vaginal, transdermal, subcutaneous, and intranasal. There are advantages and disadvantages with each mode of administration. There are two methods of transdermal administration, in the form of plaster and gel. ^{21,22}

CONCLUSION

Aging is a process that occur in all living things. Aging process is divided into external and internal aging.

External aging is aging process with visible symptoms. Alteration can be observed from the skin, hair, teeth, and posture. Internal aging is aging symptoms which is not visible, such as degenerative changes that occur in the body. These changes occurs especially in the nervous system and cardiovascular system.

There are variety of hormonal treatments that can reduce the unwanted effects of aging process, including testosterone, DHEA, growth hormone, estrogen and progesterone. Some scientific literature showed that using supplementation containing hormones such as estrogen, progesterone, testosterone, growth hormone, and thyroid hormones have the potential to improve the quality of life and prevent many symptoms and conditions associated with aging, including fatigue, depression, weight gain, weakness, osteoporosis, loss of libido, and cardiovascular disease. There are doubts about the side effects of long term use of hormonal therapy, including increased potential risk of cancer. When trying to find the idea of a balance for each patient, the doctor should be concerned not only about increasing their lifetime, but also their health, including the length of time a person experiences a high quality, strong, and happy life.

Hormonal therapy is a promising candidate for the socalled "fountain of youth". But, further study is required to make it a staple in treatment to delay aging process.

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