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The Role of Androgens and Estrogens on Healthy Aging and Longevity

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Aging is associated with a loss of sex hormone in both men (andropause) and women (menopause). In men, reductions in testosterone can trigger declines in muscle mass, bone mass, and in physical function. In women, the impact of the loss of sex hormones, such as estradiol, on bone is well elucidated, but evidence is limited on whether the loss of estradiol negatively affects muscle mass and physical function. However, deficiencies in multiple anabolic hormones have been shown to predict health status and longevity in older persons. Thus, consideration should be given as to whether targeted hormone replacement therapies may prove effective at treating clinical conditions, such as age-related sarcopenia, cancer cachexia, and/or acute or chronic illnesses. If initiated carefully in the appropriate clinical population, hormone replacement therapies in men and women may prevent and reverse muscle and bone loss and functional declines and perhaps promote healthy aging and longevity.

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AGING is a natural multidimensional process that involves physical, psychological, and social changes, which ultimately affects life span. Elucidation of the underlying physiological mechanisms that are impaired with aging may positively influence the physical aging process and extend healthy aging. A major feature of aging is loss of physical function, and an important underlying factor is the loss of skeletal muscle mass that accompanies aging. Often overlooked is the role that hormones play as key regulators of human muscle metabolism (1) and their influence on physical function. Aging is associated with a loss of sex hormones (androgens and estrogens), which in turn may be responsible for triggering muscle loss, muscle weakness, decreased functional performance, and decreased life span.

A contradiction of aging exists upon comparison of muscle loss between older men and women. This contradiction may, in part, be explained by hormones prior to and following andropause in men and menopause in women. For example, the rate and magnitude of muscle gain and loss between men and women differ throughout the life span. In women, an accelerated loss of muscle mass and strength occurs at an earlier age than in men (2–6), but life expectancy is higher in women compared with men (7). Thus, as women tend to live longer, they are more susceptible to age-related health problems and in particular to declines in muscle mass (8) when compared with men. However, whether there are positive relationships between age-related loss of sex hormones, declines in muscle mass, and physical function versus longevity has not been studied. In this review, we provide a broad overview of the physiology and role that androgens and estrogens play in enhancing healthy aging and human longevity.

Androgens

Androgen Physiology

Gonadotropin-releasing hormone (GnRH), produced and released by the hypothalamus, stimulates the production and pulsatile release of luteinizing hormone and follicle-stimulating hormone in the anterior pituitary. Follicle-stimulating hormone is primarily involved in sperm production and luteinizing hormone in testosterone secretion. Luteinizing hormone enters the circulation and is transported to the gonads where it activates the synthesis and secretion of testosterone. Ninety-five percent of androgen production occurs in the Leydig cells of the testes (9), and men have a 20- to 25-fold higher testosterone production when compared with women (10). The physiological effects of testosterone are induced by its binding to the intracellular androgen receptor, which then translocates to the nucleus where the androgen receptor–testosterone complex induces transcription of specific genes (11). Testosterone imparts multiple physiological effects including involvement in spermatogenesis, testicular function, hair growth, nitrogen retention, bone density, muscle mass and distribution, libido, and secondary sexual characteristics (12).

Androgens and the Aging Man

Aging is associated with a gradual decline in circulating testosterone concentrations and decreased musculature in men (13–16). Endogenous testosterone production gradually decreases with aging in men. This may result from reduced testicular responses to gonadotrophin stimuli with aging, coupled with incomplete hypothalamo-pituitary compensation for the fall in total and free testosterone levels (17,18). Beginning around the age of 35–40 years, circulating testosterone concentration levels decrease by approximately 1%–3% per year (19). Approximately 20% of men older than 60 years and 50% of men older than 80 years have serum testosterone concentrations below the normal range for young men (13). The most obvious clinical signs of relative deficiency in older men are a decrease in muscle mass and strength, a decrease in bone mass, and an increase in central body fat. Lowering serum testosterone concentrations in healthy volunteers decreases fat-free mass, muscle strength, and mixed muscle fractional synthetic rate (20), but testosterone supplementation increases fractional synthetic rate in young hypogonadal men (21) and older men (22–24). Moreover, restoring testosterone to youthful levels is shown to increase synthesis of myofibrillar proteins, total body cell mass, and muscle strength (24,25). Declining testosterone levels that accompany aging may also be a contributing factor to increased and redistributed fat mass and to decreased fat-free mass (musculature [26–29]). This decline in muscle mass translates to decreased muscle strength, which in turn leads to functional limitations, such as balance problems, a higher fall risk, injuries, chronic conditions, such as obstructive sleep apnea, depression, obesity, chronic obstructive pulmonary disease, type 2 diabetes mellitus, renal or liver disease (30–36), decreased quality of life, and higher risk of morbidities and mortalities with aging (37,38).

The influence of testosterone on protein metabolism is well known (21,24,39), however, testosterone also plays a significant role in glucose and lipid homeostasis (40,41) and bone metabolism. Low total testosterone levels in older men (>60 years) are associated with an increased prevalence of osteoporosis, increased incidence of rapid bone loss at the hip (42), and an increased incidence of hip fractures and nonvertebral fractures (43). Osteoporosis is an increasingly recognized problem in older men with associated fracture morbidity and mortality on the rise. Thus, not only does the loss of testosterone negatively affect muscle mass in older men, it appears to also increase the risk of osteoporosis and fractures further contributing to increased morbidity and mortality in older men (44).

Whether the age-dependent decline in androgen levels directly leads to the development of health problems in older men is being debated vigorously (17,18,45–47). Carefully controlled large-scale studies are needed to determine whether testosterone's pleiotropic effects are of benefit or harm to healthy aging and longevity.

Androgens and the Aging Woman

Although women have a 20- to 25-fold lower circulating concentrations of androgens compared with men (10), androgens are precursors for estrogen production and synthesis and play a key role in the maturation processes of ovarian follicles in women (48). While it remains to be seen whether testosterone plays a significant biological function in women, androgen deficiencies in aging women have been associated with impairments in sexual function, lean body mass and performance, cognitive function, emotions, bone loss, and frailty (49–53). Testosterone levels in women decline in the fourth decade of life and prior to menopause approach 50% of those seen in the third decade (54). Upon completion of menopause, average concentrations of testosterone in women are approximately 15% of premenopause levels (54,55). Additionally, some women experience further (~60%) reductions within 2–5 years following menopause (56). Although the biological role of testosterone in women remains unclear, the sharp and rapid decline in androgen levels that accompany aging in women may play a critical role in the functional limitations seen in aging and may increase morbidity. Thus, there may be a therapeutic role for testosterone replacement among menopausal and postmenopausal women, although careful assessment of the menopause age and monitoring of symptoms should be considered so that the lowest effective dose of testosterone can be selected.

Androgens and Inflammation

Aging is characterized by a low-grade inflammatory status. Serum levels of inflammatory markers increase with age in both sexes. The level of inflammatory markers is a strong and independent risk factor for frailty, disability, and cardiovascular events (57–59), and inflammation influences loss of muscle mass (60). The low-grade inflammatory status often detected in older persons is connected with the hormonal changes occurring with aging (58). Testosterone has been found capable of reducing systemic inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-1β (61–63) and stimulating the anti-inflammatory cytokine interleukin-10 (64,65). However, in premenopausal and older women, high testosterone and estradiol and low sex hormone–binding globulin levels are associated with insulin resistance and diabetes, conditions characterized by low-grade inflammation (66). Thus, age-related changes in sex hormones contribute to the development of a proinflammatory state. Hormonal changes and their potential effects on inflammation may, in part, affect conditions, such as atherosclerosis, cardiovascular diseases, metabolic syndrome, and type 2 diabetes. Although the role of sex hormones on aging and age-related diseases is still unclear, there are clear age associations, which are likely reducing healthy aging and negatively impacting longevity.

Estrogens

Estrogen Physiology

Estrogens are a class of steroid molecules secreted primarily by the ovaries (67) and placenta and, to a lesser extent, by peripheral steroidogenic conversion and by the testes in men (67). Women have about four times the amount of estrogens compared with men (10). Estrogens promote the development of female genital organs and features, growth of the endometrium, and inhibit the secretion of follicle-stimulating hormone by the pituitary. The important actions of the endogenous estrogens are mediated by estrogen receptors (ERs). ERs are synthesized in many cell types in two protein forms, ERα and ERβ, which function as transcription factors once bound with their ligand. ERα is expressed in several tissues including uterus, prostate (stroma), ovary, testes, bone, breast, white adipose tissue, liver, and muscle, and ERβ is expressed in colon, prostate (epithelium), testes, salivary gland, bone marrow, and vascular endothelium (68). Estrogens are primarily involved in the development and maintenance of normal sexual and reproductive function in women (69). Moreover, estrogens have also been shown to exert a wide range of biological effects in many physiological systems in both women and men (70). Estrogens mitigate postinjury disruption and inflammatory responses (67,71,72) and may play a protective role against oxidative stress (73) and muscle damage (by its antioxidant and membrane-stabilizing properties), repair, and inflammation (74). Estradiol also affects satellite cell activation and proliferation, thereby enhancing the growth and recovery potential of cells (74). Moreover, myosin function is affected by age and by estradiol in women (75). Estrogens and ERs in the skeletal muscle cells of women (76) regulate carbohydrate and lipid metabolism. These receptors have been hypothesized to play a role on muscle strength (55) through the action by both estrogens and insulin-like growth factor (IGF)-1 (76–78).

Estrogens and Skeletal Muscle

There is a body of evidence that estradiol plays a role in muscle strength. When estradiol is diminished, significant decrements in the force-generating capacity of hind-limb muscles in mice will occur (79), even when controlling for physical and muscular activities of the mice (80). The decrease in strength fully recovers after estradiol replacement, thus estradiol is an important hormone that affects muscle contractile function (79). Estradiol also plays a role in the level of antioxidant enzymes. Ovariectomized mice have lower levels of antioxidant enzymes in the heart, such as glutathione peroxidase, catalase, and superoxide dismutase (81,82). Antioxidant as well as ER-α gene expression in skeletal muscle of mice acutely and chronically responds to changes in circulating estradiol, which is another indication of estrogen-mediated mechanisms influencing contractility of skeletal muscle (83).

Treatment of embryonic zebra fish with aromatase inhibitor 4-hydroxyandrostenedione, binding to the aromatase enzyme and thereby inhibiting the conversion of testosterone or androstenedione to estradiol, denervates the zebra fish trunk muscles (84). This shows that estradiol synthesis plays an important role in not only the central nervous system (85) but also in developing the peripheral nervous system, particularly at the neuromuscular junction. In an in vitro study with fused bovine cell cultures, Kamanga-Sollo and colleagues (86) showed that protein synthesis increased and degradation decreased when treated with estradiol. The underlying mechanisms involved ERs and the IGF-1 receptor. Future studies should determine how this affects skeletal muscle function during aging, associated with a decline in circulating estrogens and muscle weakness.

Although the predominance of data demonstrating the isolated effects of estrogen on muscle tissue come from animal and in vitro studies, a few studies have demonstrated these effects in humans. The meta-analysis of Greising and colleagues (87) showed that postmenopausal women on estrogen hormone therapy had greater physical strength than those without treatment. Another study on twins showed that the siblings receiving hormone therapy had greater muscle power and maximal walking speed than the treatment naive twins (88). MacNeil and colleagues (74) have shown that 1 mg of estradiol for 2 days followed by 2 mg estradiol for 8 days attenuates exercise-induced neutrophil infiltration in young men, which may have resulted from direct neutrophil/endothelial interaction. Another human study showed that 8 days of estradiol supplementation increases lipid metabolism in skeletal muscle of moderately active men. This may be regulated by alteration the protein content of medium-chain acyl-CoA (MCAD), possibly through peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α)–mediated transcription and decrease of miR-29b, leading to increased mitochondrial gene expression (MCAD and hippuric acid [HA]) and thus lipid utilization (89).

Estrogens and the Aging Woman

During the first year of menopause, women lose on average 80% per year of their estrogens (73). They exhibit an accelerated decline in muscle mass and strength around the time of the menopause (2,4,90–95), which is related to this loss of estrogens (4,96) and causes subsequent decreases in function (76,97). Higher endogenous estrogen levels were associated with higher muscle strength and lower rates of fall-related limb fractures even after adjusting for bone mineral density in 75-year-old women (97). Estrogens may also potentially stimulate muscle repair and regenerative processes, although the mechanisms by which estrogens exert influence on muscle damage, inflammation, and repair have not been fully elucidated (98). It is thought that estrogens influence indices of muscle damage

and repair (75) by (i) acting as an antioxidant, thus limiting oxidative damage (82), (ii) acting as a membrane stabilizer by intercalating within membrane phospholipids, and (iii) binding to ERs, thus governing the regulation of a number of downstream genes and molecular targets (75). Also Vina and colleagues (73) showed that estrogens play a protective role against oxidative stress. Estrogens can participate in the antioxidant system because it decreases the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an important source of superoxide radical, and increases nitric oxide (NO) bioavailability (99). Moreover, estradiol activates mitogen-activated protein kinase and nuclear factor-κB signaling after binding to the ER. This stimulates the expression of mitochondrial antioxidant enzymes such as manganese superoxide dismutase and glutathione peroxidase and results in reduced reactive oxygen species production of mitochondria in women, possibly contributing to the longer expected life span of women compared with men. Whether (phyto)estrogens therapy leads to increasing the male life span to similar levels as that of women, remains to be elucidated.

Estrogens also play a key role in regulation of bone mass and strength by controlling activity of bone-forming osteoblasts and inhibiting activity and vitality of bone-resorbing osteoclasts (100). Bone tissue is essential for structural support and locomotion in the vertebrae and critical for hematopoiesis. Bones also serve as an endocrine organ in the regulation of calcium homeostasis (101). Besides a marked decrease in muscle mass, postmenopausal women also show a marked decrease in bone mineral density and high-turnover bone metabolism, which leads to postmenopausal osteoporosis (102). When these women are treated with exogenous estrogens, the decrease in bone mass and increase in bone turnover are reversed. This suggests that estrogens have a bone protective effect (100).

Estrogens and the Aging Man

Estrogens in men are produced through aromatization, a process in the limbic system and brain tissues by which the body converts testosterone into estradiol (103–105). Although little is known about the role of estrogens in men, with most studies conducted on animals and not humans, estrogens may have a potential role in the regulation of Leydig cell development and function. During development, estrogens inhibit development of Leydig cells from precursor cells, whereas in adults, estrogens can block androgen production and Leydig cell generation (106). In the testes, both ERα and ERβ are expressed, however, the role of gonadal ERs in mediating the effects of estrogens during development is not yet clear (107). Estrogens are important regulators of bone health not only in women but also in men (108,109), although the relative contribution of androgens versus estrogens in the regulation of the male skeleton is unclear (110). Serum levels of both estrogens and androgens decrease with age (108) and are inversely associated with the risk of fracture in aging men.

Growth Hormone and IGF-1

Growth hormone (GH), produced in the anterior pituitary gland, is released into the circulation in a pulsatile manner and predominantly stimulates the liver to produce IGF-1 (111). GH has direct effects on tissues such as brain and muscle as well as indirect paracrine and autocrine effects, via stimulation of the local production of IGF-1 in target tissues. GH and IGF-1 signaling is a vital pathway in the regulation of protein synthesis and glucose metabolism (112). The GH and IGF-1 axis in aging, like deficiencies in sex steroid hormones, appears to be linked with changes in the hypothalamic-pituitary-adrenal axis, affecting muscle and bone physiology (113). The decrease in age-associated changes in GH, caused by hormonal signals, gender, neurotransmitters, nutritional status, body composition, and physical activity levels, correlates with increasing adiposity, decreased physical performance (111), and decreased testosterone levels (114). GH levels in women fall significantly after menopause (111).

High levels of IGF-1 are a risk factor for many types of cancers (115–117), whereas low IGF-1 has been implicated in the pathogenesis of a wide range of conditions, such as type 2 diabetes (118), osteoporosis (119), and coronary heart disease (120). Moreover, a decline in IGF-1 often occurs with increasing age (121), and low IGF-1 levels are associated with frailty (122) and an increased risk of death (123).

Recent data indicate that reduced somatotropic signaling provides protection from cancer and other age-related diseases and may promote old age survival (124,125). The balance of GH and IGF-1 seems to be a well-recognized target of intervention that extends longevity. However, the role of the GH/IGF-1 pathway in the modulation of human longevity continues to be hotly debated.

Healthy Aging and Longevity: The Possible Testosterone and Exercise Link

Men.—Testosterone stimulates skeletal muscle protein synthesis (anabolic effect) and inhibits protein degradation (anticatabolic effect) in the skeletal muscle of humans, regardless of age. Similarly, resistance exercise strongly stimulates muscle protein synthesis (126,127). In combination, exercise and testosterone strongly promote muscle hypertrophy and are also thought to promote bone health. Resistance exercise can induce acute subtle increases in serum testosterone; however, a high relative intensity and a high total volume of resistance exercise must be performed to acutely induce physiologically significant increases in concentrations of testosterone necessary to increase muscle anabolism (128). It is more likely that the resistance exercise causes contraction-induced stimulation of muscle protein synthesis rather than an induction of muscle protein synthesis

as a result of acute increases in serum testosterone. The endocrine response for the days following resistance training is unclear. Very recently, Aizawa and colleagues (129) showed that 12 weeks of aerobic exercise training enhanced the messenger RNA and protein expression of enzymes involved in steroidogenesis within skeletal muscle of male rats, such as 3β-HSD, P450arom, and 5α-reductase. This suggests that chronic endurance exercise training improves the production of steroids in skeletal muscle, which may assist in the muscular adaptation in skeletal muscle after training.

The testosterone response to resistance exercise is also greatly affected by age. In older (≥59 years) men (130–133), a bout of resistance exercise can elicit a significant elevation in circulating total and free testosterone, but the magnitude of this elevation is generally smaller compared with that in younger (20–30 years) men (130,132–134). Thus, although promising, further research is necessary to establish the extent to which resistance training in older men may synergistically work with testosterone to positively influence muscle anabolism, muscle strength, functional performance, and eventually longevity.

Women.—Findings on the testosterone response to a bout of heavy resistance exercise in women are equivocal with both increases (131,135–137) and no changes observed (138–141). Kvorning and colleagues (142) have shown that the Leydig cells are likely involved in the acute resistance exercise–induced increase in testosterone in men, but women do not have Leydig cells. The resistance exercise–induced increases in testosterone in women found in some studies could be simply due to a reduction in plasma volume, which could cause an increase in circulating testosterone concentration without a change in the amount of testosterone in the circulation. Another reason for the acute increase in free testosterone in women following resistance exercise could be a byproduct of cortisol production. Adrenocorticotropic hormone concentration increases in response to heavy exercise (143) and stimulates production and release of cortisol and causes release of testosterone from the adrenal cortex (144).

The testosterone response to resistance exercise and training in aging women is similar (either an acute increase or no change) to that for younger women (128), whereas others found that in middle-aged and older women who are untrained, total and free testosterone do not change acutely in response to high (131,145) or moderate (146) volume resistance exercise. In fact, the importance of testosterone for adaptations to resistance exercise in women has not been substantially examined, but it appears that testosterone plays only a minor role. One factor worth mentioning is that the above findings may simply reflect lack of sensitivity of testosterone assays, given the small detection range in women.

Thus, whereas testosterone seems to have only a small contribution to adaptations to resistance exercise in aging women, high intensity, and volume exercise training probably does elicit a testosterone response in older men which leads to increase in muscle strength, which in turn may counteract frailty and in that way indirectly contribute to improved quality of life, extended health span, and increased longevity. Skeletal muscle is sensitive to training up to a high age (147–149), although continuing exercising does not completely counteract age-related decreases in muscle strength (150). Therefore, additional methods to preserve muscle mass with aging would be useful. Because part of the decreases in muscle size, loss of bone, and increases in fat might be related to changes in the endocrine system, additional androgens or estrogens in combination with exercise may combat the extra decline in muscle strength that occurs with andropause and menopause.

Hormone Deficiencies, Therapies, and Longevity

Hormone deficiencies of all kinds can negatively affect health and longevity, complicating such a discussion. Testosterone therapies, and to a lesser extent estradiol and GH replacement, have increased substantially over the past several years and are widely used as function promoting therapies in older men and women (36) by increasing protein anabolism and reducing protein catabolism in skeletal muscle. Whether this approach will lead to increased longevity remains unanswered, however, mounting evidence suggests that significant gains in health through enhanced functional performance is an approach worth further investigation. Additional large-scale research is needed to provide the data necessary to determine the safety and efficacy of hormone replacement with age and to elucidate what its influence is on functional performance, enhanced health span and longevity.

Androgens

Age-associated declines in anabolic hormone levels are strong independent predictors of mortality in older men (151). Beyond its influence on skeletal muscle and frailty, testosterone deficiency can be linked to premature mortality (32,37,38) and to a number of comorbidities, such as sexual disorders, diabetes, and metabolic syndrome (including dyslipidemia, visceral obesity, hyperglycemia, hypertension, and thrombus formation process [152]). Moreover, testosterone deficiency is associated with insulin resistance and may predispose older men to the metabolic syndrome or type 2 diabetes mellitus. This also further complicates issues related to cardiovascular disease in the aging male (153–156) as these metabolic processes are all likely linked. Nieschlag and colleagues (157) found no trend toward a change in life span in castrated singers versus intact singers. This may indicate that removal of the testes in prepubertal men had no influence on the longevity in men. However, as the population ages, it could very well be that androgens may be important to combat frailty in the 8th, 9th, and 10th decades of life.

Regardless of gender, testosterone replacement may be effective in reversing age-dependent body composition changes and associated morbidity (158). Testosterone administration improves body composition by decreasing fat mass and increasing lean body mass (159–162) and muscle strength (23,24,163–167); however, not all studies confirm such (direct) changes in muscle strength or physical function (162,168–170). Randomized controlled clinical trials assessing testosterone therapy would be required to investigate whether androgens can have beneficial and/or neutral effect in the male cardiovascular disease–related morbidity (171) and mortality (172).

Testosterone therapy in women, resulting in serum levels in the normal or high–normal range, may provide significant improvements in emotional, sexual, and/or physical health. For example, Sheffield-Moore (39) showed that the skeletal muscle of women is anabolically responsive to an androgen, though the full biological impact of this effect has not been studied. Physiological testosterone therapy has shown to improve vasodilatation (173) and decrease diastolic blood pressure (174) in women. The demonstrated benefits of testosterone administration, primarily on bone and muscle, warrant further study in aging women. Additional longitudinal studies are needed to establish clearly whether androgen deficiency may directly affect cardiovascular biology and whether it might be a risk factor for cardiovascular disease during reproductive aging in women. More studies are needed to investigate whether the relative low testosterone levels in women may contribute to conditions later in life, such as mobility impairment, that are linked to disability, reduced quality of life and mortality and whether testosterone replacement therapy can reduce the negative health consequences of age-related frailty.

Testosterone has shown to reverse cachexia from cancer (175) or other inflammatory-based diseases (176–178). Also, trauma decreases testosterone production which may complicate healing and recovery in a variety of traumatic conditions (179,180). Despite the prevalence of male hypogonadism in patients with advanced cancer (181,182) and the suggested role of androgen deficiency in the pathophysiology of cancer cachexia (183), clear epidemiological data showing whether male hypogonadism is independently associated with clinical and biological sequelae of cancer cachexia is not available (184). A review of Shabsigh and colleagues (185) showed that none of the included studies demonstrated that testosterone therapy for hypogonadism, restoring testosterone levels within normal range, increased prostate cancer risk.

Thus, large-scale long-term testosterone replacement studies in older men and women are needed to determine the long-term risks and benefits of testosterone administration in older people (1,166,186). Especially in individuals with restricted or impaired functional ability, the possibility of increasing muscle strength via androgen administration would be of considerable benefit. Furthermore, additional research on bone-specific components of protein complexes associated with sex hormones and steroid receptors is necessary to provide new insights about the mechanisms of their tissue-specific regulatory action. Such studies may lead to identification of novel therapeutic targets and development of more efficient strategies in the treatment of osteoporosis during aging.

Estrogens

Lowe and colleagues (187) showed that estrogens have beneficial effects on muscle strength in postmenopausal women, and declines in estrogens have been implicated in age-related losses in muscle strength (187). However, the review by Meeuwsen and colleagues (188) highlighted controversial results. Conflicting estrogen-specific effects on skeletal muscle are also shown in Table 1 in the review from Enns and Tiidus (75). Although results on the effects of estradiol on muscle structure and contractile function in humans are conflicting (188) and depend on species examined, study type, age, muscle size, and fiber type etcetera (75), two recent well-controlled studies show beneficial effects of hormone replacement therapy on skeletal muscle composition and function in postmenopausal women (88,189).

Estrogens also play an essential role in maintenance of bone health in aging women. Estrogen deficiency in older men leads to hypergonadotropism, osteoporosis, and increased testosterone levels. Estrogen deficiency has a significant effect on carbohydrate and lipid metabolism, and estrogen resistance is associated with evidence of premature coronary atherosclerosis in men (190,191). Low estrogen concentrations in both men and women are associated with an increased risk of cardiovascular events (192–195).

Estrogen-based hormone therapy helps preserve muscle strength (87). In aging women, hormone replacement is the first line and most effective treatment for menopausal symptoms and improvement of low quality of life due to estrogen deficiency (196). However, Michael and colleagues (197) showed that hormone treatment provided no overall protection against functional decline in nondisabled postmenopausal women (65–79 years). Undesirable effects of prolonged postmenopausal exposure to estrogens replacement are increased risk of cancer (198) and increased rates of venous thromboembolism and biliary tract surgery for older women with coronary disease (199,200). This is clearly an area that requires further investigation.

Growth Hormone

In both GH deficiency and GH excess, increased incidence of cardiovascular disease has been reported as a contributing factor to reduced life expectancy. Although reduced longevity observed in hypopituitarism has been attributed to GH deficiency, it is unclear whether GH deficiency or other confounding factors cause this early mortality. Aguiar-Oliveira and colleagues (201) showed that in a

selected genetic background, untreated lifetime isolated GH deficiency does not affect longevity. However, Besson and colleagues (202) showed reduced longevity in untreated patients with isolated GH deficiency and conclude that current evidence supports the use of GH replacement in adults suffering from either childhood- or adult-onset GH deficiencies. This is in line with others (203,204) who found that GH deficiency is associated with an elevated cardiovascular risk and that hypopituitary patients with lifelong GH and IGF-1 deficiency have a shorter survival period from, and premature mortality due to, cardiovascular complications (205,206). Having multiple hormonal deficiencies rather than a deficiency in a single anabolic hormone is proven to be a robust biomarker of health status and mortality in older persons (151,207).

GH replacement reduces body fat and visceral adipose tissue, reduces low-density lipoprotein cholesterol and triglyceride levels, and improves endothelial function. Elhadd and colleagues (208) found significant endothelial dysfunction in hypopituitarism, pointing to early atherosclerosis in hypopituitary GH deficient adults. GH replacement is also shown to reduce intima–media thickness of major arteries and to improve left ventricular performance. Although these results have been observed only in small series of patients treated on a short-term basis (209), they strongly support the beneficial effects of GH replacement in adults with GH deficiency.

Older patients with GH deficiency respond to GH replacement with equal improvements in quality of life and lipid profile when compared with younger patients (210) and demonstrate some improvement in mortality rate. GH therapy in older people resulted in an increase in IGF-1, lean body mass, bone mineral density in the lumbar spine, decrease in total fat mass (111), increased muscle function (167), dyslipidemia, and quality of life (206). Brill and colleagues (211) showed that 1 month of GH and/or testosterone administration improved certain measures of balance and physical performance in older men and increased muscle IGF-I gene expression. There were no significant adverse events during 30 patient-months of intervention. However, the effects of GH replacement on endpoints such as cardiovascular morbidity and mortality and fracture are not fully proven (212). As with the other hormone replacements, safe diagnosis and appropriate GH dosing are necessary to provide the aging individual with the best possible outcome (213). Further long-term efficacy and safety studies are required (111,214).

Potential Risks of Low and High Testosterone

Testosterone therapy carries a certain risk, especially when the population being treated is unhealthy or when supraphysiologic doses are administered rather than replacement doses. A meta-analysis of Calof and colleagues (215), including 13 studies in their secondary analysis, showed that the groups of men with testosterone replacement had higher rates of prostate cancer, prostate-specific antigen, and prostate biopsies, although there was a bias toward a greater number of prostate biopsies in the testosterone group. Also, testosterone-treated men had an almost four times higher chance on hematocrit of greater than 50% (erythrocytosis), the most frequent androgen-related adverse event, compared with the placebo group. Cardiovascular event rates did not differ significantly between testosterone-treated and placebo-treated men (216), whereas Basaria and colleagues (217) showed that the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. However, the men studied in this trial were already frail and had mobility limitations. Other potential side effects interrelated with long-term testosterone treatment are acne, oily skin, reduced sperm production, and fertility (36).

Low concentrations of testosterone may carry risks as well. Although Edler von Eyben and colleagues (218) found that castrated men died less than expected from myocardial infarction implying that men do not have an increased coronary heart disease risk because of low androgen levels, a number of cross-sectional, case–control, and cohort studies have shown that lower testosterone levels in older men are associated with higher atherosclerosis and myocardial infarction (62,219) and higher cardiovascular and overall mortality (32,37,38,151,171,220). Testosterone supplementation may help in these cases but is not without risks and should be carried out with prudence.

Conclusions

Changes in hormone levels contribute to the process of aging because the endocrine system plays a major role in cellular interactions, metabolism, and growth. More specifically, there is a strong clinically important relationship between decreases in androgens and estrogens with age, age-related decline in muscle and bone mass and strength, and eventually health span in humans. Continued research is necessary to establish the proper roles, efficacies, and safe applications of hormone and exercise training therapies in mitigating the sharp and rapid declines in androgen and estrogen concentrations with advancing age and the contribution of these hormones in overall human longevity.

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