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Regular Physical Exercise Increase Of Growth Hormone (GH) And Insulin-Like Growth Factor-1 (IGF-1) Activity in Elderly Improve the Aging Process and Quality of Life: A Mini Review

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By doing regular physical exercise, it is expected to improve the quality of life through increasing levels of the hormones GH and IGF-1. Many studies have been conducted to prove the effect of exercise on GH and IGF-1 levels, but still show inconsistent results. This review aims to find out whether regular physical exercise increase GH and IGF-1 levels in the elderly, and will improve the aging process and quality of life. This literature review inquiry was obtained from various PubMed and Google Scholar data bases by entering keywords, namely: It can be concluded that physical exercises may influence the secretion of hormones in the elderly and the hormonal impact of physical exercise can aid in determining the efficacy of training regimens for maintaining or improving IGF-1 and GH levels, as well as the possible impacts of various types of exercise on this hormone. This could increase elderly people's functional autonomy and quality of life.

Keywords: Aging; Elderly; Growth hormone (GH); IGF-1; Physical Exercise; Quality of Life.

Aging process is happened naturally, it is showed by the decreasing of body function, in physical and hormonal. In this step, most of hormones in body, especially testosterone, growth hormone, and estrogen, are decreased. The decreased of these hormones affect the decrease of body function generally.

In the age of 25 – 30 is known as subclinical step of aging, where the decreased level of GH is happened as well as estrogen and testosterone. By getting older, the amplitude of GH pulse is also decreased. GH secretion is dropped to 50% in every seven years after 18-25 years old. In the transition of aging process in the age of 35-45, the level of hormones is decreased to 25%. In the next step, at 40 years old and up or known as clinical step, the decrease of hormone level keeps happening, such as DHEA, melatonin, growth hormone, testosterone, estrogen and thyroid hormone. Bone density and muscle mass are decreased for about 1 kilogram every three years, which caused inability in burning calories, improve in body fat and body weight. Chronic disease will become to reality [1].

Aging is a dynamic and gradual process that includes changes in morphology, function, and biochemistry, as well as psychological alterations. These alterations result in a steady loss of environmental adaptability, resulting in a high proclivity for susceptibility and a higher

prevalence of pathogenic processes [2]. Deficiencies in balance, mobility, muscular strength, and flexibility are among the intrinsic variations in the aging process [2,3] changes in body composition, including muscular and bone mass loss [4] and endocrine problems, such as a drop in serum levels of insulin-like growth factor I (IGF-1)[5]. Aging process can be slowed down, delayed, treated, and turned back to its optimal condition in the young age with the healthy way. Certainly, there are many ways to prevent early aging, such as healthy life style, healthy diet and optimal physical exercise.

Physical exercise is a strong stimulus for GH secretion. GH works well directly through its receptor and indirectly stimulates the production insulin-like growth factor-1 (IGF-1) [6]. However, it still needs to be clarified for which mechanism of physical exercise can be used to increase GH secretion [7]. GH secretion is controlled by numbers of hypothalamus hormones, neurotransmitter, and IGF-1. IGF-1 is a primary mediator downstream to GH system, and the level of IGF-1 in a circulation has important role as the feedback of GH regulation. This is a strong reason that many researches were conducted toward the relation of IGF-1 and GH through physical exercise [7] .

Some researches had been conducted about the effect of physical exercise towards the level of IGF-1 plasma and showed inconsistent results. Some researches reported that there is an increase level of IGF-1 as the effect of physical exercise [8,9], no changing level in IGF-1[10,11]. Kim et al (2015) stated that the effect of physical activity towards IGF-1 secretion depends on energy supplementation, intensity, type and duration of physical exercise and further investigation is needed [12]. As a result, the goal of this study was to look at the impact of physical exercise on IGF-1 serum levels in the elderly, as well as the potential processes that underpin these responses.

METHODOLOGY

The review was conducted from the available literature on the internet that discuss about the effect of physical exercise to increase GH and IGF-1 level to improve aging process for better quality of life in elderly. The researchers used the search terms physical exercise, growth hormone (GH), IGF-1, elderly and aging process and quality of life on Google Scholar, PubMed, ScienceDirect, directory of Open Access Journal (DOAJ), ResearchGate search engines from 2004-2021. From the results, articles that have a definite relationship with the subject matter were included in this review and otherwise were excluded.

Regulation of Growth Hormone (GH) And Insulin Like Growth Factor-1 (IGF-1)

GH acts indirectly mediated by IGF-1 which acts on target cells to cause growth of both soft tissue and bone. IGF is produced in many tissues and has endocrine, paracrine, and autocrine actions. Peptide mediators were originally called somatomedins, but are now called insulin-like growth factors because they are structurally and functionally similar to insulin. Like insulin, IGFs exert their effects primarily by binding to receptor-enzymes that activate certain effector proteins in target cells by phosphorylation of tyrosine. IGF-1 synthesis is stimulated by GH and mediates the effects of this hormone in terms of promoting growth. The main source of IGF-1 in the blood is the liver, which secretes this peptide product into the blood in response to GH stimulation. IGF-1 is also produced by most other tissues, although they do not release it into the blood at all. Researchers suspect that IGF-1 produced locally in target tissues may act in paracrine ways [13].

Like the control of other anterior pituitary hormones, the negative feedback loop plays a role in controlling GH secretion. Complicating the negative feedback loop for the hypothalamic-pituitary-liver axis is the direct regulation of GH secretion by stimulatory and inhibitory factors. Therefore, the negative feedback loop involves both inhibition of excitatory factors and stimulation of inhibitory factors. GH stimulates the secretion of IGF-I by the liver, and IGF-I in turn is the primary inhibitor of GH secretion by the anterior pituitary. IGF-I inhibits pituitary somatotropes directly and further decreases GH secretion by inhibiting GHRH-secreting cells and stimulating somatostatin-secreting cells in the hypothalamus, thereby decreasing somatotrope stimulation by the hypothalamus. Furthermore, GH himself inhibits hypothalamic GHRH secretion and stimulates somatostatin release [13].

Neuroendocrine Control to GH Secretion Due to Exercise

The main component of neural system is

brain, while hormonal system is hypothalamus-hypophysis-adrenal axis. Both systems are working overlapped. Hypothalamus is a neural and endocrine organ. When an individual is encountered with certain stressor, so hypothalamus will coordinate the response which will be done. Hypothalamus designs body response by stimulating sympathetic nervous system and endocrine. Sympathetic nervous system supports activity which is related with "*fight or flight"* towards stress response and it is essential in managing body integrity response to physical exercise (including the increase of oxygen transportation to contracted muscle and the use of energy). Parasympathetic nervous system supports activity which is related with "*rest and digest*" and it is important to recovery process after physical exercise [14].

The main role of endocrine during physical activity is to help managing metabolic and cardiovascular system. Its secondary role is to be involved in functions of muscle, bone and tissue of fat. Hormone affects targeted-cells which is bonded to receptors of targeted-cells. The bonded-hormone and receptors are known as *receptor activation*. The response cellular area because of receptor activity depends of 3 factors [15], mainly: level of hormone in blood, amount of receptors and affinity between hormone and receptors.

Secretion and activity in most of hormones are increasing during exercise. However, the response pattern of the hormone is not clear yet and it depends on the intensity, duration of exercise and metabolic demand. The following are hormones which are involved in physical exercise.

GH is a hormone in a form of protein, it has a slow response, secretion and clearance, because of that GH is not directly improve in the beginning of exercise. The high intensity exercise will fasten the increase of GH secretion. Short and low intensity to moderate-submaximal aerobic exercise will shortly increase GH level and it is easy to be detected. Short duration of exercise with high intensity shows the peak level of GH for 15 – 30 minutes of exercise until recovery session. Aerobic exercise with moderate intensity to high-submaximal and long duration has caused an increase of GH gradually after 30 – 60 minutes, and in longer duration of physical activity, such as marathon, GH level is back to baseline. In aerobic exercise from minimum until maximum, GH

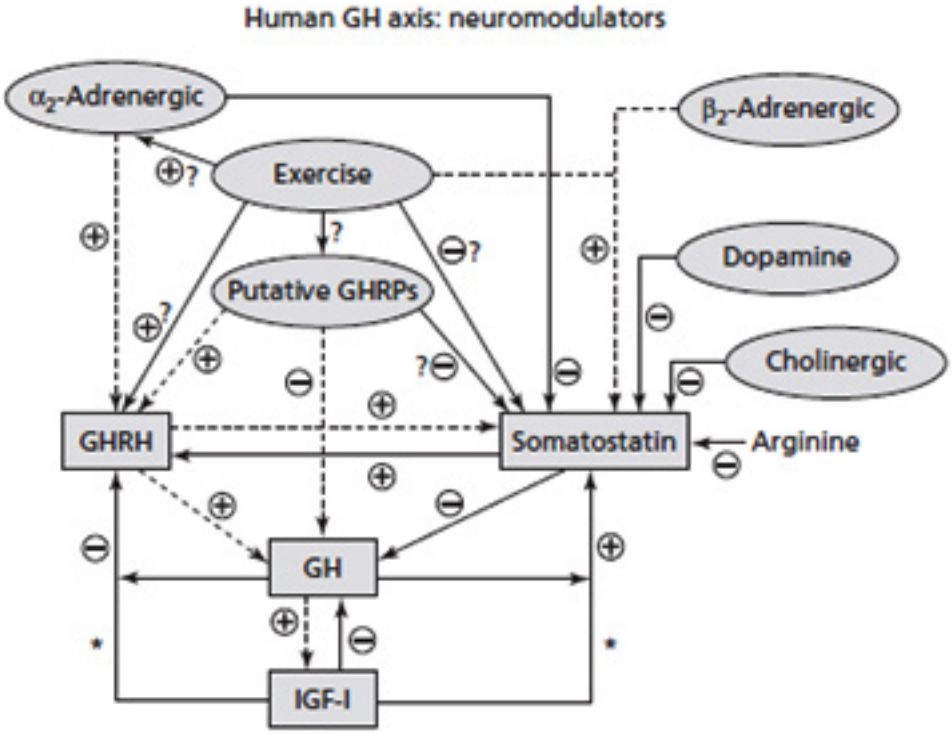

Fig. 1. Human GH axis: neuromodulators[18]

concentration is increasing along with the increase of workload [14]. The increasing level of GH also proved in the elderly who were doing exercise combination regularly for 10 weeks compared to control group[16].

The release of GH is increasing during resistance exercise. High total of working and short period of resting are related with the increase of high GH compared with low total of working and long period of resting. It is also applied if the exercises use a lot of muscle mass which caused higher level of GH compared to the exercises with less of muscle mass [17].

Neuroendocrine mechanism in induction of GH release due to exercise has not explained completely yet. Naturally, it involves a complex mechanism, even though the effects appeared due to this exercise happened through the input in hypothalamus. This mechanism is expected involving the release of GHRH and/or the withdrawal of somatostatin and probably the release of natural GHRP-like ligand (for example ghrelin) or several of these combinations (Fig.1.)[18].

Results from the previous researches about the effects of physical exercise toward level of IGF-1 are not consistent, whether physical exercise can increase the level of IGF-1 or not. A research reports about the increase level in IGF-1 serum during resistive and endurance exercise. Physical exercise is claimed to increase the level of IGF-1 serum in mutant mouse with low level of IGF-1 serum [19,20]. It is also supported by a research that has given aerobic exercise to mice and it is stated that there is an increase level in IGF-1 serum[21]. This is in line with a statement from Luo, *et al*. (2013) that an old mouse is given chronic resistance training and the level of its IGF-1 is increased [22].

Different results were obtained from a research which states that an adult mouse is given moderate physical exercise and there is no significant increase in IGF-1 serum level [23]. The same result is also shown in a study by Arikawa, et al. (2010) that aerobic exercise for a young woman do not show any change in the level of IGF-1[24].

IGF-1 secretion as the cause of physical exercise shows more correlation toward duration of physical exercise and session of single activity given [23]. Acute physical exercise in the first 10 minutes caused an increase temporarily in the level of IGF-1 serum and after that will be back to the baseline. Based on the research also found that the different research's results toward the effect of physical activity to the level of IGF-1 are all depend on types and intensity of the given physical activity [21]. The level of IGF-1 serum is reported increasing in chronic mild physical exercise and increasing in resistance exercise were inversely correlated with neurocognitive decline in the elderly [25,26].

Physical activity is also potent physiological stimulus to GH secretion for both aerobic and resistance exercise [18]. Aerobic exercise stimulates GH secretion after 15 minutes of exercise and the peak is close to the end of exercise. Intensity and duration of aerobic exercise, physical fitness, gender and age affect GH response towards exercise [27,28]. It is in line with a research conducted which state that the effect of aerobic exercise in a group of middle-aged woman and old woman can increase GH level. The stimulation of GH secretion due to exercise for older people is lower than younger people. GH secretion in postmenopausal women is lower 5,7 until 7,3 times than premenopausal women[29].

DISCUSSION

After the third decade of life, GH secretion decreases by about 15% for each decade of adult life. Integrated daily GH secretion measurements show that secretion peaks at around 150 g/kg/day during puberty, then drops to around 25 g/kg/day by age 55 [30]. IGF-I levels in the blood, the key mediator of growth hormone's trophic effects, likewise decrease with age. The liver produces the majority of circulating IGF-I under the control of GH. There is no evidence to support greater "GH resistance" as the age-related fall in IGF-I synthesis is a direct result of declines in GH. In fact, studies of GH replacement therapy in patients with pituitary disorders and dose-response studies show that older subjects require less GH to maintain normal IGF-I concentrations, though this is due in part to their increased susceptibility to GH side effects as well as the fact that their target IGF-1 is lower [31].

Exercise, sleep, food intake, stress, and body composition are all stimuli and inhibitors that affect the hypothalamic components that govern GH production [32]. The physiological patterns

of pulsatile GH secretion are generated by the interaction of all of these components. The age-related decline in GH secretion could be explained by a number of factors. Reduced GHRH or ghrelin secretion, increased somatostatin inhibition, greater susceptibility of somatotrophs to negative feedback inhibition by IGF-I, loss in pituitary responsiveness to GHRH, and pituitary and/or hypothalamic responsiveness to ghrelin are all possibilities. The age-related decline in GH secretion could be explained by a number of factors. Reduced GHRH or ghrelin secretion, increased somatostatin inhibition, greater susceptibility of somatotrophs to negative feedback inhibition by IGF-I, loss in pituitary responsiveness to GHRH, and pituitary and/or hypothalamic responsiveness to ghrelin are all possibilities.

It's critical to distinguish between normal aging-related decreases in GH secretion and actual Adult Growth Hormone Deficiency (AGHD). Aging is a state of relative physiologic GH insufficiency, but it is not a disease in and of itself, and it is distinct from AGHD. When older persons are compared to AGHD patients of similar age, they have stronger GH secretion and physiological reactions [33]. Furthermore, aging is not an indication for AGHD diagnosis testing or treatment. In older men, regular exercise has been found to boost lean body mass, muscle strength, and aerobic ability [34]. This observation led to the hypothesis that some of the effects of exercise are mediated by growth hormone and IGF-I. Insulin like growth factor-1 has been found as an index of healthy aging. A sufficient health-related quality of life depends on the ability to do Activities of Daily Living (ADL). The origin of functional impairment is complicated; nevertheless, sarcopenia (the age-related loss of muscle mass and quality) and cardiovascular system dysfunction [35].

It's important to develop a way to address functional decline by slowing down the deterioration of the musculoskeletal and cardiovascular systems while also improving the elderly's quality of life. A study by Zaid, et al (2018) who investigated the effect of moderate aerobic training on insulin like growth factor and functional capacity in elderly, reported that the result that eight weeks of supervised aerobic exercise instruction resulted in a considerable rise in insulin-like growth factor[36]. This study is also supported by Sagiv et al (2007), who discovered that physically active persons have higher levels of IGF-1 than sedentary subjects, and that IGF-1 as a mediator plays a critical role in muscle hypertrophy and angiogenesis, both of which characterize the anabolic adaptation of muscles as a result of exercise [37]. It is also supported by a study that stated circulating IGF-1 in trained older people was 17 percent lower than in untrained older people at rest [38]. Exercise training promotes local IGF-1 expression without affecting systemic GH-IGF-1 axis characteristics. These findings suggested that exercise training could help individuals with intermediate congestive heart failure reduce peripheral skeletal muscle alterations, particularly in terms of local IGF-1 expression [39]. Other study by Adamo and Farrar found that exercise increased levels of IGF-1, IGF-1 receptors, and IGF1-activated signaling pathways. Although there is evidence that the aging muscle retains its ability to produce IGF-1, there is also evidence that aging is linked to a decrease in exercise's ability to generate an isoform of IGF-1 that promotes satellite cell proliferation [40]. In addition, aged muscle may become resistant to IGF-1, which can be counteracted by exercise. Overexpression of IGF-1 in the muscle, on the other hand, appears to protect against sarcopenia as people get older[41,42].

These findings are consistent with those who discovered that older men and women who engage in at least moderate physical activity (approximately 400kcal/d) had superior physical function than those who are less active, regardless of demographic or health-related characteristics [43,44]. In other words, older persons who engage in regular exercise activities appear to reap additional benefits in terms of physical functional capacity that are not provided by daily tasks and typical walking.

CONCLUSION

Based on the explanation above, it can be concluded that

Physical activity affects level of IGF-1 through a mechanism which hasn't defined and understood completely. Thus, there are other variables to be observed to determine the work of

physical activity toward IGF-1 secretion and to give solution to different results in other researches. Physical activity has potent physiological stimulus to GH secretion for both aerobic and resistance and the effect of those exercise can increase GH level in middle age group. There is an improvement in the level of IGF-1 and functional capacity in elderly after moderate intensity aerobic training, hence decreasing the disability in geriatrics for better quality of life.

Conflict of Interest

There is no conflict of interest.

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