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## Impact of Aging on the Endocrine System

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### ABSTRACT

*The endocrine system plays a central role in maintaining homeostasis through hormonal regulation. Aging is associated with progressive dysregulation of several endocrine axes, resulting in widespread effects on metabolism, musculoskeletal integrity, immune function, mental health, etc. This paper examines the impact of aging on key systems, including the growth hormone–insulin-like growth factor-I axis (GH-IGF-I Axis), dehydroepiandrosterone (DHEA(S)), the hypothalamo–pituitary–adrenal axis (HPA Axis), menopause, and andropause. Understanding these hormonal changes is essential for addressing age-related morbidity and improving quality of life in older populations.*

**Keywords:** Endocrine Aging, Growth Hormone–IGF-I Axis, Dehydroepiandrosterone (DHEA/DHEAS), Hypothalamic–Pituitary–Adrenal axis, Menopause, Andropause.

### Introduction

The endocrine system is an integral part of the human body system, it allows for the secretion of hormones and the inhibition of the same. The endocrine system is especially impacted through the inevitable ageing process. Which causes integral hormones such as those in the body to be secreted less efficiently. This particularly concerns complex axes in the body such as the hypothalamic–pituitary–thyroid axis as well as hypothalamic–pituitary–cortisol axis and dehydroepiandrosterone and its sulphate (Chahal and Drake 173). Usually research is conducted on the counterpart, which is the adolescent age, wherein they research about the peak performance of the endocrine system in the human body. However, this paper aims to research on a contrasting topic, which is the topic of the endocrine system’s development in aging. This is due to a lack of a high-quality adaptation the endocrine system has in the declining years.

This topic is of utmost importance due to the inevitability of old age, and some of the major issues related to old age possibly stem from the inadequacy of the endocrine system in the sustainability of the body. An example of such is the decline of Growth Hormone (GH) as well as insulin-like growth factor-I (IGF-I) which in older adults is known to cause a reduction in protein synthesis, decrease in lean body mass, bone mass, and a decline in immune function (Chahal and Drake 175). Another such example is the example of Dehydroepiandrosterone (DHEA) and its sulfate form, (DHEAS) has often been linked to be the “youth hormone” but has a lack of substantial research backing any of its research.

This hormone has therefore has had a correlation made that a higher DHEA leads to higher performance, due to the fact that the substance peaks at approximately 20 years of age, and significantly goes down 90-80% of the peak DHEA levels. However, more recent research has concluded that there is no clear evidence of benefit in parameters such as body composition, peak volume of oxygen consumption, muscle strength, or insulin sensitivity (Chahal and Drake 177) (Schwartz). Thus, the poor adaptation to aging is a crucial aspect which must be understood further, the impacts of the adaptations, and the solutions, and therefore, the creation of this paper.

Before the in-depth dive into the impact of ageing on the endocrine system, an achievement that skyrocketed the development of research into the impact of aging on the fragile endocrine system was the discovery of Menopause, the natural and more importantly, a permanent cease of menstruation when the ovaries, the main female reproductive organ, stops releasing the eggs—and cease to produce most of their hormones, particularly estrogen and progesterone.

### **Growth hormone–insulin-like growth factor-I axis**

The growth hormone (GH) allows for lipolysis to take place, the process by which triglycerides (fats) are broken down into glycerol and free fatty acids (FFAs), which is catabolic in nature (Gibney et al. 1); the growth hormone itself is anabolic as in the name itself, it allows for the “growth” of the body. And despite the name, GH does not actually grow the body on its own, it takes aid by producing a certain hormone by the name of Insulin-like growth factor-I (IGF-1), which is structurally similar to Insulin.

To explain the in-depth impacts of aging on the Growth hormone-insulin-like growth factor-I axis (GH-IGF-I) we must understand what is the process of which it occurs. GH-IF-I axis begins actually from the Hypothalamus, the control centre of the brain, secretes Growth hormone-releasing hormone (GHRH) which the stimulus of which can be but is not limited to Low blood glucose, exercise, sleep or stress. This then stimulates the pituitary gland, specifically the anterior pituitary, the Somatotrophs to release GH. Then the GH travels towards the liver to stimulate IGF-I synthesis which is then released into the blood. There is then a feedback loop, wherein the IGF-I then goes back to the pituitary through blood. If there is an overload of GH, it will then reduce the amount of GHRH and increase the amount of somatostatin. Therefore, less GH is produced, which reduces the production of IGF-I, and thereby reduces the overall growth in the body.

However, when the inevitable process of aging begins, the body’s ability to sustain this integral yet fragile process decreases. With ageing the GHRH-producing neurons in the arcuate nucleus, the place where GHRH is produced, decreases, however the contrasting hormone, Somatostatin-producing neurons in the periventricular nucleus, does not decrease as rapidly, therefore a comparatively there is higher amount of Somatostatin than GHRH. This then results in a marked decline in circulating the GH and IGF-I levels with age. This age-related reduction

in GH-IGF-I activity, referred to as somato pause, contributes to decreased protein synthesis, loss of lean muscle mass, increased fat accumulation, reduced bone mineral density, and etc.

### **Dehydroepiandrosterone**

Dehydroepiandrosterone, otherwise known as DHEA and its sulfate form, DHEAS. This hormone is commonly known as the “youth hormone” due to the correlation that, at a younger age there is a higher concentration of both of these hormones. DHEA is a steroid prohormone naturally produced by the “adrenal gland”, which serves as a precursor to the sex hormones such as testosterone and estrogen, however DHEA(S) is also thought to act directly as a neurosteroid that may have cardioprotective, antidiabetic, anti-obesity, and immuno-enhancing properties (Chahal and Drake 177).

Carrying forward, when talking about DHEA & DHEAS in relation to ageing, we must understand the correlation between DHEA and ageing further. DHEA and its sulfate form both peak around the 20s of each person, and as people get older, the production of DHEA and DHEAS decreases markedly, with most elderly individuals having substantially lower levels compared to their younger years (Chahal and Drake 177). This decline has been associated with certain aspects of aging, including reduced muscle mass, increased arterial stiffness, and possible influences on cognition and mood.

DHEA & DHEAS both have had extensive research and multiple studies, all of which come to a mixed conclusion.

Some research shows that DHEA supplementation may improve skin hydration, improved insulin action (Holloszy), decrease arterial stiffness, increase lean body mass, and decrease body fat, increase sex drive, and slightly improve mood and some menopause-related symptoms such as reduction of vaginal tissue thinning (Fisher and Shmerling). In a safety aspect, DHEA is generally considered safe for use for up to 2 years, at doses up to 50 mg per day.

However, some research depicts DHEA as not as effective and not as useful as some may believe. In the largest study till date, a double blind randomized parallel study of 140 men and 140 women aged 60-79 years, who were given 50 mg or placebo daily, showed no improvement whatsoever, in either well being or cognitive function. There was a slight increase of libido in specifically women over the age of 70 years. As well as slight but significant gains in bone mineral density, however, these results were not able to be replicated in the 140 males. And any further trials were not able to demonstrate any benefit of DHEA on well-being, mood, cognition or activities of daily living (Chahal and Drake 178).

On the flip side of safety in DHEA supplementation, current users who have used the product up until 2 years should be aware about some mild side effects which can occur. This can include

sudden mood changes, acne and an upset stomach, as well as the risk that DHEA should not be used for anyone who is either pregnant, has pre-existing/high-risk liver problems, or polycystic ovary syndrome (PCOS). However, longer term use of DHEA may increase the risk of serious side effects, such as heart health, by reducing HDL Cholesterol, hormone-sensitive conditions such as breast cancer, ovarian cancer and endometriosis (where the lining of the uterus can grow outside the uterus, causing severe pain to the pelvis and reducing the chances of a pregnancy), it can furthermore strengthen pre-existing mood disorders by increasing certain emotions such as excitability, impulsiveness and irritability (Fisher and Shmerling).

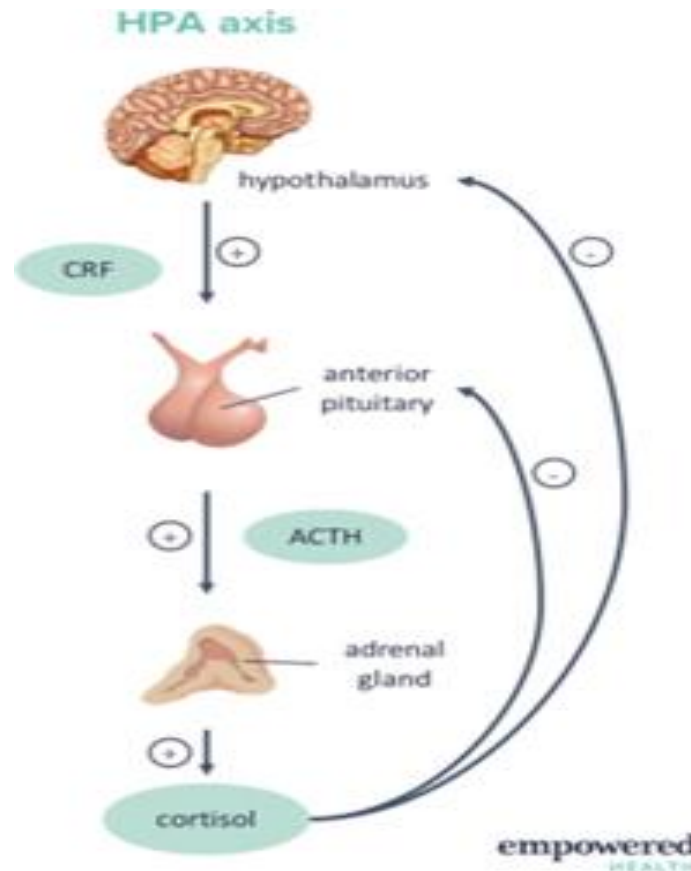
To conclude the research on DHEA(S), DHEA has had some success in a few areas, but to call it a “youth hormone” is far from the reality. The reality is that, current evidence of the supplementation of said hormone indicates that it can have impacts in delaying aspects of aging, such as wrinkled skin, decreased libido, decreased arterial stiffness, increased insulin efficiency, However, it has also shown to have side effects from an upset stomach to extreme issues such as cancer. Therefore, DHEA falls short on being the mystery cure for the aging issue.

### **Hypothalmo–pituitary–adrenal axis**

The hypothalmo-pituitary-adrenal axis is one of the key axes which are impacted via aging, the axis itself is a composition of the hypothalamus gland, the pituitary gland, and the adrenal gland.

“The anterior–superior hypothalamus is a critical region for body homeostasis and HPA axis regulation. It comprises the preoptic nucleus and PVN, which is responsible for autonomic control, including the stress response through regulation of the HPA axis. In the PVN, corticotropin-releasing hormone is released in response to stress, which controls cortisol secretion, the main stress hormone.” (Spindler et al. 2). This means that the hypothalamus acts as the primary control center for the body’s stress response and internal balance. When the body experiences stress, the hypothalamus responds by releasing corticotrophin-releasing hormone (CRH) from the paraventricular nucleus (PVN), which then activates the pituitary gland. This activation ultimately leads to the release of cortisol from the adrenal glands, allowing the body to respond appropriately to stress by mobilizing energy and maintaining homeostasis.

“Through inhibitory feedback mechanisms involving the hippocampus, amygdala, and prefrontal cortex, cortisol production is then downregulated to achieve homeostasis. It is proposed that chronic stress and obesity are associated with a desensitized HPA axis, which is reflected by faulty inhibitory feedback, atrophy and loss of glucocorticoid receptors in the above-mentioned brain regions.” (Spindler et al. 2). This indicates that once cortisol levels rise, the brain uses negative feedback mechanisms to reduce further cortisol production. Brain regions such as the hippocampus, amygdala as well as the prefrontal context will detect elevated cortisol and thereby signal the hypothalamus as well as pituitary gland to suppress any further hormone release. This feedback loop is essential for the prevention of prolonged exposure to cortisol and thereby restoring the body to a balanced state (homeostasis) after the stress has passed.



HPA axis dysfunction (i.e., obesity and long-term stress) is “a potential driving factor for inflammatory processes and iron accumulation in the anterior–superior hypothalamus during middle adulthood. Here, we assume that older subjects are more vulnerable to microstructural alterations as a result of HPA axis dysfunction as compared to younger individuals. Overall, the results of this study can help to uncover the role of detailed hypothalamic microstructure and its related functions with age.” (Spindler et al. 2). This means that as the HPA axis goes through dysfunction due to either obesity and/or long-term stress, it is a leading factor for numerous issues within the body such as inflammatory process, and iron accumulation. This can lead to chronic inflammation within the body, which usually is a short-term defense response to heal injuries. However, since the HPA axis is now dysfunctional, cortisol becomes imbalanced. This can lead to persistent, low-grade inflammation, immune system activation even when there is no infection as well as tissue damage over time. Which overall, can lead to damage in blood vessels, worsens insulin resistance, damages joints and organs, contributes to autoimmune problems, however finally, can actually accelerate aging and cell damage.

Overall, aging plays a critical role in worsening the HPA axis regulation. This is due to the fact that with increasing age, the brain regions involved in the inhibitory feedback, such as the hippocampus and the prefrontal cortex, become more vulnerable to structural and functional decline. This reduces the sensitivity of the glucocorticoid receptors, which means that cortisol is not suppressed as effectively after stress. As a result, older adults are not even more likely to experience prolonged cortisol exposure, leading to chronic low-grade inflammation, metabolic dysfunction as well as accelerated cellular aging. Thereby, many age-related changes in the HPA axis contribute to significantly increase the physiological stress seen in older individuals, showing how endocrine dysregulation is linked towards ageing.

## Menopause

Menopause refers to the age-related changes in hormone levels in females. Menopause is the permanent end of menstruation as well as fertility in women, generally occurring between the early 40s to the mid-50s. It is caused by the cease of “ovarian function, with loss of reproductive hormone production and irreversible loss of fertility” (Davis et al. 1).

To begin with, menopause is the event in which there is a permanent stop of the reproductive hormone of estrogen (as written above). With the loss of reproductive hormone production as well as the irreversible loss of fertility. It is a natural part of reproductive aging. The physiology of the menopause is extremely complex and it is not fully understood. The information which is seen is the fact that globally, menopause usually occurs at around the age of 49 years, with some amount of both geographic and ethnic differences. These hormonal changes of the menopause transition can result in both symptoms and long-term effects, usually negative effects on both the

cardiometabolic and musculoskeletal health. (Davis et al. 1).

The menopausal road can be different in difficulty for all, however the menopausal road can definitively be written as three stages. Initially, the Premenopause period, which is before the body begins with menopause, the Perimenopause, wherein the body is transitioning to the menopause as well as includes the time wherein the body is undertaking menopause, and postmenopause is the rest of a woman's life post the event of menopause.

Postmenopause has multiple challenges, this includes vasomotor effects, urogenital atrophy, osteoporosis, depression, etc. To begin with, vasomotor effects in general, impact around 75% of peri-menopausal women (Dalal). Symptoms of this can usually last around 1 or 2 years, however can lead up to 10 years or longer depending from patient to patient. Hot flushes are the primary reason why women seek care at menopause (Dalal). Hot flushes not only disturb women while they're working, however they can furthermore impact their sleep routines as hot flushes may interrupt sleep routines (Dalal). Furthermore, "Urogenital atrophy results in vaginal dryness and pruritus, dyspareunia, dysuria" (Dalal). Furthermore, Musculoskeletal impacts are seen heavily in post-menopausal women. These symptoms are characterized by backache, fractures on minimal trauma, decreased height, and mobility are common due to osteoporosis. Depression is also another example of the impacts to post menopausal women with an estimated 20% of women having depression at some point during menopause (Dalal). However, it is also important to note that many women transition to menopause without experiencing psychiatric problems.

The reasons for the above are as follows. Vasomotor symptoms are not fully understood from a physiological standpoint (Dalal). However, the best estimation towards how vasomotor symptoms are produced in post-menopausal women is in the following sequence. A central event, most likely occurring "probably initiated in the hypothalamus, drives an increased core body temperature, metabolic rate, and skin temperature; this reaction results in peripheral vasodilation and sweating in some women. The central event may be triggered by noradrenergic, serotonergic, or dopaminergic activation. Although an LH surge often occurs at the time of a hot flush, it is not causative because vasomotor symptoms also occur in women who have had their pituitary glands removed. Exactly what role estrogen plays in modulating these events is unknown. Vasomotor symptoms are a consequence of estrogen withdrawal, not simply estrogen deficiency." (Dalal).

Furthermore, the reasoning for the musculoskeletal deterioration seen in postmenopausal women is primarily linked to the estrogen withdrawal that occurs. Estrogen plays a critical role in maintaining bone remodeling balance by inhibiting osteoclast-mediated bone resorption. Following menopause, the decline in estrogen levels leads to an increase of osteoclastic activity and thereby reduced osteoblastic bone formation, which results in accelerated bone loss. This then explains the high prevalence of osteoporosis, fragility fractures, loss of height, and reduced mobility in postmenopausal women, particularly in the years immediately following menopause.

In addition to the skeletal effects as mentioned above, menopause is also associated with the significant neuropsychological changes. With the fluctuating and declining estrogen levels which influence neurotransmitter systems which are involved in mood regulation, which includes serotonin and norepinephrine pathways. As a result, many women experience symptoms such as irritability, anxiety, low mood as well as depressive episodes during the transition. However, not all women develop this psychiatric illness, this period of menopause shows a period of increased vulnerability, especially in individuals with prior mood disorders of psychosocial stressors.

Overall, menopause represents an endocrine milestone in aging, characterized by the abrupt hormonal shift rather than gradual decline. This loss of estrogen has widespread effects on numerous factors, such as mentioned above. Unlike other age-related changes that occur progressively, this is one of the few examples which showcase a sudden hormonal withdrawal, and shows clearly how rapid hormonal withdrawal can significantly disrupt physiological homeostasis, highlighting the importance of targeted management strategies during this stage of aging.

## **Andropause**

Similarly, andropause is called the 'male menopause' by many due to its immense similarities with menopause. Where menopause is the immediate estrogen cessation in a singular event, andropause is a continuous event that occurs throughout the male lifetime, starting from when the male is 40 years old, declining by 1 year every year thereafter (Singh). Symptoms for many males due to the hormonal changes are usually sexual, physical, or emotional, however, since these symptoms are nonspecific, many men have low testosterone without noticeable symptoms. True andropause mostly occurs in men who lose testicular function completely, but late-onset hypogonadism is more common, affecting 5–18% of older men and rising with age (Singh).

The impacts of andropause are varied and different across different men as mentioned above. However, main impacts of andropause are sexual health, body composition and strength, bone health, metabolic and cardiovascular risks, mood condition & mental wellbeing (onset of certain medical illnesses, such as depression), blood & anaemia, and overall quality of life. The main impact to sexual health from andropause is the fact that there are reduced morning erections, erectile dysfunction in men, and furthermore, recent studies also showcase that 33% of men above the age of 40 (however, specifically in turkey) suffer from ED. To add on, many a time men going through andropause also have low sexual motivation and pleasure.

Alongside this, body composition & strength also are reduced in andropause. While going through andropause, many men go through a loss of mass and strength, as well as an increase in body fat (especially abdominal fat) as well as reduced function or stamina (Singh). This is due to the fact that low testosterone leads to reduced anabolic activity, so men gain fat and lose muscle. This is as testosterone supports muscle protein-synthesis, and body composition muscle-fat ratio (Singh). This means that when testosterone drops, the above factors (mainly weaker muscles and more fat) occur.

Moreover, bone health is reduced in andropause. This is due to the fact that testosterone, similar to how it helps muscle protein-synthesis, testosterone also aids in stimulating osteoblasts which are the bone-building cells in your body (Singh), and converts them into estrogen via aromatization, this will then reduce osteoclast activity and this process leads to bone growth as mentioned above. Thereby, when the testosterone slowly declines due to andropause, there is a decrease of bone density leading to osteoporosis/osteopenia.

Furthermore, there is a connection to be made between low testosterone and metabolic disease. This is due to the fact that low testosterone and low SHBG are associated with obesity, insulin resistance, dyslipidemia and metabolic syndrome (Singh). Alongside the fact that testosterone decline is linked with central obesity, which worsens hypogonadism.

Alongside this, with the onset of a decrease of testosterone, mood, energy and cognition all decline. This is due to the fact that testosterone influences neuropsychological activity and motivation, and the decline of testosterone reduces energy, mental sharpness, mood stability, libido and motivation (Singh). Thereby, a lower testosterone can be associated with the decline in verbal as well as visual memory, alongside visuospatial performance (Singh). Testosterone deficiency contributes to a more depressed, fatigued mood alongside reduced vitality (Singh). Therefore, since there is a lowered testosterone, this means that there is a weaker neural androgen signaling, leading to a low mood, irritability, reduced energy and a possible cognitive decline.

Moreover, low testosterone can lead to anaemia, a condition where you lack enough healthy red blood cells (RBCs) or haemoglobin to carry sufficient oxygen to your body's tissues. This is due to the fact that testosterone stimulates red blood cell production by increasing erythropoietin from the kidney, as well as stimulating bone marrow erythropoietic stem cells (Singh). Thereby, when testosterone declines, the haemoglobin drops as well, by 10-20%, and men become more prone to anaemia and fatigue.

## Conclusion

To conclude, the findings of the paper are as follows. The paper has gone through different subsections and subtopics, it has looked throughout the different systems, different hormones and the impacts of these hormones, shown in GH-IF-I axis, HPA axis, alongside different hormones such as GH, DHEA(S), and the impact of losses of key hormones by looking at infamous issues coming from a lack of key hormones, shown by Andropause, the gradual decline of testosterone, and Menopause, the sudden decline of estrogen in both males and the females.

These subtopics went into how aging leads to the impact of these systems and hormones. For example, while menopause represents a defined endocrine transition, andropause and other age-related hormonal changes occur gradually, reflecting the reduced adaptability of the aging endocrine system. Ultimately, understanding endocrine aging is crucial for developing strategies that promote healthy aging, functional independence, and improved long-term outcomes in an increasingly aging global population.

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