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Hormonal and Metabolic Changes of Aging and the Influence of Lifestyle Modifications

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Abstract

Increased life expectancy combined with the aging Baby Boomer Generation has resulted in an unprecedented global expansion of the elderly population. The growing population of older adults and increased rate of age-related chronic illness has caused a substantial socio-economic burden. The gradual and progressive age-related decline in hormone production and action has a detrimental impact on human health by increasing risk for chronic disease and reducing life span. Here we review the age-related decline in hormone production, as well as age-related biochemical and body composition changes that reduce the bioavailability and actions of some hormones. The impact of hormonal changes on various chronic conditions including frailty, diabetes, cardiovascular disease and dementia are also discussed. Hormone replacement therapy has been attempted in many clinical trials to reverse and/or prevent the hormonal decline in aging to combat the progression of age-related diseases. Unfortunately, hormone replacement therapy is not a panacea, as it often results in various adverse events which outweigh its potential health benefits. Therefore, except in some specific individual cases, hormone replacement is not recommended. Rather, positive lifestyle modifications such as regular aerobic and resistance exercise programs and/or healthy calorically restricted diet can favorably affect endocrine and metabolic functions and act as countermeasures to various age-related diseases. Here we provide a critical review of the available data and offer recommendations which hopefully will form the groundwork for physicians/scientists to develop and optimize new endocrine-targeted therapies and lifestyle modifications that can better address age-related decline in heath.

Keywords

Hormones; Aging; Frailty; Diabetes; Cardiovascular Disease; Exercise; Dementia

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Introduction

Aging is inevitable and is the single most important modulator of human life span and health span. The substantially increased morbidity and mortality associated with advancing age contributes to the higher socio-economic cost of the older population. An unavoidable consequence of increased life expectancy is an expansion of the older population. In 2012 it was estimated that there were approximately 43.1 million people aged 65 and older in the United States, and this number is projected to reach 83.7 million by the year 2050.[1] Worldwide, the number of people aged 65 and older is projected to be 1.6 billion by 2050.[2] The abrupt increase in lifespan that has occurred since the turn of the 20th century has prompted scientists, health care organizations, and national leadership to develop approaches aimed at extending quality-of-life and reducing late-onset diseases of aging.[3] It is therefore critical to understand the "normal" age-related changes in human physiology and the underpinnings of these changes. Multiple age-related hormonal and metabolic changes greatly contribute to the principal age-related chronic diseases and decline in physiological functions which include atherosclerosis, hypertension, diabetes, hyperlipidemia, obesity, sarcopenia, osteoporosis, thrombogenesis, chronic inflammation and decline in immune functions. Another emerging health concern of aging is a decline in brain function, which is mostly related to the development of degenerative brain diseases that cause cognitive decline in the form of various types of dementias. Interestingly, the development of cognitive decline during aging is more prevalent in people with metabolic problems. Aging adversely affects not only hormonal secretions but also their biological availability (Eg; sex hormones) and their effects on targeted organs (Eg; insulin resistance). One of the most important questions is whether any or all of the hormonal and metabolic changes that occur with age are preventable and/or reversible. In addition, many metabolic changes, especially those related to hormonal actions, are related to lifestyle modifications that are common as people become older. In this review we will attempt to critically summarize the hormonal and metabolic changes that occur with age and whether and/or how these age-related alterations can be prevented or slowed down thus benefitting the welfare of humanity.

Hormone Changes with Age

A number of terms have been used to describe the loss of hormone production and their secretory patterns as we age including menopause, andropause, adrenopause, and somatopause.[4] *Menopause* is associated with an abrupt loss of estrogen and progesterone production in women at mid-age following the cessation of ovarian function.[5] Although the sudden decline in female sex hormone production in menopause has a clear consequence on cardio-metabolic health, the current review will focus on the adverse health effects of the gradual loss of hormones during aging. For more information regarding the influence of menopause on metabolism in elderly women, we refer readers to other comprehensive reviews.[6, 7] A gradual decline in testosterone (T), termed *andropause*, begins around 20-30 years of age in men and persists until death (Figure 1A). Women also experience decreased T with age, but the T level in women is approximately 10-times lower than in men,[8] thus the effects of lower T during aging may be more detrimental in men. Because of the greater decline in T in men, a majority of the studies in this area have been performed in men, therefore generalizing of the effects of andropause across genders should be carefully

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considered by readers. *Adrenopause* is characterized by reduced secretion of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) with advanced age (Figure 1B). *Somatopause* is the term used to describe a decline in pulsatile secretion of growth hormone (GH), resulting in reduced insulin-like growth factor 1 (IGF-1) that occurs with age (Figure 1C). It has been suggested that the altered hormonal profile that is associated with aging plays a critical role in the onset of many metabolic complications that also come with advancing age.[9] Thus, identifying strategies to mitigate the deleterious effects of andropause, adrenopause, and somatopause remain a high priority as the aging population continues to grow.

A widely held notion is that approaches for combating the decline in endocrine function observed during aging may improve the quality of life of elderly people. Additionally, if strategies which successfully improve endocrine function in the elderly population can improve quality of life, then a substantial burden on the national and global economy should be lessened.[10] In recent decades, hormone replacement therapy has garnered substantial attention due to promising findings, but apparently preventing an age-related decline in hormones by exogenous replacement is associated with increased risk for adverse effects in older adults.[11-13] The controversies and conflicting results on hormone replacement have more recently discouraged physicians away from prescribing hormone therapy in most healthy older people. In contrast, the emerging data from multiple studies show the indisputable beneficial effects of lifestyle changes, especially exercise [14, 15] and caloric restriction,[16-18] in mitigating many age-related physical and cognitive declines.

The current review presents an overview of the major metabolic consequences of normal aging, many of which are associated with the decline or alteration of endocrine function. Specifically, we address the metabolic outcomes of andropause, adrenopause, and somatopause. Further, we discuss the efficacy and complications of hormone replacement therapy and lifestyle changes, especially exercise, as interventions for treating the age-related declines in metabolic function. By summarizing the collective literature regarding the major hormone-associated metabolic complications that occur during aging, we hope to provide the groundwork for physicians and scientists to develop and optimize new endocrine-targeted therapies and lifestyle modifications that can better address metabolic health concerns during aging.

Reduction of Hormone Availability and Action Related to Age

Testosterone

The pulsatile secretion of gonadotropin-releasing hormone from the hypothalamus results in the release of luteinizing hormone and follicle-stimulating hormone from the anterior pituitary.[19] Luteinizing hormone then binds with specific high affinity to luteinizing hormone receptors on the plasma membrane of testicular Leydig cells in men and of theca cells in women, leading to a cascade of signaling events which results in T synthesis.[20] Because T is a steroid hormone and cannot be stored in the cells where it is produced, it is immediately secreted into the circulation. Once in the circulation, approximately 98-99% of T associates with hydrophilic binding partners.[21] The remaining 1-2% of free T is the most biologically active form of T. Sex hormone-binding globulin (SHBG) is the primary binding

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protein for T and reduces the transport of T into the cell, thus inhibiting its biological action.[22] T also binds to albumin in the blood, but the movement of T is less restricted by albumin and reaches the intracellular compartment.[23] After transport through the circulation, T exerts its effect by binding to the intracellular androgen receptor, which subsequently is transported as the androgen receptor-testosterone complex to the nucleus where it induces gene transcription.[24] Activation of this hypothalamic-pituitary-gonadal axis has a robust anabolic effect, increasing muscle mass and strength, promoting muscle protein synthesis, and increasing bone mineral density.[25-27] The term "hypogonadism" is used to describe the clinical condition of low levels of serum T and its associated symptoms of decreased libido, loss of muscle and bone mass, depression, and anemia.[12] Some or all of these features of hypogonadism are present in a milder but variable extent in older men.

The anabolic effect of T is reduced during aging due to a gradual and consistent decline in circulating T that begins around the third to fourth decade in men,[28, 29] also known as andropause. Approximately 40-50% of men over the over the age of 80 have T levels below that of normal healthy young individuals.[28, 30] By the third decade, both men and pre-menopausal women experience a decline in DHEA and DHEA-S,[31] which can serve as precursors for the production of androgenic hormones such as T.[32] The decline in total and free T levels in men occurs at a rate of approximately 1% and 2% per year, respectively (Figure 1A).[33, 34] Even though women have a considerably lower level of T, they too experience reductions in bioavailable T with age.[35] In men, this decline in T has been suggested to be due to a combination of both defective gonadotropin-releasing hormone secretion and Leydig cell responsiveness.[36] The biologically active forms of T (free T and albumin–bound T) decrease at a greater rate than SHBG-bound or total T during aging,[37] likely because of the age-associated increase in SHBG.[28, 38, 39] The increase in SHBG and SHBG-bound T reduces the mobility and effectiveness of endogenously produced T. Thus, not only is T production reduced during aging, but a greater proportion of the T that is produced is less effective.

Dehydroepiandrosterone

Approximately 75-90% of DHEA is produced in the adrenal cortex [40] and converted to DHEA-S, its sulfated form, by hydrosteroid sulfatases.[41] The remaining ~10-25% of DHEA production occurs in the testes, ovaries, and brain.[42] The secretion of DHEA-S, the most abundant circulating steroid hormone,[43] is synchronized with the secretion of cortisol in response to corticotropin-releasing hormone and adrenocorticotropic hormone.[44, 45] After traveling through the circulation and arriving at peripheral tissues, DHEA-S can be metabolized back to DHEA by sulfohydrolase.[46] DHEA-S essentially serves as a large and stable plasma reservoir for later conversion to DHEA.[42] DHEA serves as a precursor to many androgenic and estrogenic hormones.[32, 47, 48] Thus, low levels of DHEA or DHEA-S result in an even greater dysregulation of the overall hormonal profile. In fact, around 30% of androgens in men and around 75% of estrogens in premenopausal women are produced from the conversion of DHEA/DHEA-S steroids.[42]

After birth DHEA and DHEA-S levels sharply decline and do not begin to increase until around 7-9 years of age.[42, 49] By age 20-30 years, DHEA and DHEA-S levels reach their

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peak and steadily decline at a rate of approximately 2-3% per year in both men and women (Figure 1B).[33, 50, 51] The age-related trend in DHEA is unique from any other steroid hormone and suggests that the signals to produce DHEA are distinct from signals for the production of other hormones.[50] Men have around 2 times greater DHEA-S than women,[32] but women have been reported to have greater levels of DHEA.[42, 49] The cause of these gender related differences is unknown.

Growth Hormone and IGF-1

Also referred to as somatotropin, GH is a peptide hormone that is synthesized and secreted by the anterior pituitary which initiates signaling processes involved in growth of nearly all tissues in the human body. GH is released in a pulsatile fashion, with the largest peak in GH observed soon after slow wave sleep and numerous smaller peaks in GH observed shortly after meals.[52-54] Negligible amounts of GH are produced in between the 10-15 secretory bursts that can occur during a 24-hour period.[52] The primary positive and negative regulators of the pulsatile secretion of GH are GH-releasing hormone (GHRH) and somatostatin, respectively.[55] Ghrelin, an endogenous ligand of the GH secretagogue receptor, is also a potent stimulant of GH secretion.[56] GHRH is secreted by the hypothalamus in response to low levels of GH and IGF-1, and the response to GHRH is inhibited by IGF-1,[57] providing a negative feedback loop for GH secretion.[58]

The magnitude of GH pulses peak during puberty and subsequently decline at a gradual rate of approximately 1-2% per year until death in men and women.[59-61] Once released into the blood, GH signals the production and release of IGF-1 by binding to the GH receptor on the plasma membrane of liver and other peripheral tissues.[62, 63] IGF-1 is a primary mediator of cellular growth [64] and a critical component of human post-natal development. Like GH, serum IGF-1 increases with age until puberty, and then gradually declines into old age (Figure 1C).[61, 65] The reduction in GH and IGF-1 in healthy aging adults is primarily due to a reduction in the amplitude of the GH secretion, not a reduction in frequency of secretory bursts or the half-life of GH.[66] The decrease in GH and IGF-1 with age has been termed “somatopause” and appears to have a robust impact on metabolic health.[67, 68]

Metabolic and Physical Performance Decline of Aging: Related to Hormone Changes and Lifestyle Changes

The reduction in hormone production that commonly occurs with age can influence a variety of metabolic processes (Table 1).

As a consequence, physiological outcomes which are major risk factors for diabetes and metabolic abnormalities are negatively affected. Moreover, the habitual decline in physical activity that occurs with aging can exacerbate these metabolic abnormalities (Figure 2). In this section we touch on some of the physiological outcomes related to the hormonal changes of aging. However, the association between hormonal changes and these physiological outcomes cannot be fully delineated from the influence that lifestyle changes (i.e. physical activity and diet) may also have on these outcomes. Therefore, we also address

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the influence of positive lifestyle modifications, such as increased physical activity and reduced caloric intake, on important health-related outcomes during aging.

Body Composition / Obesity

Percent fat mass is an important predictor of metabolic disease.[69, 70] Altered body composition, particularly loss of lean tissue (especially muscle mass), and increased obesity (accumulation of body fat) become more evident with age and can have profound effects on metabolism. The decline in hormone production that is associated with age may play a critical role in the increased fat mass and decrease in lean tissue that occurs with age. For example, it has been observed in elderly (60-80 year-old) men with subnormal T levels that subcutaneous and visceral fat mass are elevated when compared to elderly men with normal T levels.[71] A significant negative association has also been observed between obesity and T levels by multiple groups,[72-74] emphasizing the metabolic importance of maintaining T production with age. Lower DHEA-S levels have been associated with greater body fat,[75] increased waist to hip ratio,[76] and decreased percent lean body mass [77] in men over the age of 60. An inverse correlation between DHEA and BMI has also been found, suggesting DHEA may increase lipolytic capacity and decrease body fat.[78] It is logical to speculate that because DHEA serves as a precursor to multiple androgens, such as T, that the beneficial effects of higher endogenous DHEA may be due, at least in part, to an elevation in T production. Increased adiposity [79, 80] is also associated with reduced GH secretion during aging. In fact, 40 weeks of GH administration decreases visceral adipose volume in obese subjects.[81] Taken together these data highlight the roles of T, DHEA, and GH in substrate metabolism and storage, and suggest that dysregulation of these important hormones in aging might result in deleterious effects on body composition, an important indicator of metabolic health.

Caloric restriction (CR) has been shown to robustly improve body composition and reduce obesity.[82-84] Thus, CR has been touted as an exceptional strategy for improving health and lifespan. In fact, some researchers have explored the feasibility of performing long-term CR studies in humans to assess its effect on multiple health parameters.[85, 86] In rodents it has been well established that CR can improve metabolic health and significantly extend lifespan.[87, 88] CR can also improve hormonal regulation. In obese male subjects who were calorically restricted for 3 months, total T levels are significantly increased, concomitant with a large decrease in body fat.[89] In obese subjects who lost ~30kg of body mass, GH secretion was more than two-fold greater than obese subjects who did not lose weight.[90] These findings suggest that CR is a modifiable lifestyle factor which may improve hormonal regulation, resulting in improved body composition, a major risk factor for metabolic disease. However, it is unclear if the beneficial effect of CR on body composition requires the improvement in hormonal production. If hormonal improvements are necessary for the CR effect on metabolism, then future therapies and drugs aimed at improving body composition via CR-related mechanisms should also target these important hormones for an optimal improvement in metabolic health.

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Insulin Sensitivity

Reduced insulin sensitivity is an essential precursor in the development of type 2 diabetes. Insulin resistance, type 2 diabetes, and associated clustering of cardio-metabolic changes including dyslipidemia, hypertension, and increased thrombogenesis are significant risk factors for cardiovascular disease and all-cause mortality. The rates of type 2 diabetes and insulin resistance are significantly greater in the elderly population compared to young adults,[91, 92] leading to greater risk for cardiovascular events. It is logical to speculate that the reduction in anabolic hormone production that occurs with age may play a role in the reduction in insulin sensitivity that is also commonly observed with age. In elderly men, lower T levels are associated with reduced insulin sensitivity as indicated by higher glucose levels during an oral glucose tolerance test,[71] reduced quantitative insulin sensitivity check index score,[93, 94] and lower HOMA-IR values.[95] Additionally, endogenous GH levels are positively associated with insulin sensitivity in elderly subjects.[96, 97] The decline in T production and reduction in GH with age, therefore, may have a significant influence on reducing insulin sensitivity. Low levels of both DHEA and DHEA-S are associated with elevated risk of cardiovascular disease.[98-100] Feldman et al. reported that in 40-70 year old men in the lowest quartile for plasma DHEA or DHEA-S there was a significantly greater risk for ischemic heart disease.[101] Reduced endogenous GH secretion during aging gives rise to a number of negative metabolic outcomes that collectively result in elevated risk for cardio-metabolic morbidity and mortality, which are deleterious consequences of aging. However, the mechanisms which are responsible for the decline in insulin sensitivity and increased cardiovascular disease risk with age are not entirely clear.

Increasing physical activity level is a simple lifestyle modification that can have a robust impact on health in older populations. Exercise training can significantly improve insulin sensitivity.[102] In fact, even a single bout of exercise can enhance insulin-stimulated glucose uptake in whole muscle tissue [103-105] and individual muscle fibers.[106, 107] Unfortunately, insulin sensitivity is typically reduced with age.[108] In older adults, those who partake in aerobic exercise (AE) ≥ 5 days per week have greater insulin sensitivity than those who exercise ≤ 1 day per week.[109] In a separate study, our group previously found that insulin-induced glucose disposal was greater in aerobically trained old and young subjects than in their sedentary counterparts.[110] Importantly, this study found that that there were no age-related differences in insulin sensitivity, suggesting that the commonly observed age-related reduction in insulin sensitivity is likely due to reductions in physical activity rather than aging per se. Furthermore, insulin sensitivity can be improved, irrespective of age, by either AE or resistance exercise (RE).[111] These data support the provocative idea that simply maintaining activity levels in old age can completely prevent the commonly observed reductions in insulin sensitivity with age. Of course, aging may introduce other symptoms which limit an individual’s ability to remain physically active, indirectly affecting insulin sensitivity. Since it has been well documented that exercise/physical activity can help to maintain normal hormone production with age,[112, 113] it is possible that the maintenance of insulin sensitivity in old subjects by exercise is mediated by the maintenance of hormonal production.

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Another lifestyle change which can help to maintain insulin sensitivity in aging is CR. Reducing caloric intake to ~75-80% of baseline energy requirements has been shown to maintain insulin sensitivity in overweight middle-aged humans.[114, 115] Two separate studies have shown that even in the absence of improvements in mitochondrial content and oxidative capacity, CR designed to reduce body weight by 10% within 16 weeks in obese humans can significantly improve insulin sensitivity.[116, 117] Another study demonstrated that insulin sensitivity is negatively associated with percent body fat and waist-to-hip-ratio, but age is not significantly associated with insulin sensitivity,[118] suggesting that weight loss (which can be aggressively achieved by CR) may be crucial for improving insulin sensitivity with age. A number of studies have demonstrated that life span is extended and insulin sensitivity is improved in old rodents which are subjected to ~40% CR.[119-121] Long-term CR in rats results in elevated Leydig cell production of T in old age,[122] suggesting that hormone production mediates the effect of CR on insulin sensitivity in old age. However, since these studies in rats typically employ ~40% CR, which is unfeasible for most humans, it will be critical to determine if the same effects are observed in humans with modest reductions in caloric intake that do not reduce mood and quality of life. It will also be important to determine if CR-induced alterations in hormone production or CR per se are responsible for improvements in human insulin sensitivity.

Aerobic Capacity

Age is associated with a decline in aerobic capacity (VO_2max). VO2max is highly dependent on both the amount of mitochondria and the oxidative capacity of the mitochondria in skeletal muscle.[123-125] Multiple groups have reported a decrease in skeletal muscle mitochondrial content and function with age.[126-128] The aging-associated decrease in mitochondrial content and function can result in reduced VO_2max, which is a strong predictor of early mortality.[129] In old men, low T is associated with low VO2max and low levels of muscle oxidative phosphorylation genes, suggesting that low T induces reductions in mitochondrial capacity.[130] Corroborating this, mice that are treated with exogenous T have transcriptionally upregulated mitochondrial biogenesis.[131] Further, low T levels in humans are associated with elevated mitochondrial reactive oxygen species (H_2O_2) production and enhanced inflammatory markers.[132] Together these results support the notion that the maintenance of T levels during aging augments VO_2max via maintenance of mitochondrial function. Higher levels of DHEA are also associated with increased VO_2max during aging,[77] which may be due to elevated mitochondrial biogenesis in response to high levels of T.[133] Because DHEA is the primary precursor for conversion to T,[134] the beneficial effect of DHEA on aerobic capacity during aging may be due to the maintenance of T levels. Interestingly, although IGF-1 levels decline with age, at least one group has shown that VO_2max is not independently associated with IGF-1 levels during aging.[135] Four weeks of GH administration at either high or low doses does not alter VO_2max in healthy young volunteers.[136] However, acute GH administration in healthy young humans, which increases IGF-1, promotes an increase in mitochondrial oxidative capacity and the abundance of various mitochondrial genes in skeletal muscle.[137] Therefore, the influence of GH/IGF-1 and aerobic capacity is unclear, since mitochondrial adaptations to GH are present in the absence of any detectable changes in functional aerobic capacity. However, the influences of other anabolic hormones, especially T, clearly have a robust impact on VO_2max.

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Despite the reduction in VO_2max with age, exercise training can prevent the loss of aerobic capacity in older adults. In a study by Holloszy's group, VO_2max was measured in older adults (~62 years old) who were either sedentary or aerobically trained master athletes before and after an 8-year follow up. The reduction in VO_2max in sedentary individuals was approximately 12% per decade, whereas in age-matched aerobically trained master athletes only a 5.5% reduction in VO_2max per decade was observed.[138] Since aging is highly associated with reduced mitochondrial function due to decreasing mitochondrial DNA (mtDNA) and increased DNA oxidation,[126] it has been suggested that the declining capacity of mitochondria to produce ATP during aging may contribute to insulin resistance and reduced physical function that occur with age.[126] However, AE training (AET) can prevent the loss in mitochondrial function with age. Lanza et al. demonstrated that the normal age related decline in mitochondrial oxidative capacity is not present in AE trained older individuals.[110] In fact, much of the decline in mitochondria, especially mitochondrial content and respiration, can be reversed by 3 months of high-intensity interval training (HIIT).[111] However, despite the improvements in mitochondria in older trained individuals, the beneficial effect of exercise cannot completely maintain VO_2max at levels observed in young subjects.[111] The age-associated decline in maximal heart rate is typically reported to be unaltered by exercise training,[139-142] but some evidence suggests that the decline in maximal heart rate with age can be attenuated by vigorous exercise.[143-145] It appears that stroke volume and oxygen extraction can be maintained by exercise training during aging.[140, 146] Thus, there is a possible dissociation between aging-associated declines in VO_2max and cardiac output/mitochondrial function. It will be important to clearly identify which factors prevent chronic exercise training from completely reversing the decline in VO_2max. Furthermore, it will also be important to know if the declines in these cardiac functions are irreversible.

The many effects that CR has on metabolism have prompted researchers to study the impact of CR on longevity. Because aerobic capacity is a strong predictor of lifespan,[147] it is reasonable to speculate that CR is also related to VO_2max. In fact, 2 years of 25% CR in humans results in a significant increase in relative VO_2max (mL/kg/min) compared to ad libitum controls.[148] In rodents, 40% CR prevents the age-associated decline in muscle mitochondrial function [149, 150] and aerobic capacity.[150] Moreover, 40% CR in rodents also leads to lower heart mitochondrial H_2O_2 production,[151] reducing mitochondrial damage and extending life span. Lifelong CR in mice can completely prevent the age-related loss of mitochondrial oxidative capacity and efficiency without increasing mitochondrial content,[152] suggesting that CR preserves mitochondrial function by maintaining its existing components, not by replacing damaged mitochondria with new mitochondria. However, it is important to make the distinction that CR has not been shown to improve mitochondrial function, but rather CR may prevent the age-associated decline in mitochondria. Understanding the mechanisms by which CR maintains mitochondrial integrity during aging will be important for optimizing the therapeutic potential of this robust lifestyle practice.

Muscle Mass and Strength

Both muscle mass and strength decline with age. Postmortem studies performed in relatively healthy people in Sweden originally reported lower muscle cross sectional area in older

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people. In particular, this study reported a significant reduction in the number of muscle fibers expressing the type II myosin heavy chain (known as fast-twitch muscle fibers) in older subjects compared to young subjects.[153] Cross-sectional data in 60-90 year-old men and women show a significant age-related decline in muscle mass and strength, which corresponds to a reduction in T.[154] Longitudinal data show that when older men (~65 years old) were evaluated after a 12-year follow up (at ~77 years old), there was a significant decline in muscle cross sectional area and strength,[155] and T consistently declines during this age range.[28, 29] In elderly men, low T levels are associated with reduced muscle strength.[156] Orchiectomised rats, which have drastically reduced T, display muscle atrophy and reduced muscle ribosome content, but treating orchiectomised rats with T recovers muscle ribosome content to normal values.[157] Therefore, at least in rodents, T plays an important role in maintaining muscle mass during aging through regulating ribosomal content, which is critical for protein synthesis. However, the effects of low T in elderly human populations on ribosomal biogenesis, capacity, and content have yet to be evaluated. It also remains to be determined whether maintaining T levels during aging is critical for the conservation of muscle mass and strength via ribosomal biogenesis. Reductions in GH secretion also result in a loss of lean body mass [79, 158] and decreased strength.[158] The loss of GH production in aging results in reduced circulating IGF-1, which is an important regulator of muscle mass and strength during aging.[159] IGF-1 regulates muscle mass via Akt-mediated signaling, inhibiting forkhead box type O (FoxO) transcription factors and the ubiquitin-proteasome system.[160] Further, IGF-1 increases mTOR signaling, resulting in increased ribosomal translation of transcriptome to proteins.[161] Thus, both T and GH are important regulators of muscle mass and strength during aging.

Sarcopenia, the loss of muscle mass with age, and reduced strength are well known symptoms of normal aging.[162, 163] Thankfully, RE can attenuate and partially reverse the decline in muscle mass that is observed in older adults,[164, 165] although high intensity interval training (HIIT; aerobic exercise) can also modestly increase muscle mass. In fact, RE training (RET) can increase muscle mass and strength in old individuals who were previously sedentary, but not to the same extent as younger people.[164, 165] Although HIIT modestly increases muscle mass, it is not nearly as effective at improving muscle strength as RET.[111] Factors which restrict the capacity of older adults to partake in RET such as increased soreness, risk for injury, and joint pain may be critical barriers which limit benefits of RET. Although reduced muscle mass and strength may be partially due to reduced activity in aging, inactivity does not completely explain muscle loss with age.

Bone Health

After reaching peak bone mineral density (BMD) by the third decade, a consistent decline in bone mass and BMD occurs in both men and women with advancing age, with a steeper decline in women, especially after menopause.[166, 167] The declines in bone mass and density with age are accompanied by a drastically increased risk for fractures,[168] which are associated with increasingly greater risk for mortality after the age of 60.[169] The correlation between bone loss and declining hormone production with age has sparked investigations into the influence of hormones such as T, DHEA, and GH on the maintenance of bone health with age. Although estrogen deficiency in post-menopausal women is clearly linked to

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increased osteoporosis with age,[170, 171] the influence of T, DHEA, and GH on BMD in aging men is not as clear. Although Meier et al. found no relationship between T levels and BMD in healthy older men,[172] others have reported a positive association between T and BMD in elderly men [173] and post-menopausal women.[174] However, Slemenda et al. have reported that both T and DHEA are negatively associated with BMD in older men.[175] These confounding results leave uncertainty in the relationship between T levels in aging and bone health. However, at least in hypogonadal men, T is clearly significantly correlated with BMD.[176] Furthermore, in GH-deficient adults, levels of GH are significantly associated with BMD.[177] Therefore, since hormone deficiency is increasingly prevalent in older adults and bone loss occurs more rapidly with T or GH deficiency, positive lifestyle strategies for combating declines in hormonal secretion should be considered for the maintenance of bone health.

Consistent lifelong exercise has been known to build and maintain bone health. In childhood, the loading impact of physical exercise has been shown to have a significant impact on the increase in BMD.[178-180] Although exercise may only exert minimal increases in BMD in adulthood, it can certainly attenuate the decline in BMD that is associated with age.[181] Aerobic exercise, especially exercise which produces a physical loading impact on bone, such as running, has been shown to maintain bone health.[182, 183] Resistance exercise training, especially that which encompasses the both upper and lower body exercises has a profoundly positive impact on BMD.[181, 184] Thus, for the maintenance of bone health and reducing the risk of fractures in aging, both aerobic and resistance exercise are highly recommended for older individuals.

Cognitive Processes

Aging is associated with cognitive decline, even in the absence of dementia.[185] Although the mechanisms responsible for this decline are not completely understood, mounting evidence continues to point towards metabolic derangements in the brain as the culprit for cognitive declines associated with age. Brain glucose metabolism significantly declines in old age [186] and can initiate a chain of deleterious metabolic derangements in the brain which may highly impact cognition. Increased oxidative protein damage in the brain [187] and decreased brain mitochondrial enzyme activity [188] are both associated with aging. Moreover, neuroinflammation has also been highly associated with cognitive aging.[189] These, and other, age-related effects in the brain are likely due to altered fuel metabolism. When brain glucose metabolism is disturbed in mice using an insulin receptor antagonist, brain mitochondrial structure and function are dramatically impaired.[190] It is likely that maintenance of metabolism, specifically mitochondrial metabolism, in the brain can combat the age related decline in cognitive function. As with other deleterious aging-associated outcomes, positive lifestyle modifications have been shown to prevent or reduce the cognitive decline with age.

Exercise is convincingly beneficial for cognitive health with age. For example, Rogers et al. showed in a 4-year prospective longitudinal study that older adults approaching retirement (~65 years of age) who either continued working or retired and began a regular physical activity routine had significantly better cognitive test scores than those who retired and did

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not remain physically active.[191] Older adults who were underwent AET for 3 months increased functional capacity of key attentional aspects of the brain, but the sedentary control group did not.[192] What are the mechanisms responsible for the beneficial effect of AET on cognition in older adults? Some suggest that improved blood flow and oxygen delivery are responsible for these changes.[193, 194] Others have provided evidence that improved brain mitochondrial function following AET can improve brain metabolism,[190] potentially leading to improved cognition. Perhaps multiple mechanisms are responsible for the cognitive improvements following AET. It is also important to note that RET has also been shown to improve cognitive functioning in older adults,[195, 196] but the mechanisms of its effect are even less clear than AET. AE and RE can independently improve cognition, but the brain signaling processes that occur after each type of exercise are distinct,[197] suggesting AET and RET have different mechanisms of action. Understanding how both RET and AET can improve/maintain brain function with aging will be a critical step for prescribing therapies and creating drugs which mitigate the effects of aging on the brain.

CR is another lifestyle modification which can improve cognitive function in older adults. Witte et al. showed in healthy older people (mean age 60.5 years) that 3 months of 30% CR significantly improved verbal memory scores.[16] Age-dependent cognitive deficits that are observed in ad libitum-fed mice are absent in mice that are 30% calorically restricted.[198] In these same mice it was observed that hippocampal autophagy processes were upregulated during CR,[198] suggesting the process of removing damaged and dysfunctional proteins is crucial for maintaining cognitive function during aging. It is reasonable to speculate that these processes of improved protein turnover in the brain can enhance brain mitochondrial structure and function. Supporting this idea, Sanz et al. have demonstrated that 40% CR in old rats results in reduced brain mitochondrial H_2O_2 production and lower oxidative damage to nuclear DNA.[199] Thus, the metabolic processes which occur in the brain in response to CR can have a substantial beneficial effect during aging and therefore may reduce cognitive decline.

Impact of Hormone Replacement in Aging

T replacement therapy has been introduced as a mode for treating many of the metabolic deficiencies that come with age. Various methods of T replacement such as oral tablets, mucoadhesives, injections, transdermal patches or cream, and subdermal implants have been used and are reported to provide multiple health benefits to hypogonadal men.[200] Of course the various forms of T replacement have distinct advantages and disadvantages. For example, injectable T is relatively inexpensive, but the prescribed weekly injections result in peaks in T soon after the injections that are supraphysiological and dips in T by the end of the week. Transdermal patches or cream provide a steady and consistent lower dose of T, but may result in skin irritation or inadequate absorption. Regardless of the administration method, T replacement has been shown to provide a variety of health benefits. The Testosterone Trials, a multi-center set of randomized trials across 12 clinical sites, tested the effect of T administration in 790 elderly men on 7 different primary outcomes (sexual function, physical function, vitality, cardiovascular health, bone health, cognitive function, and anemia).[201] These trials and other independent studies found that T administration in elderly men resulted in improvements in sexual function,[202, 203] lean body mass,[204, 205]

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physical function,[206] strength,[25, 205, 207] protein synthesis,[25] cholesterol,[204, 205, 208] and bone density.[209] Potentially explaining some of the positive effects of T on human health, studies using cell culture and rodent models reveal that T administration increases the activity of glycolytic enzymes (hexokinase, phosphofructokinase, and glycogen synthase) and upregulates the expression of genes and proteins involved in glucose metabolism (IRS-1, IRS-2, GLUT4, PPARγ).[210-213] However, some groups have shown that T replacement in old men does not provide significant benefits in strength [214-217] or cognition,[218] increases coronary artery plaque formation,[219] and is consistently shown to have no effect on insulin sensitivity.[216, 220] The disparate findings regarding efficacy of T replacement and its effect on metabolic health have created some controversy, especially considering the potential risks associated with T replacement treatment. Some of the risks associated with T therapy include exacerbation of prostate cancer, cardiovascular-related events, hepatotoxicity, erythrocytosis, sleep apnea, and dermatological issues.[12, 13] A meta-analysis analyzing adverse events of T therapy reported that in those who received T replacement therapy compared to placebo, the odds of developing a prostate event or having a hematocrit >50% were 1.78 and 3.69 times greater, respectively.[221] Presumably, lower doses of T may not exert such adverse health effects, but unfortunately low-dose T does not have physiologically relevant beneficial effects on health.[216] The duration of T replacement in most previous studies ranges from approximately 1-36 months, but the side effects of longer duration T replacement therapy have yet to be assessed. Moreover, most studies evaluating the effect of T replacement are performed in relatively healthy elderly men. However, those who likely stand to benefit the most from T replacement therapy are the frail elderly, yet the beneficial and adverse effects of T replacement in this population are largely unknown.[222]

Although the efficacy of T replacement therapy remains under question, some have postulated that treatment with the T precursor, DHEA, may provide improvements in health without negative side effects. Studies in cultured skeletal muscle cells and rodents have suggested that DHEA administration can increase the expression of the glucose transporter GLUT4 and key glycolytic enzymes, phosphofructokinase and hexokinase.[212, 223] However, studies examining the influence of DHEA administration in humans are less promising. DHEA has been introduced as an “anti-aging” therapy via ingestible tablets or transdermal patches. Although both of these modes of administration of DHEA clearly elevate plasma DHEA and DHEA-S levels,[224] the beneficial effect on metabolism in the elderly population is underwhelming. In old men and postmenopausal women, although DHEA administration has been shown to produce very minor elevations in bone mineral density,[216, 225, 226] these increases are not as large as those produced by other therapies. The collective literature suggests that DHEA therapy has no significant effect on muscle mass and strength [227, 228] or insulin sensitivity.[48, 216, 229-231] Long term (24 month) DHEA administration in old people, which elevated DHEA levels to that in the high-normal range for young people, did not result in improvements in body fat or muscle mass.[216] Conflicting findings regarding DHEA administration and cholesterol have been reported. One group has shown that DHEA administration seems to lower HDL in postmenopausal women,[40] but another group has shown elevated HDL, and decreased LDL and plasma triglycerides in postmenopausal women.[232] It has been suggested that DHEA supplementation may improve vascular endothelial function and cardiovascular disease, but no long term (multiple year) studies

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have evaluated the impact of DHEA therapy on cardiovascular health.[233] The current state of the literature suggests that DHEA may have minor metabolic health benefits, but long term adverse side effects are not completely known. Thus, DHEA supplementation should be approached with caution, and should be immediately terminated at the onset of any side effects.

Since the seminal publication nearly 30 years ago in the New England Journal of Medicine by Rudman et al. showing that GH replacement in elderly men resulted in increased lean body mass and decreased fat mass,[234] multiple groups have evaluated the efficacy of GH replacement in old men and women. Subsequently, other groups have also shown that GH therapy can improve body composition [235] and cholesterol [236] in GH-deficient older adults. These initial promising findings in GH-deficient adults prompted the promotion of GH replacement by the medical industry in old adults (without clinical GH deficiency) with little regard for the potential negative side effects. GH replacement has been associated with increased risk for adverse events such as soft tissue edema, carpal tunnel syndrome, glucose intolerance, type 2 diabetes, joint pain, and gynecomastia in healthy older adults.[237] Moreover, although GH-replacement may provide minor benefits in body composition to healthy elderly subjects, GH-replacement does not improve strength, VO_2max, bone mineral density, lipid levels, or fasting glucose.[237, 238] It has also been suggested that the improvements in lean body mass following GH administration may be due to elevated water retention, which artificially increases values for lean body mass using certain methods for computing lean body mass. This is corroborated by the fact that although increases in lean body mass are observed after GH treatment, no effect of muscular strength is often observed in healthy older subjects.[215, 217, 238-240] Thus, the efficacy and safety of GH replacement in the healthy aging population remains controversial. Based on the collective literature, the use of GH replacement for non-medical conditions such as aging is now strongly discouraged by the American Association of Clinical Endocrinologists.[241]

Impact of Lifestyle Modifications on Hormone Production in Aging

Aging is associated with a decrease in physical activity levels.[242] In general, this change in physical activity with age appears to be at least partially due to declines in occupational activity which are not offset by increases in leisure activity, especially upon retirement.[243] Unlike hormone replacement therapies, increased physical activity levels and calorically restricted diets in older adults rarely results in negative side effects. Although fear of injury is a commonly reported barrier to exercise in the older population, multiple studies have reported that older adults are not at an increased risk for exercise-related injuries.[244, 245] Frailty is a commonly reported side effect of caloric restriction in the aging population, which can likely be offset by maintaining dietary protein intake.[246] Frailty in older adults can also be drastically reduced by combined aerobic and resistance exercise.[247] The minimal risks that are posed by exercise or CR in the aging population are greatly outweighed by the positive impact that these lifestyle modifications can have on overall health. In particular, the following section describes the influence that regular physical exercise can have on hormone production in the aging population.

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Acute RE has been shown to increase endogenous T production in old men,[248-253] but this effect is worn of by ~2hr post-exercise.[254] It appears that a low intensity or low volume of acute RE does not result in as robust of an effect as high intensity or high volume exercise on T levels.[253, 255-258] Not surprisingly, the beneficial effects of RE (improved muscle mass and strength, elevated muscle protein synthesis, and increased bone mineral density) are similar to the primary reported functions of T on metabolism. Compared to old men, young men have a greater increase in total and free T in response to an acute bout of RE,[248] possibly explaining the larger absolute increases in strength that are observed in young men following RET compared to old men.[259, 260] However, RET, which increases muscle strength, does not result in elevated basal levels of T in middle-aged or old men.[249, 256, 261-263] RET does appear, however, to increase the effect of an acute bout of high intensity exercise on free and total T.[264] Thus, the repeated effect of multiple acute bouts of RE on T level, rather than RET per se, may underlie the beneficial effect of RE on metabolic health in old men. Table 2 summarizes the notable literature that assesses the effects of acute or chronic RE on endogenous T production in old men and women.

Interestingly, when T therapy is combined with RET, there was no additive effect of T therapy on upper or lower body strength.[265] However, RET plus T therapy showed a greater reduction in fat mass compared to RET alone,[265] suggesting T therapy in combination with RET may elicit some additional health benefits, such as body composition, but not functional improvements (muscle strength). Currently, it appears that RET is the most effective and safe approach for older adults to attenuate the deleterious effects of age-associated declines in T on metabolism. T replacement therapy in elderly people should be used with extreme caution, and may only be an acceptable therapy for clinical cases of hypogonadism if prescribed by a physician.

DHEA and DHEA-S are generally found to be increased following exercise. Tremblay et al. observed that acute RE, but not AE, increased DHEA-S in resistance trained 18-55 year-old men.[266] Copeland et al. corroborated this finding in women by showing that acute RE, but not AE, increased DHEA in young and old women.[267] Others have found either elevated[268] or unchanged [269] DHEA or DHEA-S in response to acute sub-maximal exercise in older adults. When RET was performed for 4 months in old men and women, Villareal and Holloszy found that there was no change in endogenous levels of DHEA.[228] Hersey et al. corroborated this finding by showing in 70-79 year-old men and women that 6 months of either AET or RET did not result in elevated plasma DHEA.[270] Though few studies have been conducted, it appears that increases in DHEA are present following an acute bout of exercise in elderly subjects if the intensity and volume of exercise are robust enough to elicit a response. However, like the response of T to exercise training, DHEA is not altered following exercise training in elderly subjects. Table 3 summarizes the notable literature assessing the effects of acute exercise and exercise training on endogenous DHEA production in elderly men and women.

Although DHEA administration alone has been widely shown to have little to no beneficial effect on metabolic health, some groups have assessed the combined effect of DHEA supplementation with exercise training on human health. In 65-78 year-old men and women it was shown that daily DHEA replacement therapy in addition to 4 months of heavy RET

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had a greater effect than placebo + RET on muscle size and strength.[228] Another group found that DHEA supplementation with light AE or yoga exercise in >70 year old women resulted in increased lower body strength compared to the group which did not receive DHEA.[271] However, Igwebuike discovered that when DHEA was administered during combined AET and RET in post-menopausal women that DHEA therapy provided no additional benefits in physical performance, body composition, or insulin sensitivity compared to training without DHEA.[272] These limited results suggest that DHEA in combination with exercise training may have a beneficial effect on some aspects of human health. However, the modest amount of studies in this area limits the interpretations that can be made regarding the influence of DHEA in combination with exercise training. Of note, none of the aforementioned studies provide a mechanistic explanation for the additional benefit that DHEA potentially provides when combined with exercise training. Since the underlying mechanisms regarding any beneficial effect of DHEA in combination with exercise training remain unclear, we currently do not recommend this strategy for improving metabolic health. Rather, exercise alone (without exogenous hormone therapy) currently remains the most robust and safe option for improving metabolic health in aging populations.

Exercise remains an exciting therapeutic tool that may be used to mitigate the aging-associated dysregulation of the GH/IGF-1 axis. It has long been known in young-middle aged subjects that during an acute bout of exercise there is a sharp rise in GH concentrations in the blood.[273-275] GH is also increased in old subjects in response to acute heavy RE, [256, 276, 277] but in the post-exercise recovery period the reversal of GH back to resting values occurs at a quicker rate in old subjects compared to young.[248, 278] The increase in GH during exercise appears to be dependent on exercise intensity.[273] In particular, heavy RE or very high intensity AE will result in the largest GH response.[279] In old men and women, exercise needs to be performed above lactate threshold for a significant increase in GH to occur, but younger subjects can experience increased GH at lower intensities of exercise.[280] Table 4 summarizes the notable studies which assess the acute effect of exercise on GH secretion in old subjects.

AET appears to attenuate the acute effect of exercise on GH secretion,[282] but RET does not change the acute effect of exercise on GH release in young[283] or old[281] subjects. Though the mechanisms for the exercise-mediated increase in GH concentration are not completely understood, it has been hypothesized that nitric oxide, afferent neural stimulation, or blood lactate play significant roles in the elevation of GH post-exercise.[284] The beneficial metabolic effects of exercise may partially be due to elevations of GH concentration, but a causal link between post-exercise GH and metabolism will be difficult to explicitly demonstrate. The combined effect of exercise and GH replacement has provided some insight into the effect of GH on metabolism post-exercise. Yarasheski et al. showed that RET plus GH replacement versus RET without GH replacement had a greater increase in fat free mass and protein synthesis, but not muscle strength in young men[285]. The authors attributed the lack of an additive effect of GH on functional capacity of skeletal muscle to increased non-skeletal muscle lean tissue.[285] This finding in young men resulted in a follow up study by the same group in old men. Very similar results were reported,[286] suggesting a lack of an additional functional benefit of GH therapy when combined with RET. Thus, GH

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replacement does not seem to enhance the exercise benefit on muscle strength and is not recommended as a therapy for aging individuals. Exercise remains the most optimal method for improving metabolic health in older individuals.

Twelve-weeks of CR increases total T in obese men by improving testicular function and reducing conversion of T to β-estradiol by aromatase in the adipose tissue.[89] However, this young population of unhealthy subjects is known to have lower than normal T levels. In another study in young but healthy subjects, CR actually reduced T levels.[287] Additionally, CR significantly reduces T production in healthy young rats in a dose response fashion.[288] However, when rats which have been calorically restricted early in life (reducing T production) are aged, the Leydig cell production of T is significantly greater than in ad libitum-fed controls in older age.[122] Perhaps the reduced T production at young ages and subsequently increased T production with advancing age serves as a protective effect of CR. However, in late-middle aged (~50 year-old) humans who had consistently performed CR for ~7.5 years, T production is significantly reduced compared to control subjects that were not calorically restricted.[289] The conflicting findings make it unclear how/if CR can exert an effect on metabolism by regulating T production. In obese subjects who have lost ~30kg of weight, GH secretion is significantly greater than obese subjects who remain weight stable.[90] However, as is the case with T, CR does not appear to alter GH production in normal weight subjects. Two of the only long-term CR studies in humans (CALERIE and Biosphere 2) both reported negligible effects on other important hormones discussed in this review (DHEA-S, GH, and IGF-1),[290] providing convincing evidence that CR does not influence the production of these hormones in normal weight subjects. To the best of our knowledge, no comprehensive studies have been performed in older healthy subjects that assess the effect of long term CR on anabolic hormone production. It is important to note that because older adults display a significantly lower anabolic response to low dose dietary protein than younger subjects[246] that caloric restriction in the aging population should limit the reduction in protein intake. Interestingly, Levine et al. reported a significant reduction in all-cause mortality in older adults that consumed a high protein diet (≤ 20% kcal protein) compared to older adults consuming a low protein diet (< 10% kcal protein).[291] Others have even suggested that to avoid developing frailty that aging adults who partake in CR should ingest as much as 30-35% of their total caloric intake in protein.[292] However, potential adverse effects of high protein intake in older adults, especially on renal function, will need further investigation.[293] It will be important to determine the long term effect of CR in elderly subjects on anabolic hormone production, especially when the CR includes an optimal dosage of protein. Until the effect of CR is more clearly described in the elderly population, exercise training currently exerts a more convincing impact on hormone production than CR.

Conclusion

The aging process is quite complex, and can affect a variety of hormones which are important for physical performance, body composition, metabolic health, and cognition. A host of metabolic derangements are associated with the decline in endogenous production of T, DHEA, and GH/IGF-1 during aging (Table 1). As a result, extensive research has examined various approaches for combating the detrimental metabolic impact of andropause, adrenopause, and somatopause. Hormone replacement therapy often results in

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either very minor benefit and/or increased risk for adverse events in the healthy aging population. Thus, for aging adults that do not have clinical indications of hormone deficiency based on careful assessment, hormone replacement therapy is not advised. Rather, probably the most effective and modifiable lifestyle factors that result in health benefits during aging are exercise and CR. CR and exercise can aid in preventing excess fat accumulation and maintaining muscle mass, critical factors for preventing age-related frailty and cardio-metabolic risks. As discussed throughout this review, exercise and CR can affect the regulation of multiple hormones that are important for healthy aging. Unlike hormone replacement therapy, exercise or CR rarely result in detectable negative side effects. Additionally, besides the influence that exercise and CR have on endocrine regulation during aging, there are a variety of additional health benefits that these lifestyle modifications can provide. However, the mechanisms responsible for their robust effects on endocrine regulation in older adults are still not completely understood. It will be crucial to further understand how exercise and CR exert such powerful effects on hormonal regulation of metabolism in order to more effectively treat chronic age-related metabolic disease. Because many aging adults are unable to exercise or cannot perform exercise at a high enough intensity to experience significant benefit, the development of drugs or therapies which target the exercise-mediated molecular events involved in hormonal regulation could prove to be quite valuable.

Alphabetical List of Abbreviations

AE	aerobic exercise
AET	aerobic exercise training
BMD	bone mineral density
CR	caloric restriction
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone Sulfate
GH	growth hormone
GHRH	growth hormone-releasing hormone
HIIT	high intensity interval training
IGF-1	insulin-like growth factor 1
RE	resistance exercise
RET	resistance exercise training
SHBG	sex hormone-binding globulin
T	testosterone

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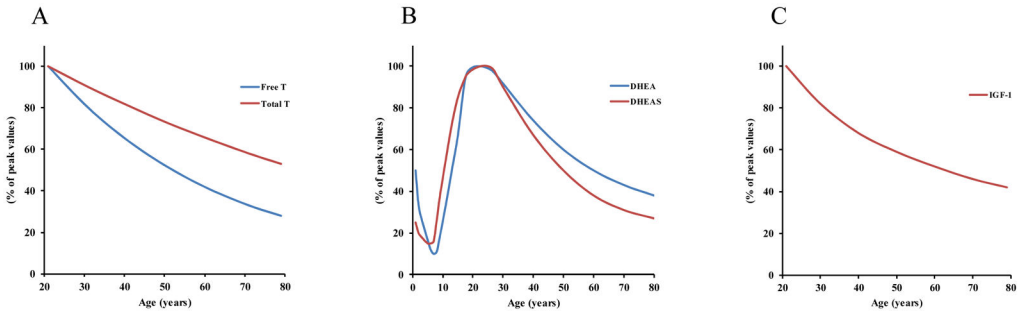

Figure 1: Decline in hormone production with age.

A: There is a gradual and consistent decline in T production with each year of age in men beginning around the 3rd decade. Free T, the most biologically active form of T, declines at nearly twice the rate of total T. **B**: Plasma levels of DHEA and DHEA-S sharply decline at birth until the age of ~6-7. A sharp rise in the levels of DHEA and DHEA-S occurs until approximately the 3rd decade. DHEA and DHEA-S then gradually decline until death in men and women, with a slightly steeper decline in DHEA-S compared to DHEA. **C**: IGF-1 consistently decreases with age beginning around the 3rd decade in men and women. Pulsatile release of GH throughout the day maintains plasma IGF-1 levels through production and secretion from the liver. [a]T = testosterone; DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate; IGF-1 = insulin-like growth factor 1; GH = growth hormone.

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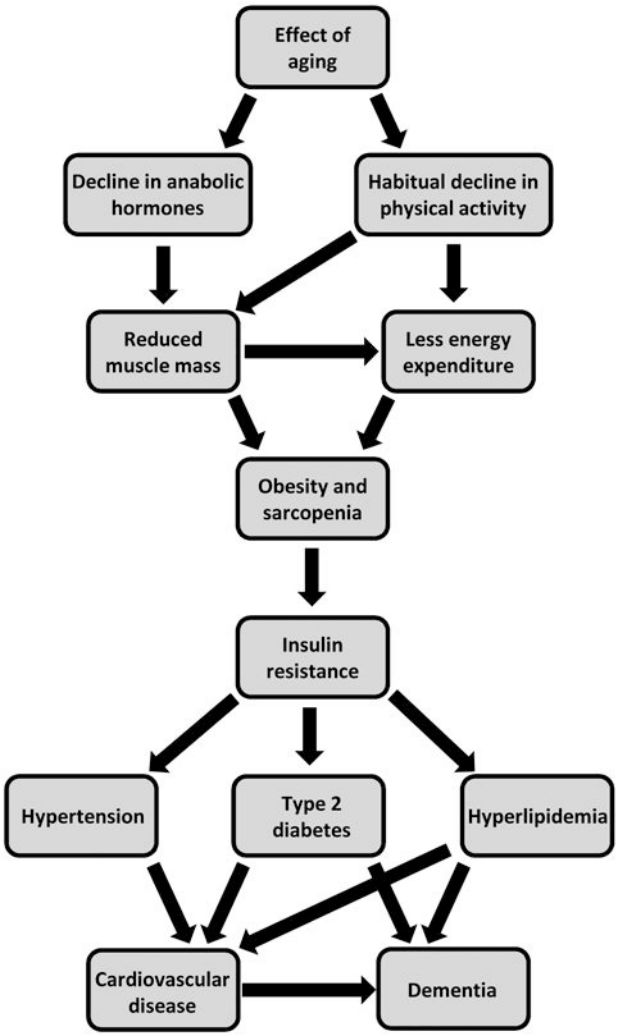

Figure 2: Schematic diagram of the aging-related influence on metabolism.

Aging results in a decline in anabolic hormone production and, as is true for a large sum of the older population, a habitual decline in physical activity. This decrease in physical activity results in lower daily energy expenditure, leading to increased rates of obesity in the older population. Moreover, both hormonal dysregulation and reduced physical activity influence the reduction in muscle mass that occurs with age, also known as sarcopenia. The increased rates of obesity in aging combined with the development of sarcopenia can have devastating consequences on metabolism. After the development of insulin resistance, obesity and sarcopenia can result in an increased risk for type 2 diabetes, hypertension, and hyperlipidemia. These metabolic disturbances are known to lead to the development of cardiovascular disease and dementia. Importantly, positive lifestyle modifications such as regular exercise and healthy diet can combat multiple nodes in this process and are critical for healthy aging and the prevention of metabolic disease.

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Table 1:

Potential age-related metabolic consequences of reduced testosterone (andropause), DHEA (adrenopause), and growth hormone (somatopause) based on both human observational studies and rodent studies. ↑, increased; ↓ decreased.

Potential Age-related Metabolic Consequences of:		
Reduced Testosterone	**Reduced DHEA**	**Reduced Growth Hormone**
• ↑ subcutaneous and visceral fat • ↑ risk for obesity • ↓ insulin sensitivity • ↑ risk for type 2 diabetes • ↑ high blood pressure • ↑ triglycerides • ↑ risk of metabolic syndrome • ↓ muscle mass • ↓ strength • ↓ bone density	• ↑ body fat mass • ↑ waist to hip ratio • ↓ lean body mass • ↓ VO_2 max • ↑ risk of cardiovascular disease • ↑ risk of ischemic heart disease • ↓ bone density	• ↑ risk for obesity • ↑ visceral adipose tissue • ↓ lean body mass • ↓ strength • ↑ risk of metabolic syndrome • ↑ risk of cardiovascular disease • ↓ bone density

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Table 2:

A summary of notable studies that examined the acute and training effect of resistance exercise on endogenous testosterone levels in old men and women.[a] T= testosterone; RE= resistance exercise; RET=resistance exercise training; AE= aerobic exercise; ↔= unchanged; ↑= increased; 1RM= 1-rep maximum; 10RM=10-rep maximum.

Author, Year	Exercise Duration	Exercise details	Gender	Age	Effect of exercise on T
Craig, 1989 [263]	Training (12 wk)	Progressive whole body RE	male	63 ± 1	↔ in resting T following RET.
Hakkinen, 1994 [262]	Training (12 wk)	Progressive whole body RE	male and female	male:64-73 female:66-73	↔ in free or total resting T post-RET in old subjects.
Hakkinen, 1995 [255]	Acute	5 sets of 10 reps (at ~10RM) for 3 exercises (bench press, leg press, sit-ups)	male and female	male:68 ± 3 female:69 ± 3	↔ in T immediately following RET in old subjects.
Nicklas, 1995 [256]	Both Acute and Training (16 wk)	Progressive whole body RE	male	60 ± 4	Resting T ↔ after RET. In both trained and untrained men, T was ↔ after an acute bout of RE.
Hakkinen, 1998 [253]	Acute	Upper body, lower body, or both upper and lower body RE	male	70 ± 4	↑ in total and free T only occurred when lower body exercises were included.
Kraemer, 1998 [248]	Acute	4 sets of 10RM squats	male	62 ± 3.2	T was ↑ immediately and up to 30 min following RE.
Hakkinen, 2000 [249]	Both Acute and Training (24 wk)	Progressive whole body RE	male and female	male:72 ± 3 female:67 ± 3	Trained and untrained men ↑ total and free T after acute RE. Only trained women increase free T after acute RE. Resting T is ↔ by RET.
Hakkinen, 2002 [261]	Training (24 wk)	Progressive whole body RE	male and female	male:65 ± 5 female:64 ± 4	↔ in basal T concentrations in old women or men after RET.
Kostka, 2003 [257]	Acute	low-volume RE: 6-16 reps of leg extensions at 30-70% of 1RM	male and female	male:71 ± 5 female:71 ± 4	↔ in T concentrations in old women or men immediately after acute low-volume RE.
Baker, 2006 [251]	Acute	Whole body: 3 sets, 10 reps at 80% of 1RM for 6 exercises	male	65 ± 1	Total and free T ↑ immediately post-RE, but was returned to baseline by 15 min post-RE.
Smilios, 2007 [252]	Acute	Whole body: 3 sets, 15 reps at 60% 1RM for 6 exercises	male	69 ± 5	T was ↑ immediately post-RE and at 15 min post-RE.
Roberts, 2009 [258]	Acute	Lower body only (squat, leg press, leg extension): 3 sets, 10 reps at 80% 1RM	male	68 ± 1	Free T was ↔ at 5min post-RE.
Ahtiainen, 2011 [250]	Both Acute and Training (21 wk)	Progressive whole body RE	male	60-65	↑ during acute RE in both trained and untrained.
Lovell, 2012 [264]	Training (16 wk)	Progressive lower body	male	70-80	↑ in free and total T in response to acute AE following RET.
Paunksnis, 2018 [254]	Acute	constant intensity: 3 sets, 10 reps, at 75% 1RM variable intensity: 3 sets, 8-12 reps, at 67-80% 1RM	male	65 ± 3	↔ T at 2h or 24h post-exercise. Trend for ↑ T at 2h post-exercise. Did not report T immediately post-exercise.

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Table 3:

A summary of notable studies that examined the acute and training effect of exercise on endogenous DHEA levels in old men and women. [a] DHEA= dehydroepiandrosterone; DHEA-S=Dehydroepiandrosterone sulfate; RE= resistance exercise; RET=resistance exercise training; AE=aerobic exercise; AET=aerobic exercise training; ↔= unchanged; ↑= increased; 1RM=1-rep maximum; 10RM=10-rep maximum; HRmax= maximum heart rate.

Author, Year	Exercise Duration	Exercise details	Gender	Age	Effect of exercise on DHEA
Hersey, 1994 [270]	Training	RET: progressive whole body AET: progressive treadmill walking/ jogging	male and female	70-79	↔ resting DHEA following 6 months of RET or AET.
Copeland, 2002 [267]	Acute	RE: 8 whole body exercises 3 sets, 10 reps at 10RM AE: 40 min cycling at 75% of HRmax	female	mean 62.3	RE, but not AE, ↑ DHEA immediately post-exercise. DHEA values returned to normal by 30 min post-exercise.
Villareal, 2006 [228]	Training	Whole body progressive RET: 2-3 sets, 6-12 reps at 65-85% 1RM for 4 months	male and female	65-78	↔ resting DHEA following 4 months of RET.
Aldred, 2009 [269]	Acute	AE: 50% of maximal treadmill workload for 30 min	male and female	65-75	↔ DHEA or DHEA-S immediately post-exercise.
Heaney, 2013 [268]	Acute	AE: incremental submaximal walk test, terminated at 75% HRmax	male and female	60-77	DHEA was ↑ immediately post-exercise and was ↔ by 1 hr post-exercise.

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Table 4:

A summary of notable studies assessing the acute effect of exercise on growth hormone secretion in old men and women. [a]GH= growth hormone; RE= resistance exercise; AE=aerobic exercise; ↔= unchanged; ↑=increased; 1RM=1-rep maximum; 5RM= 5-rep maximum; 10RM=10-rep maximum; LT= lactate threshold.

Author, Year	Exercise Type	Exercise details	Gender	Age	Effect of exercise on GH
Craig, 1989 [263]	Resistance	8 exercises, 1-3 sets, 8-10 reps	male	63 ± 1	Acute RE ↑ GH in old men immediately and 15min post-exercise.
Pyka, 1992 [276]	Resistance	13 exercises, 3 sets, 8 reps at 70% of 1RM	male and female	72 ± 1	Acute RE resulted in a small but significant ↑ in GH in old men and women.
Pyka, 1994 [281]	Resistance	12 exercises, 3 sets, 8 reps at 85% of 1RM	male and female	70 ± 1	Acute RE ↑ GH in old men and women. The same effect was observed regardless of training status.
Nicklas, 1995 [256]	Resistance	14 exercises, 1-2 sets, starting at ~5RM with decreasing weight until 15 reps achieved	male	60 ± 4	Acute RE ↑ GH in old men. The same effect was observed regardless of training status.
Kraemer, 1998 [248]	Resistance	Squats, 4 sets, 10 reps at 70% of 1RM	male	62 ± 3	Acute RE ↑ GH in old men immediately- and 5min-post exercise. GH returned to sedentary values by 15min post-exercise.
Kraemer, 1999 [278]	Resistance	Squats, 4sets, 10reps at ~10RM	male	62 ± 3	Acute RE ↔ GH in old men immediately-post exercise. Data appear to show trend for ↑ GH, but not statistically significant.
Weltman, 2006 [280]	Aerobic	Treadmill run at 75% of the difference between LT and VO_2max	male and female	male:64 ± 2 female:66 ± 4	Acute AE approached a significant ↑ in GH for old men (P=0.07) and women (P=0.09).
Manini, 2012 [277]	Resistance	Knee extension, 4 sets at 80% of 1RM until volitional fatigue	male	67 ± 5	Acute RE ↑ GH in old men.