

# Endocrine changes with aging

**Keywords:** biomarkers, endocrine, aging, chromosomes, gastrointestinal, immune system, hepatocytes, growth hormone, dna, rna, adrenocorticotrophic hormone

**Abbreviations:** DNA, deoxyribonucleic acid; GH, growth hormone; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor-1; GHRP, growth hormone-releasing peptide; AVP, arginine vasopressin; ACTH, adrenocorticotrophic hormone; SCN, suprachiasmatic nucleus; AD, alzheimer's disease; ANP, atrial natriuretic peptide; HPG axis, hypothalamus-pituitary-gonadal axis; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; BMD, bone mineral density; DEXA, dual-energy x-ray absorptiometry; PTH, parathyroid hormone; GLUT4, glucose transporter; OGTT, oral glucose tolerance test; BMI, body mass index; TNF-alpha, tumor necrosis factor-alpha; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor-1

## Introduction

Aging is a biological process that affects most cells, systems, organisms, and species. There are many predictable, progressive changes that occur with aging, and these age-related changes may cause decline in homeostatic reserves. In an older adult, when there is increased stress or demand on the body, this physiologic change can impact the individual's ability to adequately respond or heal.

Over the last century, average life expectancy has dramatically increased. This can be attributed to medical advancements, including improvements in public health standards and living conditions as well as antibiotics and vaccination use, leading to an increase in youth survival and a shift in causes of death from infection to chronic conditions and non-communicable disease.<sup>1</sup> Old age, conventionally accepted as 65 years and older, is generally characterized by physical limitations and multiple chronic diseases, leading to a greater demand on the healthcare system. Although some older adults are "successfully aging," living longer does not necessarily equate with better health. Within the older population, there is large variation secondary to individual differences, such as genetics and lifestyle. By understanding what endocrine changes our bodies undergo during the normal aging process and their consequences, we may be able to better serve the growing geriatric population and potentially uncover routes to successful aging. The purpose of this review is to describe endocrine function and how it changes with aging.

## Physiology of aging

Aging or senescence, as defined by evolutionary biologists, is "an age-dependent or age-progressive decline in intrinsic physiological function, leading to an increase in age-specific mortality rate (i.e. a decrease in survival rate) and a decrease in age-specific reproductive rate".<sup>2</sup> A general rule is that after the third decade of life, there is a one percent decrease in organ function per year.<sup>3</sup> If there is a significant decline in function, this is more likely due to a pathologic process, rather than a physiologic one.

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An important distinction to be made is chronological versus biological age. Chronological age is determined by the passage of time since birth, or the actual age of an individual. It is quantitatively measured by months or years. Biological age, on the other hand, is determined by the physiological state of an animal or tissue.<sup>3</sup> It can be measured by the rate of maturation the biologic system has undergone. Biomarkers, such as shortened telomere length, cell turnover, DNA damage, and apoptosis, may indicate higher biological age. Chronological and biological age do not necessarily match; for example, in one study, many individuals aged 92 to 100 were in good health with intact cognition and without physical restriction.<sup>3,4</sup> This successful, or healthy, aging depends on the interaction of many factors, namely genetics, environment, illness prevention, and healthy lifestyle.<sup>3</sup>

Numerous genetic and non-genetic factors contribute to aging. Several theories attempt to explain aging, but no one theory has been able to provide a complete explanation. Theories of aging fall into three general categories,

- Evolutionary.
- Cellular senescence.
- Regulation of specific genes.<sup>3,5,6</sup>

In the evolutionary theory, organisms are maintained for reproductive success, and organisms can evolve to have a longer life span if it is beneficial to fitness.<sup>6,7</sup> Molecular and cellular theories are further discussed below.

## Theories of aging

**Cellular senescence/telomere theory:** Cellular senescence is the finite replicative life span of normal human cells.<sup>7</sup> Cells undergo a certain number of divisions and become terminally arrested in the cell cycle with altered physiology. Senescence may occur due to replication or it may be stress-induced by other causes, such as deoxyribonucleic acid (DNA) damage by free radicals and mutations in signaling pathways.<sup>6</sup>

Replicative senescence ultimately results from the cumulative loss of telomeres (conserved repetitive nucleotide sequence located at the end of chromosomes, thus protecting DNA).<sup>6,8</sup> During each cell division, a small amount of DNA is lost at each chromosome end, shortening telomeres, and eventually resulting in replicative senescence; however, activation of telomerase enzyme regenerates telomeres.<sup>8</sup> Adult cells proliferate via three primary routes, continuous replication (i.e. in epidermal, gastrointestinal, and hematopoietic cells), replication in response to stress or injury (i.e. in hepatocytes), and non-replication (i.e. in neurons and cardiac myocytes).<sup>9</sup> Using fibroblasts, which undergo finite replication, a correlation between replicative potential and age of the fibroblast donor has been found *in vitro*; the older the donor, the more limited the number of cell divisions are.<sup>9</sup> Over time, replication time increases, and cells eventually stop dividing. In non-replicating cells, cell loss may lead to permanently deficient tissues.<sup>9</sup>

The tumor suppressor protein p53 regulates cellular checkpoints by activating a cellular cycle response (cell cycle arrest, apoptosis, or senescence) when there is DNA damage or telomere loss, and depending on the type of cell and stress the cell has undergone.<sup>6</sup> When p53 signaling is altered, seen in mice and humans, there is a dramatic increase in cancers. This mutation is responsible for approximately 80% of human cancers [6].

In stress-induced senescence, as damage accumulates, one theory poses that DNA undergo changes in response to these extrinsic stressors and intrinsic processes.<sup>6,9</sup> The double-stranded composition of DNA and their repair enzymes contribute to stability; but, if spontaneous somatic mutagenesis occurs or repair enzymes are dysfunctional, aging may occur [9]. In another theory termed the “error-catastrophe theory,” DNA, RNA, and protein synthesis processes may incur errors, the accumulation of which leads to “error catastrophe”.<sup>9</sup> Finally, the accumulation of byproducts of oxidative metabolism, such as superoxide and other free radicals, may react with DNA, RNA, protein, and lipids, leading to cellular damage, and eventually the cessation of organ function.<sup>3,5,10,11</sup> The Mitochondrial Free Radical Theory of Aging is one of the most well-known theories, but it remains controversial.<sup>3</sup> It has been noted that various scavenging enzymes, such as superoxide dismutase, as well as vitamins C and E can protect the cell from this oxidative damage.<sup>9</sup> However, there is no loss of scavenging enzymes with age, and vitamins C and E have not been shown to have any association with longevity in animal studies.<sup>3,11</sup>

**Gene regulation theory:** An alternative theory is that of gene regulation.<sup>9</sup> It is believed that genes are pre-programmed to control cell proliferation and death.<sup>3,6</sup> While many genes show changes in expression with aging, it is believed that some are selected to promote longevity. One study found that insulin-like signaling pathway affects the life span of worms, flies, and mice.<sup>6</sup> When there is a reduction in insulin-like signaling, a conserved transcription factor is activated, and lifespan was extended. This study showed that gene expression could be used to regulate lifespan. Another recent study is focusing on iden-

tifying a genetic component, such as a gene or multiple genes located on a locus of chromosome 4, which may promote human longevity.<sup>6</sup> Sirtuins, a family of anti-aging genes, may also control pathways that increase lifespan and influence aging.<sup>3</sup> In the future, these results could be used to develop treatments to slow aging in humans.

Other theories include the neuro-endocrine theory and immunological theory. In the neuro-endocrine theory, it is believed that hormones regulate the body’s homeostasis. In the immunological theory, the immune system weakens over time thus allowing susceptibility to infectious disease, aging, and death.<sup>5,10</sup>

While one theory alone cannot explain the complex process of aging, these theories combined demonstrate that many factors contribute to aging. As aging progresses, clinical death must also be separated from physiological death. While clinical death depends on the absence of vital signs, physiological death is determined by other factors, such as a gradual decrease in power and energy in the absence of significant illness.

## Endocrine changes

Various endocrine changes trigger processes associated with aging. Specifically, there are anatomic changes, which can occur in endocrine glands or tissue due to cell apoptosis, autoimmune destruction, or neoplastic transformation. In addition, age-related changes affecting hormone secretion can be attributed to alterations in circadian rhythm, frequency of hormonal pulses, or glandular sensitivity to hormone.<sup>10</sup> Over time, aging and pathologic processes alter and potentially deplete endocrine system storages that were previously preserved during growth to adulthood.<sup>12</sup> In women, the most dramatic effect occurs during menopause, which occurs at an average age of 51 years. Constant, low levels of estradiol replace the cycling estradiol production prevalent during reproductive years.<sup>10,13</sup> Exhaustion of ovarian follicles and age-related changes in the brain have been studied as the leading factors leading to menopause.<sup>13</sup> To stave off the various physiologic effects associated with aging, hormone replacement therapy was previously utilized; however, its adverse effects, including increased risk of various cancers and coronary artery disease, may outweigh its beneficial uses.<sup>14</sup> The male equivalent of menopause, andropause, maintains a more gradual decline in serum total and free testosterone levels.<sup>10,13</sup> This is a result of decreased number and secretion of Leydig cells in addition to decreased gonadotropin secretion with age. To target the somatic symptoms associated with age-related declines in hormone levels, various dietary supplements containing hormones, including dehydroepiandrosterone (DHEA), growth hormone (GH), and testosterone, are being prescribed off-label.<sup>14</sup> While these supplements may be portrayed as the “fountain of youth” in the media, no research has been completed that shows a specific benefit of longevity or decreased frailty with hormone therapy. As efforts continue to focus on understanding the deficits to potentially slow the effects of aging, it is important to first understand the normal physiologic human endocrine changes that occur with age.

## Hypothalamic-pituitary function

The relationship between the hypothalamus and pituitary gland within the central nervous system serves to regulate the release of hormones via stimulatory signals downstream and negative feedback upstream. With respect to the hypothalamic-pituitary function, there is some evidence to support two explanations for the age-related shifts in various endocrine hormones. One explanation is that there are small

age-related changes in the diurnal timing and amplitude of hormones released from the hypothalamus and pituitary, including corticotropin-releasing hormone (CRH), growth hormone (GH), and thyrotropin-releasing hormone (TRH).<sup>15</sup> The other explanation is that their hormone release stays about the same; however, the responsiveness of the target organs or the hypothalamus itself to negative feedback may change with aging.<sup>16-18</sup> It has also been shown that the pituitary gland becomes gradually smaller as we age, suggesting that its sensitivity or production capabilities may diminish.<sup>16</sup>

Some studies show that growth hormone-releasing hormone (GHRH) secretion is decreased with age as is its pituitary response, resulting in an overall decrease in GH release and serum concentrations.<sup>15-16</sup> Insulin-like growth factor-1 (IGF-1) is the primary mediator of the effects of GH, and its production by the liver is signaled by GH. Therefore, the age-related decrease in GH results in a decrease in IGF-1.<sup>15-17</sup> While there is no change in the frequency of pulsatile GH secretion with age, the pulses are smaller in amplitude resulting in an overall decrease in pulsatile GH secretion and IGF-1 production.<sup>17</sup> GH pulsatile secretion is mediated by the hypothalamus via somatostatin, GHRH, and possibly growth hormone-releasing peptide (GHRP)/ghrelin, the latter two of which are under the negative feedback control of GH, IGF-1, and free fatty acids, and are stimulated by gastric ghrelin. It has been suggested that L-arginine, a somatostatin antagonist, along with both GHRH and GHRP/ghrelin are able to normalize GH secretion in the acute setting.<sup>17</sup> This supports the idea that there may be reduced hypothalamic signaling to the anterior pituitary in aging.<sup>17</sup> Additionally, older adults secrete less GH during fasting, exercise or sleep and in response to nearly all its stimulatory factors than young adults.<sup>17</sup> However, its secretion remains the same in response to insulin-induced hypoglycemia in both the elderly and young.<sup>17</sup>

Two recent studies report that these decreased levels of GH and IGF-1 in mice are generally beneficial in aging. Decreased GH and IGF-1 are associated with several life-prolonging factors, including slower aging, decreased risk of frailty, decreased age-related disease and functional decline, and overall extended longevity.<sup>19,20</sup> Similar conclusions were made by a study of GH-deficient and GH-resistant mice that were found to live longer. These mice showed slowed aging, intact physical and cognitive functions, and resistance to stress and age-related diseases. Mechanisms or factors which contribute to such longevity include increased insulin sensitivity and reduced insulin levels, reduced adipose tissue, central nervous system inflammation, and increased Adiponectin.<sup>21,22</sup> However, in older adults, exogenous GH administration has been shown to reverse some of the decline in lean body mass and bone density.<sup>15</sup> Especially in adult growth hormone deficiency, there are measurable benefits from GH replacement therapy, including decreased mortality, fewer cardiovascular events, and less incidence of fractures.<sup>20,23</sup>

Hormonal release from the pituitary gland has downstream effects on target organs such as the adrenal glands, thyroid gland, and gonads. The stimulatory effect of these target organs is, in turn, regulated via negative feedback on the hypothalamus and pituitary. It has been suggested that the hypothalamus and pituitary gland may have impaired responsiveness to steroid feedback in older adults.<sup>18</sup> Cortisol stimulates both glucocorticoid and mineralocorticoid receptors. Downstream, the activation of these receptors mediates the effects of cortisol, including negative feedback onto CRH and arginine vasopressin (AVP) neurons of the hypothalamus as well

as onto pituitary adrenocorticotrophic hormone (ACTH) secretion.<sup>17</sup> The effects of age on the hypothalamic-pituitary-adrenal axis are influenced by obesity, sex, and the type of stress activating the system. Intra-abdominal adipose tissue mass increases ACTH and cortisol secretion.<sup>18</sup> Older adults seem to be more sensitive to stimulators of ACTH and cortisol such as cholinergic agonists, CRH and vasopressin injection, and hypertonic saline infusion.<sup>17</sup> Feedback disinhibition using a mineralocorticoid receptor antagonist also increases ACTH secretion in older adults more so than in the younger population. Negative feedback by glucocorticoid and mineralocorticoid receptor agonists seems to be less effective in older adults when compared to the young.<sup>17</sup> The diurnal release of ACTH and cortisol appears to have decreased amplitude, and the timing is such that the peak occurs earlier in the day by approximately two hours in older adults. In aging rats, the reduced responsiveness to negative feedback was seemingly due to reduced glucocorticoid receptor and mineralocorticoid receptor expression in the brain.<sup>17</sup> Similar findings were reported in more recent work, stating that with aging there is increased ACTH and cortisol; decreased glucocorticoid negative feedback at the level of the paraventricular nucleus of the hypothalamus, hippocampus, and prefrontal cortex; and decreased amplitude of diurnal cortisol release patterns. Perhaps the increase in cortisol secretion is secondary to peripheral conversion from cortisone.<sup>24</sup>

The hormone prolactin is secreted by the anterior pituitary via a combination of pulsatile as well as continuous manner. Prolactin helps initiate secretion of milk by mammary glands.<sup>25</sup> With increasing age, estrogen and progesterone gradually decline, thus affecting the glandular and ductal components of the breast; the ducts and lobules become atrophic, which, in turn, causes the breasts to be filled with stromal tissue and adipose.<sup>26</sup> At the level of the hypothalamus, prolactin is stimulated by TRH and inhibited by dopamine. The few studies conducted within the last five years report a general decrease in prolactin levels in older adults, with a greater decrease in women than in men.<sup>17</sup> Typically, prolactin levels are higher at night than during the day. However, as we age, the nighttime prolactin secretion declines. This decrease in prolactin can be counter-balanced in overweight individuals, as adipose tissue and estrogen enhance the pulsatile secretion of prolactin in older adults.<sup>17,27</sup> The decline in prolactin secretion may be due to decreases in TRH synthesis, expression, and activity which have been found in aging individuals. Specifically, however, these deficits in TRH have been implicated in age-related neurodegenerative diseases such as Alzheimer's and Parkinson's.<sup>28</sup> A different approach to the age-related changes in prolactin levels involves its effect on T-cell development in health and disease. T-cell differentiation within the thymus is vital to the body's immunological defenses against pathogens and disease. The thymus progressively atrophies with age, leading to a decline in such cell-mediated immunity and one's overall ability to fend off infection or disease. New research suggests that hormones such as prolactin and GH can bolster thymocyte proliferation and migration, in an effort to restore the thymus and improve T-cell defenses.<sup>29</sup>

Oxytocin is one of the two hormones secreted by the posterior pituitary. Oxytocin is most commonly known for its stimulatory effects on milk ejection in lactating mothers, uterine contraction during labor, and promoting bonding between individuals.<sup>30-33</sup> In recent decades, oxytocin has been shown to play a role in various other physiological mechanisms including cardiovascular control, fluid balance, and skeletal muscle regeneration.<sup>30,32</sup> Regarding its role in aiding muscle tissue regeneration, it seems that myoblasts,

undifferentiated cells that are capable of forming muscle cells, express oxytocin receptors.<sup>30</sup> These receptors are a type of G-protein-coupled receptor which is stimulated by binding of oxytocin to activate protein kinase C, which subsequently releases intracellular calcium to promote differentiation and the fusion of the myoblasts.<sup>30</sup> This study reported an age-related decline in both the plasma levels of oxytocin and in the levels of oxytocin receptors within myoblasts, suggesting that oxytocin is important to the maintenance and repair of muscle tissue. Researchers administered oxytocin to old mice and found that it restored muscle regeneration in these mice by improving muscle stem cell function. These researchers also administered an oxytocin-selective antagonist to young mice and found that it altered their muscle regeneration capability. Additionally, oxytocin-deficient mice showed signs of premature muscle tissue loss.<sup>30</sup> A related study took mesenchymal stem cells, cultured them with oxytocin for one versus seven days, and looked at their therapeutic effect on an infarcted heart. Those stem cells that were incubated with oxytocin for seven days demonstrated less cardiac fibrosis, less macrophage infiltration, and a greater ejection fraction than those incubated for one day.<sup>34</sup> Thus, there are implications for the role of oxytocin in preventing osteoporosis and in enhancing myocardium repair following an ischemic injury.<sup>30,34</sup> As oxytocin decreases with age, women are also more prone to depression.<sup>35</sup>

### Vasopressin and water balance

Vasopressin is released by the posterior pituitary. The previously discussed concept of decreased target organ responsiveness with age is relevant here as well. Release of the hormone does not seem to change, but the kidneys become less responsive to vasopressin in older adults. This results in a decrease in the thirst response, making older adults more vulnerable to dehydration. While the etiology is unknown, older adults are also vulnerable to hyponatremia.<sup>15</sup> In general, sodium and water imbalances occur more commonly in the elderly.<sup>36</sup> This is thought to be due to age-related decreases in efficient homeostatic adjustments to high and low fluid or salt intake. There is evidence of age-related deficits in the renin-angiotensin-aldosterone system, plasma volume, thirst response, baroreceptor reflexes, expression of the AVP receptor and aquaporin-2 receptor, and hypothalamic osmoregulation.<sup>17,36,37</sup> There is also evidence that AVP is secreted in physiologic disproportion with experimentally imposed hypertonicity, water deprivation, ethanol exposure, and volume contraction. Therefore, the risks of both high and low sodium concentrations are increased in older adults, especially in circumstances of extreme physiologic stress and illness such as anesthesia, acute coronary syndrome, diarrhea, burn injuries, hematologic losses, and various others.<sup>17</sup> Thus, older adults are likely more susceptible to the consequences of these situations, without an appropriate response mechanism.

### Pineal function

The pineal gland synthesizes melatonin under control of the suprachiasmatic nucleus (SCN), which regulates the physiological circadian rhythm.<sup>38,39</sup> Melatonin maintains the body's circadian rhythm as well as serves as an antioxidant, immune system enhancer, and neuroprotector as we age.<sup>39</sup> When environmental light cues are received by the retina, light intensity information is transmitted to the SCN, which signals the pineal gland to rhythmically secrete melatonin. Light suppresses the production of melatonin, while darkness promotes it. Extensive research has shown that there is a decrease of melatonin production with age, especially at night, but the exact age at which decline in melatonin production begins and why this change occurs has not been determined.<sup>39</sup>

Over time, like most tissues, the pineal gland can start developing calcifications. Histologically, one study found that mineralization and fibrosis of the pineal gland were common in older rats, whereas it was a rare occurrence in young ones.<sup>38</sup> Some studies have hypothesized that the anatomical change may contribute to sleep-wake cycle disturbances in the elderly and therefore a decrease in melatonin production.<sup>39</sup> However, other studies found that calcifications do not directly affect the metabolism of melatonin; instead, the noradrenergic innervation of the pineal gland from the SCN may be what is more affected with aging.<sup>39</sup>

Because the endogenous circadian rhythm is being affected with age, some have theorized that the SCN may be the principal structure being affected. Specifically, one of the most prevalent peptides in the SCN is vasopressin, whose levels demonstrated a diurnal rhythm with peak values in the early morning and troughs at night, notably seen in youths.<sup>39,40</sup> However, in older individuals, there are decreased vasopressin-expressing neurons, and this diurnal cycle is progressively disrupted, evidenced by reduced amplitudes of circadian rhythms.<sup>40</sup> These findings along with experimental animal studies with partial lesions of the SCN suggests that the amount of deterioration of the SCN has direct consequences on rest and activity cycles.<sup>40</sup>

Sleep-wake cycle disturbances are prevalent in the aging population, and another potential cause for this is dysfunction of the retina-SCN-pineal axis.<sup>39</sup> In particular, the pineal gland's production of melatonin is significantly lower in elderly patients suffering from insomnia in comparison to those who do not. These changes are even more visible in patients with Alzheimer's disease (AD).<sup>39</sup> One theory behind this is that the elderly are less exposed to light than their younger counterparts.<sup>39</sup> Studies have shown that by providing supplemental melatonin and supplemental light therapy to aging individuals and patients in the early stages of AD, circadian rhythms may be restored along with a reduction in time it takes to fall asleep, an increase in hours slept and daytime alertness, and general cognitive improvements in AD.<sup>39</sup>

### Adrenocortical function

The adrenal cortex comprises of three functional zones on the outer part of the adrenal gland. The outermost tissue of the cortex is the zona glomerulosa, which releases mineralocorticoids such as aldosterone to regulate mineral balance and blood volume. The middle aspect of the adrenal cortex is the zona fasciculata, which releases glucocorticoids such as cortisol to regulate glucose, protein, and fat metabolism. Finally, the innermost tissue of the adrenal cortex is the zona reticularis, which secretes androgens including DHEA. DHEA is later converted to the hormones testosterone and estrogen that eventually act on the gonads.<sup>41</sup>

There are subtle changes in ACTH and cortisol as aging occurs. The average 24-hour serum cortisol levels are increased by 20 to 50 percent from the 2<sup>nd</sup> to 8<sup>th</sup> decades of life in older men and women.<sup>42</sup> Glucocorticoid excess can lead to memory and cognitive impairment via attrition and degenerative changes in the hippocampus. Since the hippocampus normally inhibits glucocorticoid secretion, degenerative changes impede the hippocampus's ability to halt cortisol secretion. This subsequently contributes to the higher serum cortisol levels seen in the elderly because the hippocampus cannot interrupt cortisol production.<sup>42</sup> Glucocorticoid excess can also result in visceral obesity, reduced lean muscle mass, hypertension, diabetes, osteopenia, sleep disturbances and an overall reduced quality of life.<sup>43</sup> It is worth noting that though cortisol levels were higher in older individuals, the circadian rhythm pattern of cortisol levels in the body was

relatively preserved.<sup>42</sup> Therefore, serum cortisol level in the elderly is still highest in the early morning and decreases throughout the day with the lowest levels in the first half of the night. This is similar to young adults. In terms of circadian rhythm, the cortisol nadir is three to four folds higher in both men and women older than 70 years of age when compared to young adults.<sup>42</sup> Thus there was no difference between elderly men and elderly women when observing nadir levels. However, from early adulthood to old age, women had an increase in early morning cortisol levels whereas this change was not seen in men, exhibiting a difference between the two sexes as they age. Between the second and eighth decades of life, the rise of the circadian rhythm was advanced by roughly three hours in both men and women even though the timing of the acrophase remained constant throughout aging. The quiescent period of cortisol concentrations in the body had a later onset and earlier offset in older individuals. These two findings can help explain the sleep cycle disturbances often seen in older individuals, such as fragmented sleep. During aging, nocturnal cortisol levels are higher, and there is a delayed onset of the quiescent period. This loss of resiliency is consistent with the hypothesis of “wear and tear” of lifelong exposure to stress and glucocorticoids and is likely to reflect neuronal loss in the hippocampal area.<sup>42</sup> For example, the serum cortisol responses to stress are longer in older individuals as they cannot recover from a challenge nearly as quickly as young adults.<sup>44</sup>

Serum aldosterone concentrations may decrease by as much as 50 percent by 70 years of age.<sup>45</sup> It is not due to increased salt intake as this aspect is normal or just below normal as a person ages. It was initially suggested that decreased secretion of aldosterone could be secondary to blunting of sodium excretion because of the reduced renal blood flow. However, in congestive heart failure patients where there is often reduced renal blood flow, the serum aldosterone concentration actually rises.<sup>45</sup> Another theory is reduced metabolic clearance rate of aldosterone, which is almost completely metabolized in the hepatocytes, with only a small portion going through extra-splanchnic metabolism. There is a strong correlation between the metabolic clearance rate and secretion of aldosterone. A decreased clearance rate inhibits secretion in a feedback fashion, though the secretion decreases disproportionately more. There is decreased hepatic blood flow in the elderly, and therefore, a decreased metabolic clearance rate of aldosterone.<sup>45</sup> This subsequently leads to a disproportionately reduced secretion of aldosterone. The strongest evidence explaining decreased serum concentration of aldosterone in the elderly may be that it is secondary to reduced plasma rennin.<sup>46</sup> Renin is an enzyme that plays a role in the renin-angiotensin-aldosterone system, and therefore, reduced renin eventually leads to hypoaldosteronism, especially in patients who already have renal failure. Finally, atrial natriuretic peptide (ANP) levels increase with advancing age.<sup>47,48</sup> This leads to decreased release of aldosterone from the adrenal cortex.

DHEA is the precursor to the active hormones, androgens and estrogens. The secretion and serum concentration of DHEA undergoes a significant decline starting after the third decade of life. In fact, the concentrations of DHEA in individuals 70-80 years of age are approximately 20 percent of those in persons 20-30 years of age.<sup>49-51</sup> Elderly individuals were administered DHEA up to levels seen in younger persons to determine the clinical importance of reduced DHEA levels. After two years of administration of DHEA, there was no significant improvement in body composition, oxygen consumption, muscle strength, or insulin sensitivity.<sup>49-53</sup> However, higher endogenous DHEA levels have been associated with better health. Lower levels are often seen in debilitated versus healthier older individuals.<sup>52</sup> Therefore, waning serum DHEA concentrations may be

a marker for aging, but there is not yet enough information to deduce a clinical significance of that decrease. Some research states that DHEA can help improve cognition, improve bone density, improve skin status, reduce fat, and increase muscle.<sup>50</sup> However, there is a greater amount of evidence stating that this is not necessarily true. In addition to DHEA, the serum concentrations of testosterone decrease in men as they age, and the concentration of estrogen decreases significantly in women post-menopause.<sup>51,53</sup> The mechanism regarding decreased DHEA is still unknown. A decrease in the size of the zona reticularis has been previously suggested.<sup>51</sup> Additional studies are required to determine the selective reduction in mass of zona reticularis and to confirm that this is observed in both males and females.<sup>52</sup>

### Adrenomedullary function

The adrenal medulla is the inner part of the adrenal gland. It is not essential to life, though it helps a person cope with physical and emotional stress by releasing hormones after the sympathetic nervous system is stimulated. The two main hormones released are epinephrine and norepinephrine. Epinephrine increases the heart rate and contractility of the heart, resulting in increased blood flow to the brain and muscles. It also increases the blood glucose level by aiding the conversion of glycogen to glucose. Norepinephrine secretion results in vasoconstriction, thereby increasing blood pressure.<sup>41</sup>

The increase in norepinephrine seen in the elderly is secondary to both an increase in plasma concentration and a decrease in clearance.<sup>54</sup> Studies have thus far been inconclusive on the age-related changes in epinephrine.<sup>54</sup> Most previous studies have shown that plasma epinephrine concentration does not change significantly, or might just decrease slightly, as a person ages.<sup>54</sup> Eight younger subjects aged 19-26 years and eight older subjects aged 64-74 years were administered norepinephrine or epinephrine until they reached a steady state concentration. The older individuals had higher plasma norepinephrine levels when compared to the younger subjects.<sup>54</sup> However, the concentration of plasma epinephrine was nearly identical between the two groups.<sup>54</sup> Additionally, there was no significant difference in the plasma clearance between norepinephrine and epinephrine in the young adults. However, the clearance of plasma norepinephrine was lower than epinephrine in older subjects.<sup>54</sup>

Another study measured norepinephrine and epinephrine release during rest and laboratory stressors. Laboratory stressors were used because blunted adrenal medullary sensitivity could result in some impairment of cardiovascular and metabolic responses to stress in the elderly.<sup>55</sup> In the younger subjects aged 20-30 years, epinephrine levels doubled or tripled during mental stress, isometric exercise, or dynamic exercise.<sup>55</sup> Levels were comparatively reduced in the elderly subjects aged 60-75 years by 33-44% during stress.<sup>55</sup> Even at rest, epinephrine secretion was lower in the older subjects.<sup>55</sup> The same study looked at the effect that epinephrine levels had on norepinephrine. After uptake from the plasma, epinephrine is sometimes released from the sympathetic nerves as a co-transmitter that in turn stimulates the release of norepinephrine. Epinephrine release from the heart was measured to determine if it stimulates norepinephrine release because it had been previously studied that there is an increased release of cardiac norepinephrine when a person ages.<sup>55</sup> Epinephrine was released from the heart at rest in older men only; this was interesting because there is actually a decrease in epinephrine release from the adrenal medulla as a person ages.<sup>55</sup> This increased cardiac epinephrine release at rest was not seen in sympathetic excitation during laboratory stress, suggesting epinephrine could arise from somewhere besides the sympathetic nerves.<sup>55</sup> It is possible that it could arise from extra-neuronal synthesis in the heart.<sup>55</sup>

The higher levels of norepinephrine in the elderly subjects are possibly secondary to an increase in sympathetic nervous system activity, not the adrenal medulla. A study looked at the relationship between sleep and plasma norepinephrine concentration in young and aged men. In both subject groups, the disruption of sleep/wake pattern had little consequence on the 24-hour plasma norepinephrine levels, suggesting that the elevated levels may not be due to altered sleep/wakefulness alone.<sup>56</sup> However, there was a strong correlation between wakefulness and higher norepinephrine concentrations while in bed, indicating that it is the heightened sympathetic nervous system activity that may lead to fragmented sleep in the elderly.<sup>56</sup>

Aging has been associated with hindered arterial alpha-adrenergic receptor function.<sup>57</sup> Therefore, it is possible that the increase in norepinephrine levels seen in the elderly might be due to compensation for the age-related decrease in responsiveness of some tissues to norepinephrine.<sup>57</sup> Forearm blood flow was monitored during brachial artery administration of alpha-adrenergic agonist norepinephrine and noradrenergic agonist, angiotensin II, in younger and older subjects. Greater plasma norepinephrine levels were seen in the older subjects but there was less norepinephrine-mediated reduction in forearm blood flow.<sup>57</sup> There was no difference in angiotensin II mediated reduction in forearm blood flow when comparing the younger and older subjects.<sup>57</sup> This indicates that arterial alpha-adrenergic receptor responsiveness to norepinephrine is decreased in the elderly. Therefore, there is a compensated increase in norepinephrine levels to have the same effect.

### Pituitary-thyroid function

Throughout life, thyroid function is imperative for normal development and retaining cognition in human aging. By studying cretinism, caused by deficiencies in iodine and thyroid, the link between thyroid hormones and cognition was observed.<sup>58</sup> At any age, low thyroid function is also associated with cognitive decline, since hypothyroidism is associated with brain hypometabolism. In the aging population, this low uptake of glucose has been associated with Alzheimer's disease and may even present decades prior to any clinical symptoms of neurodegeneration are observed.<sup>58</sup> It is therefore possible that cognitive decline may not solely be a byproduct of the aging process but potentially due to physiological effects in thyroid function. With increasing age as well as body weight in more sedentary aging adults, thyroid volume increases slightly.<sup>59</sup> Other factors, such as cigarette smoking, chronic kidney disease, acute hepatic disease, and seasonal changes, can also increase thyroid volume.<sup>59</sup> Interestingly, however, there are no age-related changes of serum free and total T4 levels.<sup>60</sup> In aging individuals, the nocturnal pulses of TSH secretion decrease in comparison to their younger counterparts, likely accounting for decreased T4 renal clearance with age.<sup>60,61</sup> Due to this decrease in renal clearance, T4 levels may increase slightly; but, since aging decreases TSH secretion, this effect is counterbalanced, leading to unchanged T4 levels.<sup>15,58,60,62</sup> Generally, T3 levels also remain stable with aging, but, in a small subset of elderly patients, serum T3 levels were found to be slightly lower than in young, healthy individuals.<sup>63,64</sup> This could be a direct result of aging as opposed to thyroid disease. However, because the brain maintains a narrow range of levels of these hormones, even small changes in their quantities with aging may impact cognitive function, potentially having dire consequences on aging adults.<sup>58</sup> Malnutrition and chronic illness are also important confounders to keep in mind when assessing thyroid function in the elderly.<sup>60</sup> Both of these factors can cause decreased serum T3 levels in absence of thyroid disease.<sup>60</sup> It has also been proposed that other

non-thyroidal illnesses with aging can decrease T4 conversion to T3.<sup>63</sup> Lastly, medications also play an important role in thyroid function in the elderly. Lithium (hyperthyroidism), amiodarone (hyperthyroidism), estrogens and glucocorticoids (thyroid binding globulin status) are some of the well-studied medications commonly used by the elderly that can affect thyroid function.<sup>60</sup>

With age, the normal range of serum TSH concentration in elderly patients with normal T4 broadens compared to younger individuals.<sup>62,64</sup> This change can be specifically noticed in ages below 50 to above 60. Due to the progressive increase of TSH with age, some studies have raised the question whether age-specific parameters for normal serum TSH levels need to be established.<sup>64</sup> Also, with age, there is an increased prevalence of anti-thyroperoxidase and anti-thyroglobulin antibodies, especially in females above 60 years of age.<sup>60</sup> However, in centenarians, interestingly, thyroid antibodies are rare in comparison to hospitalized patients or other unselected individuals.<sup>60</sup> Furthermore, when comparing males and females, one study found a linear decrease in free T3/free T4 ratio with age in males, but not females, suggesting impaired T4 to T3 conversion in males.<sup>62</sup> The same study also reported increase T3 resistance index with age in males, but not females.<sup>62,65</sup> The physiological reason behind these finding remains unclear and warrants further investigation to determine clinical significance in terms of maintaining homeostasis.

Given elevated TSH levels with age along with normal T4 levels, a question about subclinical hypothyroidism arises along with its consequences. Ischemic heart disease and its association with thyroid function has been looked at in multiple studies.<sup>60,64</sup> Subclinical hypothyroidism has failed to show any association with ischemic heart disease.<sup>64</sup> In fact, the incidence and prevalence of ischemic heart disease in individuals with subclinical hypothyroidism is higher in younger individuals compared to individuals ages 65 and older [60,64]. Furthermore, treatment of subclinical hypothyroidism has been shown to be associated with fewer events of ischemic heart disease in the younger population but not in individuals older than age 70 [64]. Moreover, multiple observational studies have shown an inverse correlation between subclinical hypothyroidism and ischemic heart disease.<sup>64</sup> These findings indicate increased TSH levels likely play a cardiovascular protective role.

Individuals with high TSH levels and low T4 levels have been associated with a lower mortality survival benefit.<sup>64</sup> Studies have shown centenarians have significantly higher median serum TSH levels and lower T4 levels when compared with control group of thyroid disease-free individuals (median age of 68 years). This effect can possibly be explained by lower metabolic rate leading to caloric restriction, which by itself has been shown to improve mortality rates in animal studies.<sup>64</sup>

Hyperthyroidism, on the other hand, is not as common as hypothyroidism, but its prevalence does increase in the elderly.<sup>60</sup> Depending on iodine intake in the given area, Grave's disease and toxic multinodular goiter are most common causes. Occurrence of atrial fibrillation due to hyperthyroidism is higher in the elderly, but other symptoms such as heat intolerance, tremors, and ocular manifestations are less frequent.<sup>60</sup>

Subclinical hyperthyroidism similarly has a much lower prevalence rate compared to subclinical hypothyroidism at 3.2% for general population and less than 2% after excluding patients with known thyroid disease.<sup>60</sup> Prevalence increases in groups with low iodine intake, in elderly females and African Americans. Non-

thyroidal illness, fasting, and drug-induced causes must be ruled out before making the diagnosis. Only 1-2% of individuals will progress to overt hyperthyroidism. This is especially true for individuals with serum TSH levels between 0.1 and 0.45mU/L and many of these individuals will automatically self-correct TSH level with time. Also, non-thyroidal illnesses and drugs suppressing TSH levels will rarely cause TSH levels to be depressed below 0.1mU/L. In individuals with TSH levels less than 0.1mU/L they are at higher risk of developing atrial fibrillation and other cardiovascular diseases.<sup>60</sup> As stated above, elevated TSH levels can be associated with cardio-protective properties, and thus, treating individuals with subclinical hyperthyroidism with TSH levels less than 0.1mU/L should carry a low threshold.<sup>60,64</sup> However, current studies do not provide any clear definitive conclusions regarding when to treat patients with subclinical hyperthyroidism. In general, whether to treat or not should be decided based on a combination of factors including signs and symptoms, age, risk factors, and other associated comorbidities.<sup>60</sup>

Thyroid hormone regulates metabolism via adrenergic stimulation and glucose uptake.<sup>66,67</sup> It plays a role in mitochondrial gene expression, affecting mitochondrial oxidation in skeletal muscle. Effects of hypothyroidism with aging can lead to lipid accumulation, compromising metabolic activity. This can result in insulin resistance and other features of metabolic syndrome.<sup>67</sup> On the other hand, increased metabolic rate has shown to cause early mortality by accelerating aging.<sup>68,69</sup> Basal metabolic rate usually declines with aging indicating a healthier functional status and low energy requirements for maintaining homeostasis.<sup>69</sup> In studies looking at basal metabolic rates in the young (less than age 64) and older individuals (above 64), it has been shown that the higher the metabolic rate in the younger the higher the predictability for mortality. In older individuals who fail to down regulate the metabolic rate with age usually have poor health status and shown to have higher risk of mortality, independent of other risk factors such as body mass index, smoking status, daily physical activity, blood pressure and diabetes.<sup>68,69</sup> Further investigation needs to be done to study how metabolic rate influences health status specifically and if there are any other hormonal regulators besides thyroid.

### Pituitary-gonadal function

The hypothalamus-pituitary-gonadal axis (HPG axis) helps regulate reproduction in men and women. Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. These hormones, in turn, help release estrogen and testosterone in females and males, respectively.

**Men:** In males, FSH is responsible for spermatogenesis, and LH aids in the production of sex hormones, known as androgens. FSH stimulates Sertoli cells in the testes to produce sperm cells and inhibin B. Inhibin B acts as a negative feedback of FSH production in the anterior pituitary gland. LH stimulates the production of androgens in Leydig cells of the testes; testosterone is the most widely known androgen, and it promotes sperm production and male secondary sexual characteristics.

There is a gradual decline, with age, in total and free testosterone in men.<sup>70</sup> This steady decline of male sex hormones, especially testosterone, is termed andropause, and it starts between ages 20-30 and continues after that at a rate of 1% per year. This can be related to decreased hypothalamic or testicular function over time.<sup>71</sup> Free testosterone is bound by sex hormone-binding globulin (SHBG), which decreases the bioavailability of free testosterone; since SHBG con-

centrations increase with age, there is a steeper decline of free testosterone with time.<sup>70</sup> Moreover, GnRH decreases with age, leading to less LH production by the pituitary gland.<sup>71</sup> The number of Leydig cells in the testes also decreases with age; therefore less testosterone is produced. These reduced levels affect the feedback loop with the hypothalamus, which then stimulates production of serum gonadotropin, FSH, and LH.

More than 70% of men over the age of 70 have free testosterone levels consistent with hypogonadism.<sup>15</sup> Hypogonadism can be defined by testosterone levels less than 200ng/dL, and if hypogonadism is present in younger men, a diagnostic work-up is advised.<sup>70</sup> Along with a decline in testosterone levels, the testes also shrink with age, which may reflect a decline in their volume.

Reduced testosterone levels may cause patients to complain of decreased sexual desire and thus activity, mood changes, difficulties falling asleep or staying asleep, reduced energy, and a decline in cognitive abilities.<sup>71</sup> Low testosterone has many physiologic effects, including decreased bone mineral density (BMD), skeletal muscle weakness, and diminished physical stamina. Some studies have found cardiovascular effects linked to low testosterone, such as an increase in systolic blood pressure, greater left ventricle mass, and an increase in overall cardiovascular disease, which is currently under investigation.<sup>71</sup> Various metabolic effects associated with low testosterone include an increase in central obesity and an increase in hemoglobin A1c. Low androgen exacerbates co-morbidities such as diabetes mellitus due to insulin resistance.<sup>15,72,73</sup>

There is a variety of testosterone preparations and treatments available to help alleviate the above symptoms of Andropause.<sup>71</sup> Currently, there is no "normal" level of serum testosterone, because testosterone levels have much variability between patients and within a single day. While there is no concrete evidence that testosterone supplementation can cause prostatic carcinoma, it is highly recommended to screen for this prior to the use of testosterone treatments.<sup>71</sup>

**Women:** In females, FSH stimulates ovarian follicle growth, while LH stimulates ovulation and corpus luteum development. Specifically, FSH stimulates primordial follicles in the ovaries to start maturing into primary and secondary follicles that produce estrogen during the follicular phase of the menstrual cycle. LH helps the follicle mature and initiates ovulation to develop the corpus luteum. The corpus luteum produces estrogen and progesterone during the luteal phase of the menstrual cycle.

In their mid-30s, women have a gradual decline of estradiol production, which is accentuated during menopause (which occurs at an average age of 51).<sup>13,74</sup> Decreased estrogen has a negative feedback to the anterior pituitary gland, which stimulates the production of FSH and LH. Menopause can be verified by FSH levels greater 30mIU/mL, and no menses for at least one year.

One of the most common symptoms that women experience during the peri-menopausal and menopausal time periods is hot flashes, which occur due to a declining estrogen's effect on the body's thermal regulation. The decrease in estrogen can also cause genitourinary atrophy symptoms, such as vaginal dryness and dyspareunia.<sup>74</sup> Vaginal dryness can be treated with low-dose topical vaginal estrogen. Low estrogen levels may also affect mood, resulting in depressive symptoms. Low estrogen can also have an effect on BMD, which can be detected by a dual-energy X-ray absorptiometry (DEXA) scan. DEXA scans are recommended for women ages 65 or older and also those who have a fracture risk equal to that of a woman who is 65 years or older.<sup>74</sup>

Estrogen replacement treatment can be used in women with severe postmenopausal symptoms. Estrogen can be consumed orally or applied topically, with transdermal patch, or intravaginally. Low-dose estrogen is effective in relieving hot flashes. The lowest dose should be used first to decrease adverse effects of HRT. Exogenous estrogen side effects include higher risk of cardiovascular disease and elevated serum triglycerides. It has been shown that HDL does play a protective role in menopausal women.<sup>75</sup> There are prothrombotic effects and increased hepatic synthesis of vascular inflammatory markers as well. In addition, risk of stroke increases dramatically, and venous thromboembolism has been found to have a two-fold increase.<sup>74</sup> Contraindications for solely estrogen HRT include history of breast or endometrial cancer, being a chronic smoker, cardiovascular disease, previous venous thromboembolism, previous stroke or transient ischemic attack, hepatic disease, and unexplained vaginal bleeding.<sup>76,77</sup>

### Calcitropic hormone production and calcium balance

Calcitropic hormone production and calcium balance gradually decline with increased age. BMD, or skeletal mass, increases until approximately age 20, remains at its peak level until approximately age 35, and subsequently declines at a steady rate throughout the remainder of life.<sup>12</sup> Parathyroid hormone (PTH), vitamin D, and calcium can contribute to these changes.

In older individuals, serum PTH concentration is slightly higher than in their younger counterpart.<sup>78</sup> This may be due to a decline in renal function with age, which precipitates phosphate retention, as well as decrease in serum calcium concentration due to mild vitamin D deficiency.<sup>10,12,79</sup> PTH indirectly stimulates osteoclastic activity, enhancing bone resorption. Therefore, PTH may play an important role in age-related bone loss. In studies of older individuals with low 25-hydroxyvitamin D, increasing concentrations with supplementation to an adequate range of greater than or equal to 30nmol/L reduced PTH levels, demonstrating that correction of vitamin D deficiency decreases parathyroid function and potentially suppresses some degree of bone turnover.<sup>80-82</sup>

Mild vitamin D deficiency is common in the elderly population for a number of reasons, including reduced nutritional intake and less sunlight exposure secondary to activity restriction. There is also decreased endogenous vitamin D absorption and synthesis in human skin with age.<sup>83</sup> Vitamin D can only be produced in sufficient quantities on skin with adequate ultraviolet B light and skin surface exposure.<sup>84</sup> Also, the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is also reduced in the kidneys with age.<sup>12,83</sup> Elderly women also have impaired intestinal response to the action of 1,25-dihydroxyvitamin D.<sup>79</sup> Since renal function declines with age, creatinine clearance and glomerular filtration rate, phosphate excretion, and  $1\alpha$ -hydroxylase activity are affected.<sup>10,12</sup> The enzyme  $1\alpha$ -hydroxylase aids in the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the active metabolite of vitamin D; vitamin D is hydroxylated to 25-hydroxyvitamin D in the liver, then  $1\alpha$ -hydroxylated to 1,25-dihydroxyvitamin D in the kidney.<sup>84,85</sup> Therefore, if the 1,25-dihydroxyvitamin D level is reduced, vitamin D-dependent calcium absorption declines.<sup>12</sup> When calcium absorption is decreased, the body depends on skeletal bone calcium to maintain its serum levels, causing increased bone turnover.

Women also have a higher rate of BMD loss post-menopause. In women aged 52-77 years being screened for osteoporosis, individuals with low 25-hydroxyvitamin D had reduced vertebral bone density, lower serum calcium and phosphate levels, and increased immunoreactive PTH, suggesting secondary hyperparathyroidism.<sup>86</sup>

Some studies suggest that estrogen may actually enhance intestinal calcium absorption.<sup>12,13</sup>

Decreased BMD, poor nutrition, and low vitamin D levels predispose the aging population to a higher incidence of osteoporosis, subsequent falls, and fractures.<sup>80,84,85</sup> One study of an Australian nursing home demonstrated that residents who fell were found to have lower serum 25-hydroxyvitamin D level and higher serum PTH level than residents who did not fall.<sup>87</sup> Some studies in women suggest that supplementary vitamin D and calcium may reduce the incidence of certain fractures.<sup>12</sup> Low vitamin D levels have also been associated with cardiovascular disease risk factors, certain cancers, and muscle weakness and reduced physical mobility.<sup>84,85,88-91</sup> Supplementation of vitamin D is advised to the aging population to reduce these risks. The recommended dose is 800 IU of vitamin D plus 1200mg calcium intake per day to reduce the risk of fractures in hospitalized patients, and 400 IU of vitamin D plus 1000mg calcium per day for persons greater than age 65 who live at home.<sup>84</sup>

### Changes in fuel regulation

Aging adults undergo changes in their fuel regulation. While the human body utilizes the same mechanisms for storing and retrieving energy throughout life, aging adults adjust the mechanisms to meet their current demand. Aging has a direct role in determining how the body's fuel is stored and retrieved.

Age has a primary role in causing declining glucose tolerance, even when data were adjusted for obesity, fitness, and fat distribution.<sup>92</sup> The decline in glucose tolerance has been linked to increasing fasting glucose levels and higher hemoglobin A1c levels in aging adults. Type 2 diabetes mellitus was shown to have a strong correlation with age.<sup>93</sup>

The risk of diabetes mellitus increases with aging due to both increased insulin resistance and decreased insulin secretion. Aging adults have a decreased concentration of insulin-stimulated glucose transporter (GLUT4) in skeletal muscle in older individuals which reduces the amount of insulin uptake.<sup>94</sup> The inverse relationship between GLUT4 and increased age held true even after the study was corrected for adiposity and cardiorespiratory fitness. Meaning that age alone has a role in increasing the risk of diabetes. Additionally, insulin secretion by pancreatic beta cells decreases with aging. These cells have decreased response to the increased levels of glucose in aging adults.<sup>95</sup> Even after patients were assessed with an oral glucose tolerance test (OGTT), older patients were found to have a decline in insulin sensitivity by their pancreatic beta cells, suggesting that the compensatory capacity of beta cells deteriorates with age.<sup>96</sup> Increased insulin resistance and pancreatic beta cell dysfunction result in aging adults having increased visceral and subcutaneous fat.<sup>97</sup> The increased risk of developing type 2 diabetes mellitus with age is multifactorial; however it is clear that aging plays a direct role in developing this disease.<sup>98</sup>

Aging adults have been linked to increased adiposity and body mass index (BMI). Adipokines are bioactive substances secreted from adipose tissue and include leptin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and adiponectin. These hormones regulate the storage and utilization of adipose. Leptin is a hormone found in adipose cells that serves to decrease food intake and increase activity. Aging adults, independent of BMI and other age-related endocrine changes, have decreasing leptin with age.<sup>99</sup> The decreased leptin results in less satiety and increased food intake. This causes accumulation of adipose cells and increases risk of metabolic disorders affecting the circulatory, respiratory, and reproductive systems.<sup>100,101</sup>



Adiponectin is another hormone secreted by adipocytes that reduces insulin resistance and decreases risk of atherosclerosis. Older men have increased adiponectin compared to younger men, while there was no significant change in adiponectin levels with women.<sup>102</sup> Increased adiponectin will decrease the risk of metabolic diseases, allowing for a healthier adult life and longer lifespan.

The changes in fuel regulation with aging reveal irregularities that will impact aging adults. Decreased glucose tolerance and increased insulin resistance result in higher incidence of type 2 diabetes mellitus in aging adults. Similarly, the changes in leptin levels alter each person's metabolic activity, and it is unknown how these changes affect longevity. Adipokines are increased to help protect aging adults from the metabolic changes that occur due to increased body adiposity.

All of the aforementioned studies show the body is attempting to increase adipose storage. For instance, increased insulin resistance along with decreased pancreatic beta cell activity results in hyperglycemia. Leptin, when decreased with aging, will cause increased adiposity as well due to decreased hunger suppression. These changes all increase the body's fat reserve.

Understanding the body's adaptations in fuel regulation is important to help aging adults form appropriate expectations about their body habitus as they continue to age. As adults age, changes in the body's energy regulation may cause an increased BMI even with proper diet and exercise. Helping adults realize these normal changes associated with aging can help aging adults prepare for the future.

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## Conflicts of interest

The author declares there are no conflicts of interest.

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