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# SEDENTARY LIFESTYLE AND THE ROLE OF EXERCISE IN *ANTI-AGING MEDICINE*: A Literature Review

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## ABSTRACT

**Background**. The concept of anti-aging medicine is very popular these days. Many studies discuss how to inhibit the aging process so as to prevent various degenerative diseases and improve quality of life. In the concept of anti-aging medicine, aging prevention is not only based on one aspect for example aesthetics procedure that is currently popular. **Method**. The study was literature review from various international journals and books with related keywords, including anti-aging medicine, sedentary, aging, exercise, which were published in the last 10 years. **Result and Conclusion**. In the concept of anti-aging medicine, a comprehensive approach is needed to slow down the aging process, including hormonal, skin, nutritional approaches, including a healthy lifestyle. A healthy lifestyle plays an important role in the aging process itself, including physical activity. Sedentary or inactive behavior is closely related to an increased risk of diseases associated with aging.

Key word: *healthy life style; sedentary behavior; exercise; aging*

## INTRODUCTION

Aging is natural for every human being. The aging process causes a decrease in all organ systems in physiological and structural functions. Various diseases associated with the aging process will arise, such as cardiovascular disease, hypertension, diabetes, and other degenerative diseases. With age, changes occur in all components of the body naturally in the respiratory system, cardiovascular, immune system, hormonal, gastrointestinal, musculoskeletal and others. Cellular processes and the functions of organs and tissues physiologically also begin to decline, age, until various diseases associated with the aging process arise.

There are many factors that cause a person to age, generally these factors can be grouped into two, namely internal factors and external factors. External factors are unhealthy lifestyle, unhealthy diet, wrong habits, environmental pollution, stress and poverty. Internal factors are free radicals, reduced hormones, glycosylation processes, methylation, apoptosis, decreased immune system and genes (1,2). Unhealthy lifestyle, e.g., physical inactivity or sedentary behavior has major metabolic consequences, due to decreased function of several organ systems, which ultimately leads to an increased risk of degenerative diseases. The sedentary lifestyle, contributes to the increasing prevalence of obesity, diabetes, cardiovascular disease and is a major cause of premature death (3,4)

In previous studies, the sedentary population had an increased risk of developing cardiovascular disease by 46%, as well as the mortality rate. A sedentary lifestyle is someone with low physical activity with MVPA (moderate-to-vigorous physical activity) of less than 30 minutes a week and a total sitting time of 540 minutes on weekdays (5). Sedentary lifestyles were associated with 9% of premature deaths, or more than 5.3 million of the 57 million deaths that occurred worldwide in 2008. Studies estimate that eliminating sedentary lifestyles will increase the life expectancy of the world's population by 0.68 years (6,7).

Various health consequences arising from a sedentary lifestyle. For example, an increase in the percentage of body fat and the risk of obesity which can trigger conditions of oxidative stress or decrease and increase in hormone levels. This is also exacerbated by a decrease in the ability of endogenous antioxidants such as SOD (Superoxide dismutase), CAT (catalase) and GSH-Px (glutathione peroxidase), along with aging (8,9). Research in Atlanta in 260 women aged 18-55 years previously showed that sedentary women experience increased inflammation and levels of oxidative stress. Avelar

et al mentioned that a sedentary lifestyle is one of the causes for the formation of reactive oxygen compounds, in addition to smoking, an unbalanced diet, and other environmental factors (10,11).

Over the last few years, physical activity has been recognized as a major health-enhancing behavior. There is the concept of *exercise medicine*, in which exercise training is used to prevent or even as an additional therapy in pathological conditions. However, the link between sedentary lifestyle, exercise and the aging process through the mechanism is still unclear and is still widely debated. This literature review is to discuss the relationship between sedentary behavior and aging, and the role of exercise in the concept of *anti-aging medicine*.

## METHOD

This article was a review study from several international journals and books. The method of the study was literature review from various international journals and books with related keywords, including anti-aging medicine, sedentary, aging, exercise. Criteria inclusion was reference literature obtained through Google Scholar, research gate and Pubmed databases, which were published in the last 10 years.

## DISSCUSSION

### Aging Processes and Concept *Anti-Aging Medicine*

Aging is a multifactorial process that is not only influenced by genetic factors, but also by environmental factors. The aging process is associated with hormonal and metabolic changes. Aging has been defined as a progressive post maturational decline in physiological capacity, accompanied by an increased susceptibility to disease and an increased risk of mortality (12,13). The aging process can be considered as a disease that can be prevented, treated and even reverse (1). The concept of *Anti-Aging Medicine* seeks to overcome the aging process so that complaints, dysfunctions or diseases do not arise by carrying out early detection, prevention, treatment and improvement of various dysfunctions, disorders and diseases related to aging, with the aim of prolonging life in a healthy state. The concept of Anti-Aging Medicine is extended to eliminate disability, deformity, pain, disease, suffering and sadness in old age (2).

### The Changes Associated with The Aging Process

In the aging process there will be a decrease or even cessation of the functions of various organs of the body. The decline in the function of various organs of the body results in various signs and symptoms of the aging process, both physical and psychological signs. Physical signs of the aging process such as decreased muscle mass, increased fat, wrinkled skin, reduced memory, impaired sexual function, decreased work ability and bone pain. The psychological signs include decreased passion for life, difficulty sleeping, easily anxious, easily offended and feel insignificant(2,14). The decline in function that occurs due to the aging process actually begins at a young age but without symptoms. The aging process occurs through several stages, namely (1): 1. Subclinical stage (age 25-35 years). At this stage the body's hormones have decreased and the formation of free radicals begins to affect the body, but the damage caused is not yet visible from outside the body.; 2. Transitional stage (age 35-45 years). At this stage hormone levels have decreased to 25%. Reduced muscle mass while increasing body fat composition, this situation causes insulin resistance, increased risk of heart disease, blood vessels and obesity. The damage caused by free radicals begins to impair genetic expression, leading to diseases such as cancer, arthritis, memory loss, coronary heart disease and obesity.; 3. Clinical stage (age 45 years and over). The decline continues in hormone levels, and losing the ability to absorb food, vitamins and minerals. Bone density and the muscle mass decreases. The chronic diseases begin to manifest themselves affect the organ systems failure. Disability is the main factor that interferes with daily activities.

Age related to derivation of circulating levels of particular hormone that can contribute to another symptoms of aging. The decrease in hormonal levels along with aging does have an impact that is not only limited to the organs that produce these hormones, but also seen on other tissues or organs as an effector of the trophic hormones produced. Hormones that decrease with aging such as dehydroepiandrosterone, estradiol 17 beta, testosterone, growth hormone as well insulin-like growth

factor-1 (IGF-1) (15,16), and others. Decreased hormone levels contribute to various organ system functions such as the endocrine system which plays a role in cellular interactions, metabolic systems and growth, defense against oxidative stress(17). Few studies showed that decreased levels of the hormone estrogen with aging show an inverse correlation with levels of body fat, as well as an increase in osteoporosis and cardiovascular risk (14), but linear with decrease in muscle mass, bone mass and density, and ultimately reduce the human health range (18,19). In skin aging, decreased estrogen levels affect reduced skin elasticity, increased wrinkle and dryness of the skin and reduced vascularity. Reducing the hormone estrogen contributes to a decreased ability in metabolic regulation that regulates mitochondrial function through genomic and nongenomic pathways, and reduces the ability to prevent oxidative stress conditions (12,20).

The hormone IGF-1 (insulin-like growth factor-1) also decreases with aging. The release of the hormone IGF-1 from the liver is influenced by the Growth Hormone (GH) which is released from the anterior pituitary gland. Reduced secretion of IGF-1 and GH contributes to decreased ability to defend against oxidative stress, muscle strength, and functional capacity. Reduced secretion also has an association with abdominal (central) obesity (21,22). The reduction in circulating anabolic hormones, namely growth hormone (GH) and IGF-I, has been termed 'somatopause'(23).

The drastic decrease in systemic testosterone with age is well explained. Testosterone is a sex steroid hormone with a major effect on various tissues. Sex hormone binding globulin (SHBG) is positively correlated with age, thereby weakening the unbound fraction of testosterone available for androgen receptor interaction. The derivation production of anabolic hormones, decreases in cardiorespiratory fitness, muscle strength and this decline are closely related to age (24).

Aging also contributes to decreased activity of SIRT1 as an $NAD^+$ dependent deacetylase. As a member of sirtuins, sirtuin 1 (SIRT1) is the one that has the closest relationship with metabolic regulation. SIRT1 deacetylates a number of proteins related to apoptosis, cell cycle, circadian rhythms, mitochondrial function and metabolic processes (25). There are studies show that along with aging SIRT1 levels decrease. This decrease has an impact on the ability to maintain mitochondrial function and prevent oxidative stress, through mediation of acetylation such as PGC-1α, FOXO3, p53 and NF-κβ. In maintaining metabolic homeostasis, SIRT1 can also interact directly with PPARγ and the FOXO transcription factor as the main regulator of tissue metabolism (26,27). The protein deacetylase sirtuin 1 (SIRT1) and activate peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) pathway can directly regulate the skeletal muscle functions and promotes a change in muscle fiber type (28).

The anatomical and physiological changes associated with aging begin many years before the appearance of external signs, and continues with age. These changes not only in hormonal imbalance but also accompanied by a gradual decline in physical fitness and physical activity. This alteration of the cardiovascular and respiratory systems during the aging process starting from the age of 20 where by the decline is about 10 % per decade in maximum oxygen uptake. With age, the neuromuscular system was changes and the type II fiber loss leading to decreased anaerobic performance. In other side, around $30^{th}$ the decrease in muscle capacity at the rate of contraction, either in muscle strength and mass, is around 15% per decade. Age-related decline in physical performance and muscle weakness are changes in the endocrine system. For example, growth hormone (GH) secretion decreases with age which is associated with loss of muscle mass, physical function, and an increased risk of frailty, cardiovascular disease, and adiposity, among others (29–31).

**Effect Sedentary Lifestyle in Aging Processes**

A sedentary lifestyle is a condition when a person with low physical activity with MVPA (moderate-to-vigorous physical activity) is less than 30 minutes a week and the total sitting time is 540 minutes in 5 working days (weekdays) (5). A sedentary lifestyle causes a decrease in physiological function that increases the risk of obesity, hypertension, hyperlipidemia, and insulin resistance, which are risk factors for cardiovascular disease (CVD). The sedentary population has an increased risk of developing cardiovascular disease, is about 46%, and the mortality rate due to cardiovascular disease is higher, is about 80%. This is strongly related to the risk of excess weight in sedentary leading to oxidative stress conditions (6,32,33).

Sedentary behavior is associated with excess adiposity and obesity increase the risk developing cardiometabolic disease including diabetes type 2, hypertension and others degenerative disease.

Obesity caused by inactivity lifestyle that related to imbalance in energy homeostasis whereby the calory intake is exceeds the energy expenditure (32,34).

A sedentary lifestyle is a major cause of obesity and other degenerative diseases. Doing regular physical activity is known to increase muscle mass and decrease body fat mass, while lack of physical activity is associated with reduced muscle mass and increased fat tissue. About 25-30 percent of energy is used for muscle activity every day. Increasing physical activity is an effective way to reduce fat stores.

During aging, oxidative stress increases and causes many in the normal and pathological characteristic in elderly(12). Oxidative damage can compromise cell metabolism, differentiation, proliferation, survival and reproduction and long-term effects of oxidative damage are implicated in skin aging, cancer and inflammation. Antioxidants are cell affective mechanism for the defense against oxidative damage. The oxidative stress theory of aging emphasizes that a progressive and irreversible escalation of oxidative damage caused by reactive oxygen species (ROSs) exerts severe influence on the critical aspects of the biology of aging and contributes to impaired physiological functions, increased incidence of diseases, and shortening of life span (35). Long-term sedentary behavior is one source of free radicals.

Growth hormone secretion decrease from puberty varied between 1–1.5 mg/day, become 50 µg/day in elderly. Several factors may be responsible for this decline, including physical inactivity, contribute to the alteration of hypothalamic and somatostatin hormones (29). Lifelong sedentariness was associated with lower systemic IGF-I, either GH secretion (23).

**The Role of Exercise in Delays Aging Process**

Physical activity is movement activity or the act of contracting skeletal muscles that function to make the body move. A muscle activity requires energy, so that all forms of motor activity involve energy expenditure depending on the duration, intensity, and type of activity (36,37). According to the WHO (World Health Organization), physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels (4).

Human physical activity can be included in several types. Spontaneous physical activity includes small motoric actions that occur during everyday life without conscious thought, such as fidgeting, standing, holding a book, and walking around the house. These activities are expressed as actual energy expenditure under the classification of non-exercise thermogenesis, or NEAT activities. Voluntary physical activity is that which is planned and purposive, including activities that expend energy. Such a wide range of physical activities such as gardening and many recreational activities such as dancing, tennis, basketball and golf, as well as traditional aerobic exercises (e.g., walking, running, cycling and swimming), stretching (6,38,39). Physical exercise is a part of physical activity that involves muscle action that requires an increase in the metabolic rate. Physical exercises are generally grouped into aerobic exercise, anaerobic exercise (28).

Exercise training attenuates many biological markers of aging(29). Doing physical activity is known to provide various benefits to the body. As stated by a previous study, aerobic dance exercise after 6 weeks of moderate intensity in sedentary women, can significantly reduce MDA levels and increase VO2max (10,40). Physical training is also known to be one of the efforts to increase the body's endogenous antioxidants so that it can further prevent oxidative stress conditions. As in research, exercise training with submaximal intensity can increase plasma levels of antioxidants CAT, SOD, and GSH-Px in untrained subjects (11,41,42).

The body's response to physical activity begins when the skeletal muscles contract, as an active process that requires ATP as an energy source. The physiological response depends on the intensity, duration and frequency of the physical exercise performed. Although there are other factors that influence the physiological response such as environmental conditions. During physical exercise, the need for oxygen and substrates in skeletal muscles increases, as well as the disposal of metabolites and carbon dioxide (43). Chemical, mechanical and thermal stimuli affect changes in metabolic, cardiovascular and ventilation functions to meet increased metabolic demands. Furthermore, when physical exercise begins, input of mechanoreceptors from the extremities will activate the control centers of both the respiratory, cardiovascular and other organ systems. In the circulatory system, mechanosensory input activates the cardiovascular control center in the medulla oblongata which then

elicits a response by sending sympathetic impulses that increase cardiac output and cause vasoconstriction of various peripheral arterioles. Likewise with the ventilation response of the respiratory system to exercise, which begins with signals from mechanoreceptors and proprioceptors in the muscles that send information about physical activity to the motor cortex (44–46).

When the body does physical exercise it will cause an increase in $NAD^+$, which will become a metabolic sensor that triggers SIRT1 activation (25). With aging there is a decrease in tissue $NAD^+$ levels associated with decreased SIRT1 activity. Reduced $NAD^+$/NADH causes an increase in ROS formation in mitochondria (47). SIRT1 is one of the mammalians sirtuins, a group of NAD+-dependent deacetylases, which regulate a wide variety of cellular processes, including metabolism, development, cell survival and aging. SIRT1 has an important role in maintaining lipid homeostasis through PPARα mediating beta-oxidation of fatty acids in the liver and mobilization of fat from fat cells during fasting. SIRT1 inhibits PPARγ which triggers a decrease in adipogenesis and increases lipolysis (48). This prevents excessive accumulation of fat in the body, and can reduce the risk of obesity. SIRT1 has been shown to interact directly with PGC-1 to increase PGC-1α expression. PGC-1α has been characterized as a major regulator of glucose homeostasis, lipid catabolism, mitochondrial biogenesis and mitochondrial functions (49,50). The PGC-1α signaling pathway is associated with the regulation of the mitochondrial antioxidant system, which can mitigate oxidative stress damage.

Physical exercise can increase Cxc-Chemokine receptor Type 4 (CXCR4) and Janus kinase-2 (Jak-2) signaling which decreases with aging(49). The increase in signaling can further increase the capacity of the body's endogenous antioxidants such as SOD. The increased antioxidant defense can inhibit the formation of free radicals. The accumulation of free radicals can trigger oxidative stress which is associated with various pathological conditions and degenerative diseases. Hormonally, physical exercise can also increase estrogen levels through activation of estrogen receptors and growth hormone which, in addition to having the ability to increase the body's antioxidant capacity, can also prevent oxidative stress through inhibition of Forkhead BoxO- (FOXO) by activating Phosphatidyl Inositol 3 kinase (PI3k) and Akt (Wackerhage, 2014). This inhibition will then increase the content of endogenous antioxidants such as SOD, which play a role in inhibiting the formation of free radicals (50,51).

Exercise training impact hormone secretion, depending on the frequency, duration, intensity, and mode of exercise. Recent studies have reported the anti-aging effects of exercise training on the endocrine system including estrogen, cortisol, growth hormone and insulin. Physical exercise essential for hormonal homeostasis including sex steroid hormone. Physical exercise also plays a role in increasing the expression of estrogen receptors in several tissues(52). The effect of physical exercise on the hormone estrogen is also mentioned through the hypothalamus-pituitary-ovarian axis and affects the hormones secreted (53). Recent studies have shown that insulin-like growth factor-1 (IGF-1) signaling pathways have an important influence on the rate of aging. The most important effect of increasing age on the hormone IGF-1 is an increase in fasting insulin and a decrease in insulin sensitivity. Recent studies have shown that exercise training of different modes, volumes, and intensities has increased insulin levels in older adults (29).

Physical exercise, especially acute aerobic exercise is the most potent stimulus to release GH. Secretion of GH is corelate to exercise intensity whereby GH level will increase 5,1-fold after exercise (54). GH regulates whole body metabolism, increase lipolysis and free fat acids mobilization. Aerobic exercise modulates hormone, and neurotransmitter levels depends on factors such as genes, age or hormonal status (55). Regular endurance exercise showed to prevent age-related endothelial dysfunction (56). Exercise may therefore be a protective stimulus to promote healthy vascular and metabolic aging (57).

Regular exercise improves endogenous antioxidant defenses and immune system (58,59). The total number of leukocytes circulating in peripheral blood is strongly influenced by physical exercise (60), however these depend on the intensity and duration of the single bout exercise compare with repeated bouts exercise, training status, age, nutritional status and infection history. Exercise is effective in preventing cancer and infectious diseases by enhancing cell-mediated and adaptive immune responses. One study shows a significant increase in NK cell activity in aerobic exercise (61). Exercise also effect Nrf2, the master regulator of antioxidant defenses, this evidence indicates that Nrf2 signaling plays a key role in how oxidative stress mediates the beneficial effects of exercise (59,62).

In exercise applications, the understanding of acute exercise-induced cell signaling as well as physiological adaptive responses resulting from accumulation after several bouts is advancing. Acute

exercise activates key messengers such as calcium, adenosine monophosphate (AMP), and mechanical stress; and secondary messengers include calcium/calmodulin-dependent protein kinase (CAMK), AMP-activated protein kinase (AMPK), and mitogen-activated protein kinase p38, causing acute changes in mRNA transcription. Transient changes in redox balance (or redox potential) are also important messengers stimulated by acute exercise, leading to a more oxidized state through production of reactive oxygen species (ROS). During muscle contraction it was shown that SIRT1 increased after endurance exercise to facilitate such metabolic adaptation (28). During muscle contraction it was shown that SIRT1 increased after endurance exercise to facilitate such metabolic adaptation (28). Therefore, SIRT1 activation involves metabolic and transcriptional rearrangements which are the indirect sequences induced by AMPK activation (28). AMPK as a sensor of metabolic energy deprivation, activated by exercise due to increased AMP/ATP ratio and Ca2+ flux during muscle contraction, increases PGC-1α transcription and activity. PGC-1α has a regulatory mechanism for the expression of endogenous antioxidant proteins.

It has been published that aging is associated with increased free radical generation and oxidative damage being the etiological basis for many diseases. Cell senescent is associated with impaired antioxidant defenses and the ability to adapt to oxidative stress due to structural and functional disturbances.

## RELEVANCE IN ANTI-AGING MEDICINE

The concept of Anti-Aging Medicine strives for overcome the aging process by carrying out early detection, prevention, treatment and improvement of various dysfunctions, disorders and diseases related to aging, with the aim of prolonging life in a healthy state. These prevention or improvement efforts can be based on the factors that cause aging. The aging process does not come by itself. There are many factors that can cause the aging process to go faster than it should be. Functional changes related to aging can be caused by both internal and external factors. External factors are unhealthy lifestyle, unhealthy diet, wrong habits, environmental pollution, stress and poverty. Internal factors are free radicals, reduced hormones, glycosylation processes, methylation, apoptosis, decreased immune system and genes(1).

One of them as an external factor that causes aging is an unhealthy lifestyle such as sedentary behavior and lack of physical activity. Internal factors are one of the causes of aging, namely reduced function of the hormonal system and decreased levels of body hormones. Many theories have been put forward in an attempt to explain the aging process. Broadly speaking, there are two groups, namely wear and tear theory and program theory. Aging is a progressive loss of physiological integrity and involves a very complicated process, and leads to impaired function and increased susceptibility to death(63). Program theory includes limited cell replication, immune processes and neuroendocrine theory. The wear and tear theory includes DNA damage, glycosylation and free radicals. The wear and tear theory states that organs, tissues or cells that are used continuously will eventually be damaged and eventually cannot be used again. Misuse of organs, wrong habits, exposure to toxins can also accelerate the damage caused. In program theory, it states that the human body and all the structures in it have a programmed biological clock, starting from the process of conception to old age and death. One of them is the hormone theory. Physiologically hormones are secreted by several organs under the control of the hypothalamus, but with age, the body's ability to produce hormones will decrease, resulting in a decrease in the function of the body's organs so that various related complaints appear.

If the aging process is left without preventive measures, it can lead to a decrease in the various functions of the body's organs, then it will reduce the quality of life. Prevention can be done through efforts to avoid factors that cause aging both internally and externally, such as adopting healthy habits and healthy lifestyle behaviors, so that the aging process can be slowed down. A healthy lifestyle and regularly exercise, has long-term beneficial effects by promoting metabolic adaptation, slowing biological aging and reducing the risk of various age-related diseases such as type 2 diabetes mellitus, cancer, cardiovascular disorders and inflammation, thus prolonging a healthy life (64). With regular exercise, promotes upregulation of endogenous antioxidant defenses and increase ability to counteract the damaging effects of oxidation to nucleic acids, proteins, and lipids (58,59). Exercise plays an integral role in maintaining muscle mass, metabolic health, improving cardiovascular function, and quality of life, in aging (23).

## CONCLUSSION

Aging is a multifactorial process that marked as a gradual loss of homeostasis associated with hormonal and metabolic changes. Aging is a decrease in various body functions, caused by internal and external factors. Unhealthy life style, such as sedentary behavior, is one of the external factors that cause aging. Regularly exercise training may reduce signs of aging. Physical activity driven by muscle contraction is one of the most powerful stimuli for the physiological adaptation of the body systems. Exercise that performed at proper intensity and duration obtain the desired biological benefits. Exercise can modulate beneficial effects by inducing metabolic adaptations, thereby reducing the risk of age- and lifestyle-related diseases such as cancer, type 2 diabetes mellitus, hypertension, cardiovascular and others, thereby slowing biological aging and improving quality of life. Lack of physical activity, in addition to the aging process itself, is thought to play a role in the progressive decline in the body's functional activity.

## CONFLICT OF INTEREST

The author declares no conflict of interest

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