REVIEW ARTICLE

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Role of sex steroid hormone on hand grip strength and cognitive function in the elderly

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ABSTRACT

The aging process is associated with changes in hormone levels. There is a noticeable change in estrogen levels in women, while in men, there is a change in testosterone levels. In the elderly, as a result of the aging process, changes in these hormone levels affect handgrip strength, and cognitive function. In both women and men, the function of several organs is influenced by sex steroid hormones, namely Oestrogen and androgens. There are two theories of steroid action mechanism on target cells, namely steroid hormone action mechanism genomically and non-genomically. The function and action mechanism of steroid hormone is important because it is the basis of the hormonal aspect for muscle mass, handgrip strength, and cognitive function. Due to the aging process, hormonal changes in the elderly are different compared to the previous period. This has consequences for changes in metabolic processes that affect the body's condition, including changes in the composition of bones, muscles, and other tissues, such as the brain. In the aging process, it is important to pay attention to nutritional factors because they contribute to hormone levels that help maintain muscle mass, body mass index, hand grip strength, and cognitive function. In the brain, the sex steroid hormone has activating and organizational effects mediated by intracellular or transmembrane G-protein-coupled receptors. Articles published in English in the last 9 years (from 2014 to 2023) were retrieved from Science Direct, PubMed, Springer link, Oxford and Nature using relevant searching terms. The fact that testosterone bioavailability is predominated in the brain in relation to its activity and significant positive association with processing speed, sustained attention, and working memory in older men. To obtain a better quality of life for the elderly, nutritional factors must be considered to maintain optimal sex steroid hormone levels, hand grip strength, and cognitive function.

Keywords: Steroid sex hormone, handgrip strength, cognitive function, Alzheimer's disease, dementia

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INTRODUCTION

In women and men, the function of some organs is influenced by sex steroid hormones, namely estrogens and androgens.[1] Estrogen (female sex hormone) is the main hormone in the female body produced by the ovaries. Estrogen is responsible for developing female sexual characteristics. Estradiol and estrone are included in the estrogen hormone. Although estrogen is known as the main hormone in women, it is also produced in the male body, but its quantity is small.[2] Androgens (male sex hormones) are the main hormones in the male body that are produced in the testes. Testosterone and dihydrotestosterone are included in the androgen hormone. Androgens are known to be the main hormones in men. However, in the female body, androgens are also produced, but their amounts are few.[3]

Estrogen, produced by the female reproductive organs, plays a role in biological systems in the body.[4] Systems in the body that involves estrogen include neuroendocrine, vascular, skeletal, and immune systems.[5] Estrogen in a woman's body plays a role in reproductive maturation and sexual characteristics; however, androgens are also necessary for sexual health.[6] In the female body, estrogen levels are much higher than in men. In addition to estrogen, in the female body, there are also androgen hormones. Biologically active androgens in women are dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and dihydrotestosterone.[7] In women, about 25% of androgen production occurs in the adrenal glands, 25% occurs in the ovaries, and the rest occurs in the periphery.[8] In women, testosterone and dehydroepiandrosterone (DHEA) play a role, among others, in the reproductive organs, breasts, muscles, bones, mood, cognition, and blood vessels. Given the complex physiological effects of testosterone in women, its use for therapy needs to be considered so that its safety aspects are guaranteed.[7]

It has been stated that testosterone is a sex steroid hormone mainly produced by Leydig cells in the testes. Testosterone is responsible for regulating sex differentiation, resulting in male sex characteristics, spermatogenesis, and fertility.[9,10] Testosterone inside the testes is called intratesticular testosterone. A portion of intratesticular testosterone is used for spermatogenesis, and the rest is secreted into the circulatory system. Testosterone in the circulatory system is called circular testosterone. There are two types of circular testosterone, namely total testosterone, and free testosterone. Only free testosterone in the circulation system can be used by target cells.[11,12]

In this review paper, a total of 4,120 articles published in English in the last nine years (from 2014 to 2023) were retrieved from Science Direct, PubMed, Springer link, Oxford Academic and Nature databases using the following keywords: sex steroid hormone, handgrip strength, cognitive function, cognitive impairment, Alzheimer's disease, dementia, geriatrics. Initially, 4,120 articles were found to match the inclusion criteria, but in the end 437 articles were removed due to duplication, failure of access, and irrelevant topics (shown in Figure 1). Finally, this review was written using the 12 articles that met the inclusion criteria to be written into a full paper. Along with the aging process, there are changes in hormone levels in both men and women. Changes in hormone levels affect muscle strength and cognitive function. Therefore, this narrative review presents the current knowledge on association of sex steroid hormones with hand grip strength an cognitive decline in elderly.

Functions and action mechanism of steroid sex hormones

In both women and men, the function of several body organs is influenced by sex steroid hormones, namely estrogen and androgens. Estrogens and androgens are steroids. Estrogen is generally derived from androgens via the aromatase enzyme.[3] Estradiol and estrone include estrogen hormones, while testosterone

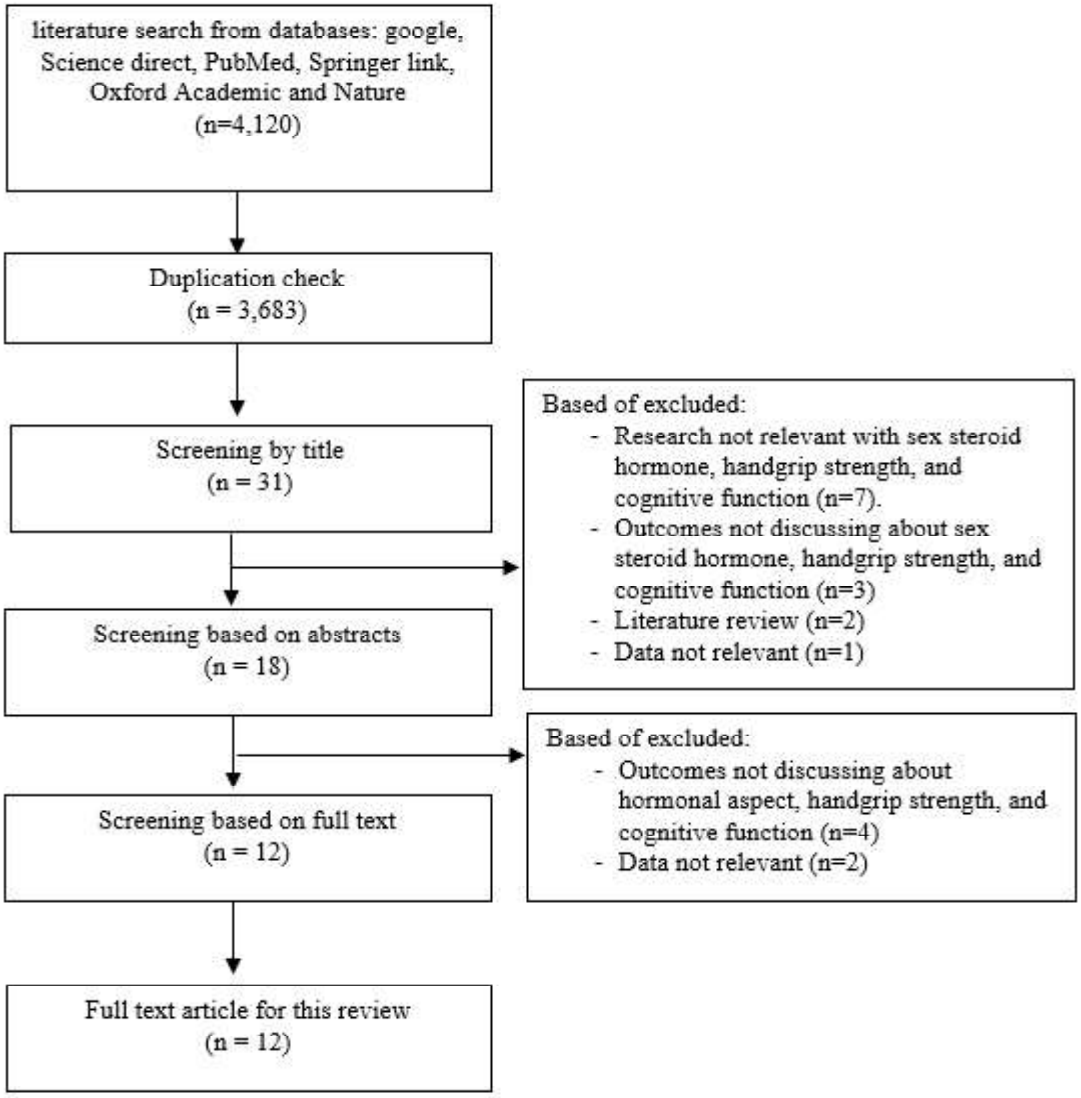

Figure 1. Flowchart of literature study in journals using relevant keywords

and dihydrotestosterone include androgen hormones. Although estrogen is known as the main hormone in women, the male body also produces estrogen but in small amounts. The ovaries mainly produce estrogen in the female body. Estrogen plays a role in reproductive maturation and sexual characteristics. Androgens are known as the main hormones in men, but in women's bodies, androgens are also produced in small amounts. In addition to estrogen, androgens are also required for sexual health in both women and men.[13] Androgens in men are, among others, responsible for the development of reproductive organs, bones and muscles. In women, androgens, such as testosterone and dehydroepiandrosterone, play a role, among others, in the reproductive organs, the breast, muscle, bone, mood, cognition, and vasculature.[7]

Keep in mind that only free steroids, in this case, free testosterone (bioavailable testosterone) in the circulatory system, can act against target cells. In the steroid action mechanism, free testosterone inside the testes is mediated by a testosterone-binding protein called androgen binding protein (ABP), while the action mechanism of free testosterone on target cells (somatic cells) is mediated by a sex hormone-binding protein called sex hormone binding globulin (SHBG).[11,12]

There are two theories of the free testosterone action mechanism on target cells. The long-held theory is that free testosterone

diffuses to target cells, then binds by intracellular receptors until it acts at the gene level.[14] The action of these steroids is called the genomic steroid action mechanism. In addition to these old theories, free testosterone in the circulation is bound by the SHBG-SHBG receptor complex (SHBG-R_{SHBG}), thus forming a bond testosterone-SHBG-R_{SHBG} on the target cell membrane. The action of the steroid is called the non-genomic steroid action mechanism.[15-17] The function and action mechanism of steroid hormone is important because it is the basis of the hormonal aspect for handgrip strength and cognitive function. The action mechanism of genomic and non-genomic androgens is presented in Figure 2.

Sex steroid hormone and handgrip strength

The aging process of being elderly is associated with changes in hormone levels,[18,19] a decrease in some body functions, including musculoskeletal function.[20,21] It has been shown that estrogens and androgens regulate critical biological and pathological processes in both women and men.[3] Estrogen has an effect on musculoskeletal function, including on muscles, tendons, and ligaments.[22] Recent research results demonstrate that decreasing estrogen levels have the potential to affect skeletal muscle strength in the elderly.[23] Administration of the estrogen

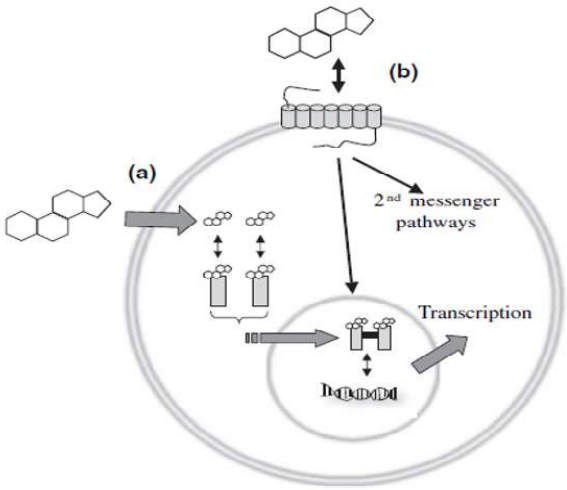

Figure 2. Action mechanism of genomic and non-genomic androgens. a. Genomic steroid action mechanism. b. Non-genomic steroid action mechanismo [15-17]

group (17ß-estradiol) has the effect of preventing the decrease in skeletal muscle activity.[24] With regard to aging, it has been shown that postmenopausal women experience a rapid decline in muscle mass and strength. The rapid decrease in muscle mass in postmenopausal women is caused by the speed of muscle protein breakdown is greater than the rate of muscle protein synthesis.[25] Moreover, it was also demonstrated that the rate of muscle protein breakdown in postmenopausal women was higher than that of premenopausal women and men of their age.[26] Furthermore, estrogen was used for therapy for persons with insulin resistance.[27] In addition to its effect on skeletal muscle, estrogen replacement therapy in postmenopausal women increased tendon collagen synthesis.[28] Based on these results, there is hope that estrogen can be used to reduce the rate of muscle protein breakdown and increase the rate of muscle protein synthesis and tendon collagen synthesis. If the benefits of estrogen can be realized in postmenopausal women,[29] it is hoped that estrogen can also be used to maintain the handgrip strength of the hand muscles. In addition to estrogen, androgens regulate important biological and pathological processes in both women and men.[3] Therefore, it is necessary to conduct human studies to confirm the pathway for the action of non-genomic testosterone on skeletal muscle. The research in question is devoted to proving the relationship between testosterone fluctuations to physiological changes in skeletal muscle cells and overall performance in muscle exercise.[30]

The results of other studies also show that decreasing estrogen weakens the response to anabolic stimuli.[25] In postmenopausal women, the response to anabolic stimulation to estrogen is decreased. Based on this fact, postmenopausal women who follow an estrogen replacement therapy program so that estrogen levels in the body resemble those of premenopause, show a normalized response to anabolic stimuli.[26,27] In addition, the estrogen replacement therapy program is also beneficial in maintaining skeletal

muscles during aging.[23] In addition, it has been shown that in postmenopausal women, female sex hormones play an important role in skeletal muscle mass. Therefore, female sex hormone therapy is considered in elderly women for the maintenance of skeletal muscle mass.[31] The results of other studies show that estrogen is beneficial for muscle mass and strength.[32] In addition to estrogen, which can be used as an option for replacement therapy for elderly women, there are several other hormones that can be used, including testosterone and progesterone. It has been proven that testosterone and progesterone can be used to stimulate muscle protein synthesis in postmenopausal women.

A study involving women and men, aged 6-80 years in the United States showed that average hand grip strength decreased with age.[33] The results of another study involving men aged 60-75 years showed that there was a tendency for a positive relationship between testosterone levels and hand grip strength. However, the relationship between testosterone levels and right handgrip strength was not significant (p=0.245), as was the case with left handgrip strength (p=0.354).[34] Therefore, both hormones affect handgrip strength.[26, 33]

Sex steroid hormone and cognitive function in the elderly

Sex steroid hormones play an important role in the formation of brain structures, including areas of the limbic system and prefrontal cortex during perinatal development. In the brain, the sex steroid hormone has activating and organizational effects mediated by intracellular or transmembrane G-protein-coupled receptors.[35] It is important to study the relationship between steroid hormones with aging and cognitive function. Previously it was mentioned that the aging process is associated with changes in hormone levels [18,19]; as a result, these hormone levels reduce several body functions, including cognitive function.[21] It has been demonstrated that androgen deficiency is an important cause of cognitive impairment in older men and deserves attention.[36] The results of recent research also demonstrate that there is a relationship between serum bioavailable testosterone and cognitive function in men.[37] The results of different studies show that testosterone supplementation has no effect on cognitive function in men with normal testosterone levels, and are not sufficient to be of clinical relevance. Therefore, it still needs to be proven whether testosterone supplementation has a clinical effect on cognitive function in hypogonadal men.[38] Based on the results of this research, research is still needed on increasing the bioavailability of sex steroid hormones in cerebrospinal fluid, and not just increasing sex steroid hormone levels.

To understand the relationship between sex steroid hormone levels and decreased cognitive function in the elderly, it is necessary to first understand the action of sex steroid hormones on target cells in the brain. The action of sex steroid hormones on target cells involves receptors that mediate their action. Estrogen receptors, and androgen receptors are widely distributed throughout the brain. This is related to the presence of dehydroepiandrosterone which is synthesized de novo in the brain.[39] We know that the presence of dehydroepiandrosterone is related to estrogen and testosterone. It was also shown that steroid levels in the brain were not associated with cognitive performance in elderly women.[39,40] It further stated that low SHBG levels still need to be proven to be associated with good processing speed in the brain.[39] We agree with the above, but bioavailable steroids take precedence. The fact that testosterone bioavailability is predominated in the brain in relation to its activity, is consistent with the results of research showing that bioavailable testosterone presented a significant positive association with processing speed, sustained attention, and working memory in older men over 60 years of age.[37] In relation to brain cognitive function, therefore, based on the results of research on steroid hormones in cerebrospinal fluid, the focus on bioavailable steroids is more important than steroid levels.

The results of other studies demonstrated that there was no significant difference in plasma SHBG levels in the group of mild Alzheimer's sufferers who had dementia with normal healthy people. Furthermore, it was found that plasma SHBG can contribute to accelerated decline in cerebrospinal fluid Aâ42 ($p<0.0005$), decreased brain metabolism ($p<0.05$), and hippocampal atrophy ($p<0.01$), cognitive decline ($p<0.01$), as well as a higher risk of dementia in Alzheimer's disease ($p<0.05$). These findings suggest that plasma SHBG could be a biomarker for predicting the development of Alzheimer's disease.[41]

Although, previous studies have shown that testosterone supplementation in men who have normal testosterone levels does not show a strong association with cognitive function and is not clinically relevant.[38] The results of this study are reasonable because testosterone levels are still within the range of normal values. Supposedly, focus testosterone supplementation to increase bioavailable testosterone, not just increase testosterone levels. Whereas estrogen therapy has been shown to have an age-dimorphic effect, which is neuroprotective in young females, but non-neuroprotective, even neurotoxic in acyclic females.[42]

There is no denying that many elderly people have cognitive dysfunction. The results of a recent study showed that 20% of USA adults aged 65 years had mild cognitive impairment. It was also shown that one in seven USA adults aged 65 years has dementia.[43] Impaired cognitive function often occurs in individuals with dementia and individuals with Alzheimer's disease. We need to refresh our understanding of dementia and Alzheimer's disease. In general, dementia is defined as a collection of symptoms (syndromes) of decreased cognitive function due to biological aging. Dementia is characterized by an overall decline in memory, thinking skills, and activities.[44] Alzheimer's disease is a progressive neurological disease that causes brain cells to die so that the brain shrinks (atrophy). Dementia occurs due to various diseases and injuries that affect the brain, such as stroke or Alzheimer's disease.[45]

Many people are not detected with dementia, even though dementia can cause sufferers to become senile and change their way of thinking. The results showed that the prevalence of people with undetected dementia was 61.7%. Such a large percentage is due to the fact that there has never been a cognitive examination in the population. It should be noted that cognitive examinations in primary health facilities are rarely performed.[49] One of the reasons is that the mini-mental state examination and the Montreal cognitive assessment require special skills. In addition, it takes a long time to examine a patient, which is about 15 minutes.[47]

Anatomically there are differences in brain morphology of healthy individuals compared to individuals with Alzheimer's. The brain of people with Alzheimer's atrophy causes the frontal and temporal horns of the lateral ventricles to enlarge. The results of observations of most people with Alzheimer's showed that their brain weight decreased.[48] A comparison of brain anatomy in healthy individuals with the brains of Alzheimer's patients is presented in Figure 3.

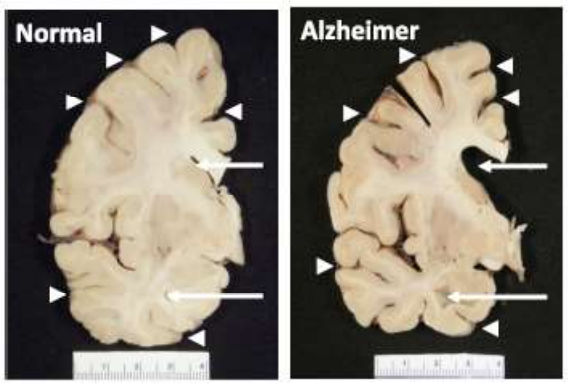

Figure 3. Brain anatomy schematic of healthy people compared to people with Alzheimer's. A. Brain lateral section of a healthy person showed no widening of the sulcus space and no narrowing of the gyrus. B. Brain lateral section of an Alzheimer's patient showed widening of the sulcus spaces (arrows) and narrowing of the gyrus.[48]

It is very popular in the community that cognitive decline is an early symptom of Alzheimer's disease and other dementias.[49] The results of a recent study showed that physical and cognitive function were significant predictors of quality of life in older adults with cognitive impairment.[50] Identification of variables related to cognitive decline in the elderly needs to be done in-depth research. The hope is that the elderly who experience a decline in cognitive function whose cause is known can be cured with appropriate medical care.[51] The results of previous studies demonstrated that Alzheimer's sufferers experience a loss of motor function.[52] Research results have also demonstrated that neurodegenerative disorders occur in people with Alzheimer's, resulting in a progressive decline in cognitive function and often a decrease in non-cognitive functions, for example, a decrease in muscle strength.[53]

Even though there are technical shortcomings, the results of measuring handgrip strength can be used as a marker of decreased cognitive function in the elderly. To determine muscle strength, handgrip strength can be measured using a handgrip dynamometer or handgrip dynamometer.[54] Handgrip dynamometers are relatively inexpensive, easy to carry, non-invasive, have a short measurement time, are reliable, and do not require extensive training to use them. Several studies have also shown handgrip dynamometers have low variability and high reliability in patients with mild cognitive impairment and dementia.[55,56] It has been stated that low-handgrip strength is associated with decreased cognitive function in the elderly. Moreover, handgrip strength can be used as an indicator for early detection of cognitive impairment in the elderly. Although until now, the exact mechanism between decreased motor power that underlies a decrease in handgrip strength and decreased cognitive function in the elderly is still unclear.[56]

Handgrip strength and cognitive function

The handgrip strength of a person's hand muscles is the gripping force exerted by the hand muscles. The handgrip strength can be measured using a handgrip dynamometer.[57,58] A person's cognitive function can be assessed using the mini-mental state examination and the Montreal cognitive assessment. In Indonesia, the Montreal cognitive assessment has been modified into the Indonesian version of the Montreal cognitive assessment (MoCA-Ina), which can be used to assess the cognitive function of Indonesians.[54] Examination of handgrip strength is relatively easier to do compared to assessing a person's cognitive function either by mini-mental state examination or Montreal cognitive assessment.[58]

In older adults, of course, handgrip strength and cognitive function should be maintained by implementing a physical activity training program. The baseline of handgrip strength is an important factor in determining the effectiveness of a physical exercise program and cognitive function.[59] These cognitive functions include attention, memory, language, visuospatial and executive functions.[60] In this regard, it is important to state that physical exercise is important to maintain nerve function so that cognitive function and motor activity are balanced.[61]

Handgrip strength is associated with decreased cognitive function in the elderly. Therefore, handgrip strength can be used as an indicator of changes in cognitive function in the elderly.[62-64] Several studies have shown a positive relationship between handgrip strength and cognitive function.[50,65] The results of the latest research show how to calculate handgrip strength using a handgrip dynamometer and measuring cognitive function.[57,58] The results of another study showed that every 5 kg decrease in handgrip strength was associated with 1.10 times the probability of a decrease in cognitive function. In addition, it was also shown that weak handgrip strength had a higher odds ratio of 1.14 for cognitive decline. The addition of age was also shown to have a 1.01 higher odds ratio for cognitive decline, as well as low physical activity, which had a 1.24 higher odds ratio for cognitive decline. It should be noted in this study that low handgrip strength initiates cognitive decline. In

addition, it was also demonstrated that a high prevalence of mild cognitive impairment was found in a group of subjects who had low handgrip strength.[64] The results of other studies also strengthen the statement that low handgrip strength is associated with decreased cognitive function.[66] In addition, a clinical syndrome caused by the accumulation of the aging process in the elderly is characterized by, among other things, a decline in physical function as a trigger for cognitive decline. In detail, it is stated that the handgrip strength can be used as an indicator of cognitive decline in dementia and Alzheimer's disease.[67]

The study's results in Brazil showed that men had a handgrip strength of 43.4 kg, while women had 27.6 kg. Handgrip strength in Brazilian men is 57% higher than in women. Brazilian men aged 30-39 years had a handgrip strength of 46.9 kg, whereas in women, 29.4 kg. These data indicate that handgrip strength is negatively correlated with age in both men and women in Brazil.[68] Previous research involved 2729 participants aged 60 years or more. The results show that lower cognitive performance in the elderly is associated with handgrip strength.[69] The results of this study are in accordance with research in Russia which demonstrated that handgrip strength is associated with a high risk of malnutrition, low autonomy, decreased physical and mental function, and risk of death over the next five years.[70]

It has been demonstrated that skilled hand movements and control of handgrip strength involve not only cortical motor areas but also higher cognitive performance. This occurs because there is more activity in the frontal lobe area in healthy elderly people. It is more clearly stated that physical activity in the elderly is needed to increase the influence on cognitive and motor functions.[71] In addition, the results of other studies also show that people with fronto-temporal dementia experience frontal lobe atrophy, so their motor and cognitive functions decline. It should also be noted that the level of atrophic damage can be assessed based on visual atrophy scales, which can then be used to estimate the patient's level of long-term deterioration (longitudinal clinical deterioration).[72] Research results at the molecular genetic level show that genetic fronto-temporal dementia sufferers are influenced by genetic groups, namely the progranulin gene, microtubule-associated protein tau, and chromosome 9 open reading frame 72 (C9orf72 or C9orf72-SMCR8 complex subunit). For the treatment of genetic frontotemporal dementia patients, it is necessary to know about the presence or absence of mutations in the microtubule-associated protein tau gene. In addition, it is also necessary to pay attention to environmental factors that trigger the emergence of these three types of genes in families suffering from genetic frontotemporal dementia.[73] Compared with the general population, people with fronto-temporal dementia have an 8x increased risk of death. Women have double the standard mortality ratio compared to men.[74]

Several study results that demonstrated the association of sex steroid hormone with handgrip strength and cognitive function are presented in Table 1.

Consequences of hormonal changes in the elderly on hand grip strength and cognitive function

Previous research has shown that estrogen has a neuroprotective effect on the brain. It is evident that the risk of memory problems increases after ovariectomy in pre-menopausal women.[75] It has also been demonstrated that decreased estrogen levels in postmenopausal women can have an impact on organ function and have secondary effects on cognition, such as memory loss through vasomotor symptoms.[7] The results of a study on Korean menopausal women with a mean age of 54.93 ± 6.20 years showed that 54.2% of 164 subjects showed vasomotor symptoms. Sarcopenia in subjects without vasomotor symptoms was 18.5%, while sarcopenia in subjects with vasomotor symptoms was 6.9%. The prevalence of sarcopenia was inversely related to the prevalence of vasomotor

Table 1. Summary of the evidence on the association of sex steroid hormone with handgrip strength and cognitive function in the elderly

Title	Research design	Results	References
The relationship between handgrip trength and cognitive function in elderly Koreans over 8 years: a prospective population-based study using Korean Longitudinal Study of Ageing.	The analytical observational method with a longitudinal approach.	In elderly women, the average maximum handgrip strength was 19.2 kg, and the average Mini-Mental Status Evaluation score was 25.1. In elderly men the average maximum handgrip strength is 30.7 kg, and the average Mini-Mental Status Evaluation score is 26.2. Handgrip strength at the beginning of the measurement is positively correlated with the Mini-Mental Status Evaluation score.	Kim et al.[57]
Handgrip strength Is associated with poorer cognitive functioning in aging Americans.	The analytical observational method with a longitudinal approach.	Each 5 kg decrease in handgrip strength showed an Odd Ratio of 1.10 times to cognitive decline (95% Confidence Interval: 1.05-1.14).	McGrath et al.[62]
Association between handgrip strength and cognitive impairment in elderly Koreans: a population-based cross-sectional study.	The analytical observational method with a cross-sectional design	Handgrip strength is associated with the risk of mild cognitive impairment in the elderly. Greater handgrip strength is associated with higher cognitive function in cognitively normal elderly individuals.	Jang et al.[63]
Associations between handgrip strength and mild cognitive impairment in middle-aged and older adults in six low and middle income countries.	Analytical observational method with cross-sectional design	Low handgrip strength shows an Odd Ratio of 1.41 to the occurrence of mild cognitive impairment (95% Confidence Interval: 1.23-1.61).	Vancampfort, et al.[64]
Physical frailty predicts future cognitive decline - A four-year prospective study in 2737 cognitively normal older adults.	The observational analytical method with a prospective cohort approach.	Low body weight, low handgrip strength, slower chair-stand test results, shorter step length in men, and weaker handgrip strength in women are associated with decreased cognitive function.	Choi et al.[72]
Estrogen replacement, muscle composition, and physical function: the Health ABC Study	The analytical observational method with cross-sectional design	Two hundred fifty-nine postmenopausal women who took the estrogen replacement therapy program showed that muscle cross-sectional area (CSA) and handgrip strength were greater than 581 postmenopausal women who did not take the estrogen replacement therapy program.	Juppi, et al.[31]

Association between vasomotor symptoms and sarcopenia assessed by L3 skeletal muscle index among Korean menopausal women	The analytical observational method with a cross-sectional design	Elderly women with a mean age of 54.93±6.20 years showed that 54.2% of 164 subjects showed vasomotor symptoms. Sarcopenia in subjects without vasomotor symptoms was 18.5%, while sarcopenia in subjects with vasomotor symptoms was 6.9%. The prevalence of sarcopenia was inversely related to the prevalence of vasomotor symptoms (Odds Ratio, 0.32; 95% Confidence Interval, 0.15-0.67). In addition, the paraspinal muscle index was positively associated with the prevalence of vasomotor symptoms (Odds Ratio 1.06; 95% Confidence Interval: 1.01-1.11).	Ki-Jin, et al.[76]
The role of oestrogen in female skeletal muscle ageing: a systematic review	A systematic review	Sex hormone deficiency is associated with poorer muscle mass. Exogenous estrogen supplementation has the potential to correct this hormone deficiency.	Critchlow et al. [23]
Handgrip strength and muscle quality: results from the National Health and Nutrition Examination Survey Database	Cross-sectional study	Handgrip strength change with age. Handgrip strength increases with age, then stabilizes, and decline	Wen et al. [33]
Relationship between testosterone levels with hand grip strength, calf diameter, lung function, body mass index and blood pressure in elderly men	Cross sectional studies	The relationship between testosterone levels and right handgrip strength was not significant (p=0.245), as was the case with left handgrip strength (p=0.354).	Datau et al. [35]
Associations of bioavailable serum testosterone with cognitive function in older men: results from the National Health and Nutrition Examination Survey.	Survey	Subject of this studies including 208 participants with aged ≥ 60 years. Bioavailable testosterone was significantly associated with cognitive function.	Giannos et al. [37]
Testosterone supplementation and cognitive functioning in men—a systematic review and meta-analysis	Systematic review and meta-analysis	Testosterone supplementation has no effect on cognitive function in men with normal testosterone levels, and are not sufficient to be of clinical relevance.	Buskbjerg et al. [38]

symptoms (Odds Ratio, 0.32; 95% Confidence Interval 0.15-0.67). In addition, the paraspinal muscle index was positively associated with the prevalence of vasomotor symptoms (odds ratio 1.06; 95% confidence interval 1.01-1.11).[76] The results of another study also demonstrated a relationship between vasomotor symptoms and skeletal muscle index in Korean menopausal women.[76] Based on the research results described above, estrogen, testosterone, and progesterone can be used as options to improve the quality of life of elderly women. However, it should also be noted that estrogen significantly affects the central nervous system. Therefore, it is necessary to consider the extent to which the decrease in blood estrogen levels that occurs with age (especially during menopause and beyond) has an impact on cognitive function and individual health in general.[77] However, it should be noted that the use of hormone replacement therapy in elderly women must be carried out carefully so as not to cause adverse side effects. Our statement is consistent with the results of studies showing that low serum testosterone levels in women should be interpreted with caution. In the context of therapy, the use of testosterone to increase serum testosterone levels needs to be considered so that the safety aspect is guaranteed.[7]

It has been explained that in both women and men, after the peak of reproduction then, with age, the production of sex hormones decreases. The results showed that after puberty peaks, the production of testosterone by Leydig cells decreases with age. The statement is based on research results that demonstrate that aging is associated with stress and decreased testosterone in Leydig cells.[78] The results of a previous study involving 250 healthy men aged 31-60 years showed that total testosterone levels were negatively correlated with increasing age.[79] The results of another study showed that the rate of decline in testosterone production by Leydig cells was about 1% per year.[80] It has been demonstrated that testosterone is important for muscle growth in youth, but testosterone is not essential for maintaining muscle mass in adult male rats.[81] another study showed a positive correlation between serum testosterone levels and appendicular lean mass index but a negative correlation with appendicular fat mass index in men aged 20-59 years.[82] In addition, it was also demonstrated that testosterone was positively correlated with fat-free mass and handgrip strength in the early-mid puberty group. The positive correlation between free testosterone and fat-free mass was stronger in the late-post-pubertal group than in the early-mid-pubertal group.[83]

The results of other studies show that the aging process causes a decrease in muscle mass and strength.[84] Several studies have demonstrated that hypogonadal men (men who experience testosterone production below normal values) directly experience muscle atrophy.[85-87] The results of this study are in line with the results of other studies which have demonstrated that sex hormone deficiency in the synthesis or action of sex hormones on target cells affects organ function.[3] The use of testosterone therapy is important for individuals who experience muscle atrophy because of the clinical impact of decreased testosterone production. Under these conditions, testosterone plays a significant role in increasing muscle mass by shifting the protein balance, resulting in an increase in muscle protein. Therefore, testosterone is required for the maintenance or restoration of muscle mass.[88,89]

Based on the fact that normal organ function can occur if the tissue function is normal. Tissue function can be normal if the function of its constituent cells is normal. With regard to normal cell function, certain cells (target cells) can perform their functions normally when sex hormones are present. Sex hormones can act on target cells, for example, the action of testosterone (as a sex hormone) on skeletal muscles. The effects of these sex hormones on body tissues are very complex.[7] It should be remembered that only free steroids, in this case, free testosterone (bioavailable testosterone) in the circulatory system, can act on target cells (e.g. skeletal

muscle) if mediated by sex hormone-binding proteins called sex hormone-binding globulins (SHBG). The availability of free testosterone and the constellation between free testosterone and SHBG in circulation determines the action of free testosterone on target cells.[11,12] Based on the description of the results of the study, testosterone production is highest at the peak of the reproductive period, and its levels decrease with age. Testosterone functions, among other things, to maintain optimal muscle activity. We argue that muscle strength is influenced by the bioavailability and action of free testosterone. Our statement corresponds to the results of research showing that SHBG and testosterone have an effect on body mass index. SHBG levels are negatively correlated with body weight, namely increasing body weight lowers SHBG levels. Moreover, SHBG showed a negative correlation with body mass index and waist circumference.[90]

The level of SHBG in the elderly needs to be considered because the level of sex hormone-binding globulin in the cerebrospinal fluid correlates with decreased cognitive function.[91] The results of our study showed that supplementation of isoflavones for the postmenopausal elderly for six months reduced SHBG levels by 31.1%.[29] In addition, it was also shown that age, gender, and genetic factors had an effect on body mass index.[92]

In an effort to obtain a better quality of life for the elderly, nutritional factors must also be considered to maintain the ideal body mass index, muscle mass, hand grip strength, and cognitive function. It has been proven that nutritional factors affect body mass index. The results showed that subjects with BMI <18.5 kg/m2 actually had a low intake of macronutrients (protein, fat, and carbohydrates), resulting in chronic energy deficiency with low status.[93] Based on the results of this study, the intake of macronutrients must be met so that the elderly do not experience chronic energy deficiency and their quality of life becomes better.

CONCLUSION

In women and men, the function of several organs of the body is influenced by sex steroid hormones, namely estrogen and androgens. Along with the aging process, both women and men experience changes in sex hormone levels that affect the function of several organs, including muscles. In addition to estrogen, which can be used as an option for replacement therapy for elderly women, there are several other hormones that can be used, including testosterone and progesterone. Of course, the use of these hormones considers the side effects. It has been proven that testosterone and progesterone can be used to stimulate muscle protein synthesis. Based on the results of this review, it can be focused that there is a relationship between testosterone levels, muscle mass, hand grip strength, and cognitive function in the elderly. In connection with efforts to obtain a better quality of life for the elderly, nutrient factors must also be considered to maintain an ideal body mass index, muscle mass, handgrip strength, and cognitive function.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares that they have no competing interests.

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AUTHOR'S CONTRIBUTION

Conceptualization: EP. Data acquisition: DT, EP, HA, and NH. Data analysis or interpretation: EP, HA, NH, HJE. Drafting of the manuscript: EP and NH. Critical revision of the manuscript: EP, HA, HJE, RAD, AVO, and ND. Approval of the final version of the manuscript: all authors.

DATA AVAILABLITY STATEMENT

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