

Ageing and endocrinology 1



The physiology of endocrine systems with ageing

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During ageing, the secretory patterns of the hormones produced by the hypothalamic–pituitary axis change, as does the sensitivity of the axis to negative feedback by end hormones. Additionally, glucose homeostasis tends towards disequilibrium with increasing age. Along with these endocrine alterations, a loss of bone and muscle mass and strength occurs, coupled with an increase in fat mass. In addition, ageing-induced effects are difficult to disentangle from the influence of other factors that are common in older people, such as chronic diseases, inflammation, and low nutritional status, all of which can also affect endocrine systems. Traditionally, the decrease in hormone activity during the ageing process has been considered to be detrimental because of the related decline in bodily functions. The concept of hormone replacement therapy was suggested as a therapeutic intervention to stop or reverse this decline. However, clearly some of these changes are a beneficial adaptation to ageing, whereas hormonal intervention often causes important adverse effects. In this paper, we discuss the effects of age on the different hypothalamic–pituitary–hormonal organ axes, as well as age-related changes in calcium and bone metabolism and glucose homeostasis.

Introduction

Throughout adult life, all physiological functions begin to gradually decline. Ageing is characterised by changes in virtually all biological systems. Major changes to the endocrine system, as described in this Series paper, result in healthy ageing individuals with well recognised phenotypes. However, other factors, such as inflammation and calorie intake, also affect the ageing process, and are often associated with age-related chronic diseases. These factors make the role of changes in hormonal activity difficult to disentangle and clarify in clinical practice.¹ During ageing, the secretory patterns of hormones produced by the hypothalamic–pituitary axis change, as does its sensitivity to negative feedback by end hormones. The triggers that determine the ageing process in the hypothalamus and pituitary have previously been reviewed.² In this paper, we review the response of the different components of the human endocrine system to the ageing process, including the response of the thyrotropic, somatotropic, adrenal, and gonadal axes, including bone growth, calcium, and glucose homeostasis (figure 1).

Hypothalamic–pituitary–peripheral organ axes

Thyrotropic axis

Changes in thyroid function during ageing

Several population studies,^{3–6} but not all,^{7,8} show that after the exclusion of people with thyroid disease and people with positive anti-thyroid antibodies, normal ageing is accompanied by an increase in the concentration of serum thyroid-stimulating hormone (TSH). However, changes in TSH concentration seem to be dependent on the regional iodine status, and could reflect a survival bias.⁹ Free thyroxine (FT₄) concentrations remain stable with increasing age,⁴ although a study reported a rise in FT₄ concentration with age,⁷ whereas free tri-iodothyronine (FT₃) concentrations decrease over the course of a

lifespan.¹⁰ The magnitude and pattern of changes in thyroid function during ageing are highly variable amongst individuals. For instance, some people have rising TSH and FT₄ concentrations, whereas others have rising TSH accompanied by falling FT₄ concentrations.⁹ Additionally, individuals can have low T₃ concentrations accompanied by high reverse T₃ concentrations, reminiscent of non-thyroidal illness, whereas others have low T₃ concentrations and low reverse T₃ concentrations (figure 2).¹¹ These different patterns might result from altered hormone metabolism due to disease, low-grade inflammation, or energy restriction.^{4,10,12} Additionally, changes can occur in TSH bioactivity with increasing age, making TSH less effective, or in the setpoint of the TSH receptor, making the receptor less functional.¹³ Finally, the increased prevalence of thyroid autoimmunity and autonomous nodules with increasing age can lead to altered thyroid hormone concentrations.³

Clinical relevance of changes in thyroid hormone concentrations during ageing

Whether the increased prevalence of subclinical hypothyroidism and hyperthyroidism at an older age¹⁴ and the increase in TSH within the normal reference range during ageing is of clinical relevance remains a matter of debate. Pooled data show that subclinical hyperthyroidism is associated with an increased risk of overall and cardiovascular-related mortality, especially in older people and patients with comorbidities.¹⁵ However, a subsequent study showed that individuals aged 85 years with subclinical hyperthyroidism did not have a significantly worse 9-year survival than their euthyroid peers.¹⁶ Further, subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation,¹⁷ hip and other fractures,¹⁸ and dementia,¹⁹ particularly among people with TSH concentrations that are lower than 0–10 mIU/L, and those with endogenous thyroid

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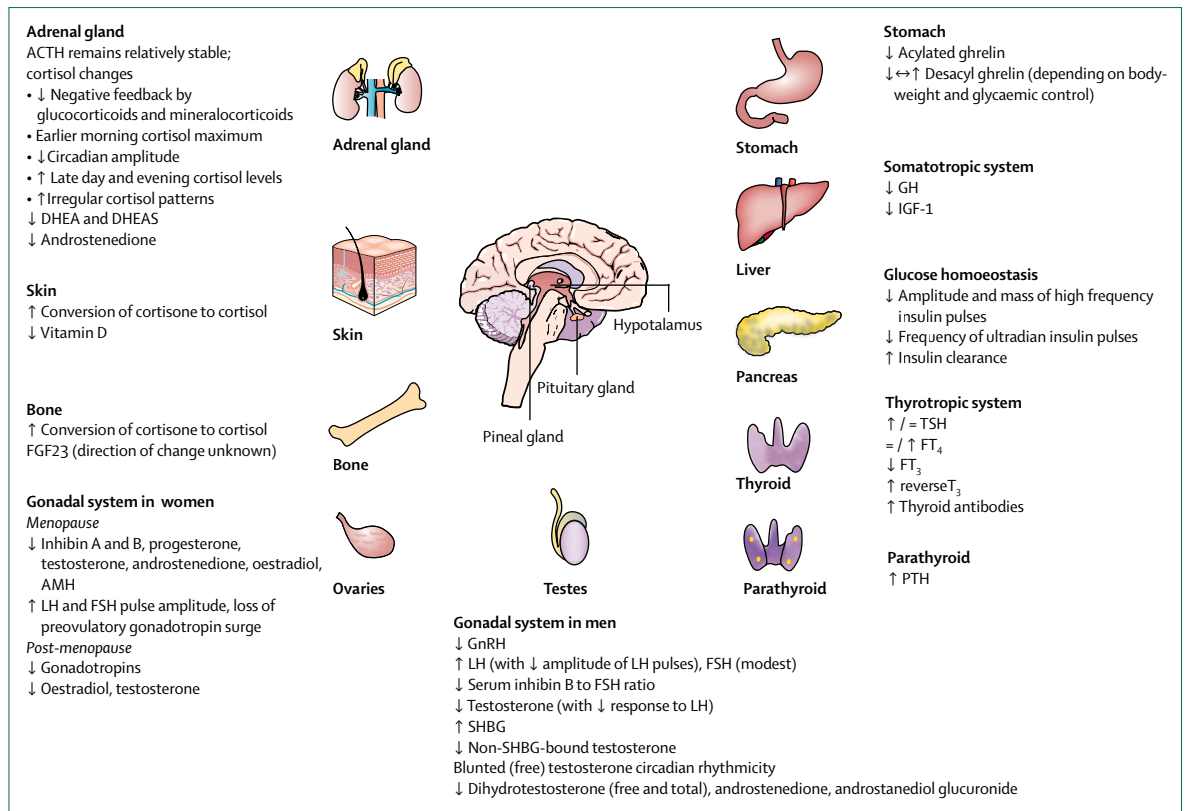


Figure 1: Most-reported changes in circulating hormone concentrations and hormone profiles with ageing

ACTH=adrenocorticotropic hormone. DHEA=dehydroepiandrosterone. DHEAS=DHEA sulphate. FGF23=fibroblast growth factor 23. AMH=anti-Müllerian hormone. LH=luteinising hormone. FSH=follicle-stimulating hormone. GnRH=gonadotropin-releasing hormone. SHBG=sex hormone binding globulin. GH=growth hormone. IGF-1=insulin-like growth factor 1. TSH=thyroid-stimulating hormone. FT₄=free thyroxine (T₄). FT₃=free tri-iodothyronine (T₃). PTH=parathyroid hormone.

disease. In contrast, older individuals with subclinical hypothyroidism or higher TSH concentrations within the normal range have a lower mortality than do euthyroid individuals or people with lower TSH concentrations.^{20–22} Although subclinical hypothyroidism in younger individuals (aged <65 years) is associated with increased risk of atherosclerosis, in older patients with TSH concentrations of up to 10 mIU/L such an association is not present.²³ However, data from another meta-analysis showed that individuals aged 65–79 years with a TSH concentration above 10 mIU/L also have a greater risk of coronary heart disease, whereas this risk was not increased for those older than 80 years.²⁴ Therefore, the higher risks found in younger individuals seem to attenuate with advancing age. Higher TSH concentrations within the reference range appear to even decrease the risk of stroke.²⁵

These findings suggest that slightly lower hypothalamic–pituitary–thyroid axis activity is beneficial during the ageing process. This hypothesis is also supported by a series of studies that link low thyroid hormone concentrations to reduced frailty.^{26,27} Among older populations, lower FT₄ concentrations were associated with higher physical function,^{11,28} whereas

lower TSH concentrations predict future disability.¹⁶ This potential adaptive mechanism could also be a hereditary phenotype that contributes to longevity, since the nonagenarian offspring of centenarians were shown to have higher circulating TSH and lower thyroid hormone concentrations than did the offspring of parents who died at younger ages.²⁹

In conclusion, the ageing process modulates the concentration of thyroid hormones. These alterations are highly variable among individuals, but overall thyroid hormone axis activity seems to decline with age, and this decline in activity is reflected by an increase in TSH and a decrease in T₃ concentrations. However, these age-associated changes are not related to a detrimental ageing process, and might even be beneficial. Therefore, age-specific hormone reference ranges are useful to avoid misclassifying and overtreating older people, although so far, these age-specific thyroid function reference ranges are still lacking.

Somatotropic axis

The hypothalamic–pituitary–somatotrophic axis is a hypothalamic–pituitary axis that includes the secretion of growth hormone (somatotropin) from the somatotropes

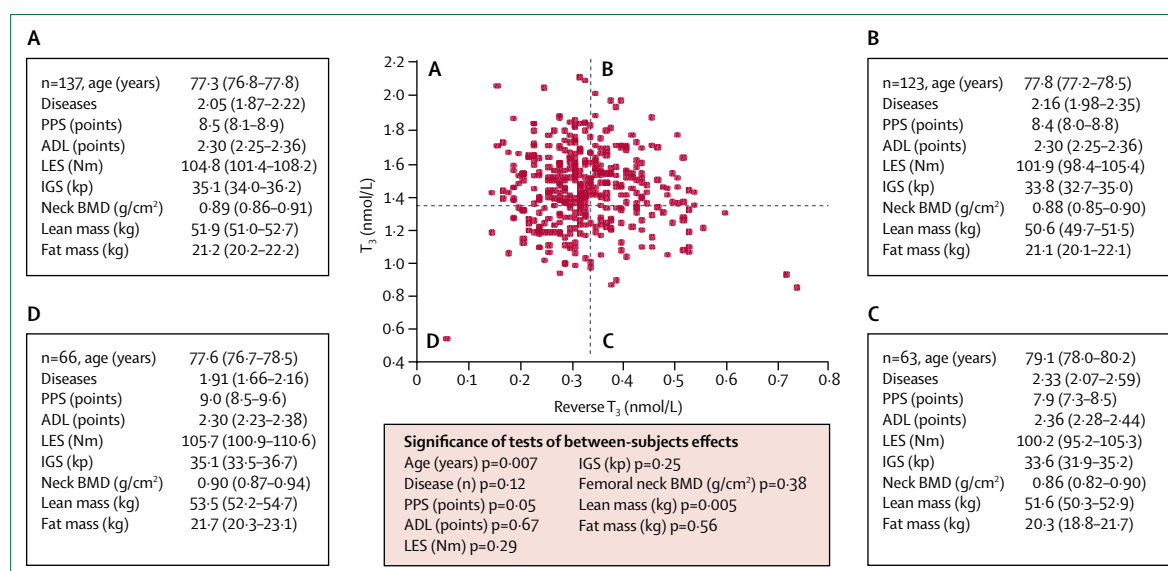


Figure 2: Concentrations of T_3 and rT_3 within a population of 403 elderly men

Each datapoint represents one of a cohort of 403 men aged 73–94 years living in the Netherlands.¹¹ The dotted lines indicate the normal concentrations of T_3 and rT_3 . Number of participants, mean age, mean number of diseases, and mean values for various other measures of physical performance are provided for each quadrant, with accompanying 95% CIs. T_3 =tri-iodothyronine. rT_3 =reverse T_3 . PPS=physical performance score. ADL=activities of daily living. LES=leg extensor strength. IGS=isometric grip strength. BMD=bone mineral density. kp=kilopond. NM=physical unit measure (maximum strength in newtons \times the distance of the dynamometer of the knee in m). Reproduced from van den Beld and colleagues,¹¹ by permission of Oxford University Press.

of the pituitary gland into the circulation, and the subsequent stimulation of insulin-like growth factor-1 (IGF-1). The somatopause is a gradual and progressive decrease in growth hormone secretion that occurs normally with increasing age during adult life, and is associated with an increase in adipose tissue. This decline in growth hormone after puberty continues during adult life and ageing, and consequently plasma growth hormone concentrations, and therefore IGF-1 concentrations, in older individuals are lower than in young adults. Age-related decline in growth hormone concentrations is well documented, consistent across different mammalian species, and primarily due to the reduced hypothalamic secretion of growth hormone-releasing hormone, causing the decline of growth hormone biosynthesis and release by the anterior pituitary.^{30,31} Overall, the age-dependent decrease in IGF-1 concentrations are not accompanied by elevated growth hormone concentrations, which suggests that the changes are not caused by age-dependent growth hormone resistance in the liver.³² Although the age-related decline in the activity of the growth hormone–IGF-1 axis is considered to contribute to age-related changes that are similar to those observed in growth hormone-deficient adults, growth hormone–IGF-1 deficiency or resistance is also known to result in prolonged life expectancy, at least in animals.^{33–35} These data raise the question of whether or not growth hormone deficiency constitutes a beneficial adaptation to ageing, and therefore requires no therapy. Moreover, although growth hormone therapy has been shown to exert

positive effects on growth hormone-deficient patients, its safety, efficacy, and role in healthy older individuals is highly controversial.³² Several mutations that decrease growth hormone–IGF-1 signalling are associated with extended longevity in mice.³⁵ In human beings, corresponding or similar mutations have been identified, but whether these mutations alter longevity has not been established.³⁵

Research focused on investigating brain structure and function in patients with Laron syndrome, the best characterised congenital IGF-1 deficiency, suggests that, compared with controls, older patients with Laron syndrome have brain structure and function that are consistent with those of younger adults.³³ Further investigation could lead to an improved understanding of the mechanisms underlying these differences in brain structure and function, and could contribute to the identification of treatments for age-related cognitive deficits. This observation raises the possibility that growth hormone receptor inhibition has the potential to protect against age-dependent cognitive decline.³³

In conclusion, ageing and the so-called somatopause are accompanied by a decrease in the concentrations of growth hormone and IGF-1, but no single intervention has been proven to be effective at halting or reversing somatopause.

Control of appetite and food intake

Appetite and food intake decrease with normal ageing, predisposing older individuals to become undernourished. Undernutrition is common in older people

(aged >65 years), and has been implicated in the progression of chronic diseases commonly affecting older people, as well as increasing mortality.³⁶ Understanding the factors that contribute to the decline in food intake in older people might result in effective prevention and treatment.³⁷ Ageing affects many of the endocrine factors involved in the control of appetite and feeding, but few studies have been done in human beings to clarify these changes. Possible hormonal causes of the anorexia of ageing include increased activity of cholecystokinin, leptin, and various cytokines, and reduced activity of ghrelin.³⁷

As early as 1999, MacIntosh and co-workers³⁸ reported that human ageing is associated with increased cholecystokinin concentrations. Intravenous cholecystokinin-8 infusion produces greater suppression of food intake in older adults than in younger individuals, indicating that sensitivity to the satiating effects of cholecystokinin is at least maintained with age, and might even increase. These results raise the possibility of using cholecystokinin antagonists as stimulants of appetite and food intake in malnourished older people.³⁷ Central leptin resistance can increase with age, and low concentrations of circulating leptin have been observed among frail older people.³⁹

In conclusion, ageing is accompanied by changes in ghrelin, cholecystokinin, and leptin physiology. All these changes seem to result in a significant and clinically relevant decrease in appetite. Future research will determine whether these changes can be corrected by pharmacological interventions.

Adrenal axis

Glucocorticoids

Ageing of the hypothalamic–pituitary–adrenal axis is generally associated with late-day and evening increases in cortisol concentrations, an earlier morning cortisol concentration peak, lower circadian cortisol amplitudes, and more irregular cortisol secretion patterns.^{40–43} Most studies, but not all, show that glucocorticoid feedback inhibition after intravenous or oral administration of glucocorticoids is reduced in older individuals.⁴⁰ Similarly to the other hypothalamic–pituitary axes, whether these changes in cortisol secretion patterns are due to ageing per se, or whether these instead reflect other effects such as the presence of low-grade inflammation, impaired sleep, or changes in social or emotional status associated with ageing, remains unclear.

The changes in the hypothalamic–pituitary–adrenal axis that occur during ageing can have clinical implications. Previous studies have shown that a more dynamic activity of the axis (ie, a greater diurnal decline) relates to better physical performance⁴⁴ and cognitive function in older adults than does a lower activity.⁴⁵ Additionally, urinary free cortisol concentrations in the high-to-normal range are associated with an increased risk of Alzheimer's disease.⁴⁶ Further, independent of disease, higher morning

salivary cortisol concentrations in men and higher night salivary cortisol concentrations in women are associated with increased all-cause 6 to 7·5-year mortality.⁴⁷

Ageing can also influence tissue cortisol availability, since 11- β hydroxysteroid dehydrogenase activity, which transforms inactive cortisone into active cortisol, increases during ageing (eg, in the skin).⁴⁸ This increase in cortisol availability leads to increased local glucocorticoid generation, which can cause adverse changes in older people. In muscle, for example, higher 11- β hydroxysteroid dehydrogenase activity is associated with reduced muscle strength.⁴⁹

Dehydroepiandrosterone and its sulphate

Not only does cortisol homeostasis change with age, but also adrenal secretion of the steroid precursor dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) gradually decrease over time.^{50,51} By the time a person reaches age 70–80 years, concentrations of DHEAS are approximately 20% of peak values in men, and 30% of peak values in women, compared with people who are younger than 40 years.⁵² DHEA and DHEAS are inactive precursors that are converted into androgens and oestrogens in peripheral tissue. In older men, this source of androgens is important since less than 50% of these hormones are of testicular origin. Higher concentrations of DHEA and DHEAS have been associated with psychological wellbeing and improved physical functioning, including muscle strength and bone density, and with anti-inflammatory and immunoregulatory actions.⁵³ Lower DHEAS concentrations have been associated with an increased risk of cardiovascular events and cardiovascular related mortality in people older than 50 years.⁵³ Although the administration of 50 mg of prasterone (ie, DHEA) per day to older individuals increases DHEAS, free and total testosterone, oestrone, oestradiol, and IGF-1 concentrations,⁵⁴ this treatment has little reproducible beneficial effects on measures such as sexual function, bone density, serum lipids, or glucose concentrations.⁵⁵

In conclusion, changes occur in cortisol secretion patterns during ageing. The question remains whether these alterations reflect or cause ageing-associated changes in functional ability, cognition, and mood. DHEA concentrations decrease substantially during ageing, but few data point to a clinical significance of this decrease.

Gonadal axis

Ageing of the female reproductive system

Ageing of the reproductive system in women and the accompanying hormonal changes are driven by the accelerated depletion of the ovarian pool of primordial follicles, with lower oocyte quality in the remaining follicles contributing to decreased fertility from the fourth decade of life onwards.⁵⁶ The decreasing number of follicle-stimulating hormone (FSH)-sensitive antral

follicles, which is proportional to the reduced reserve of primordial follicles, is reflected in the declining serum concentrations of granulosa cell-secreted anti-Müllerian hormone (a marker of ovarian reserve produced in primary, secondary, and early antral follicles), and inhibin B (a marker of ovarian activity, produced predominantly in developing antral follicles during the follicular phase of the menstrual cycle).^{57–59} The rapid shrinking of the ovarian reserve during reproductive life remains long unnoticed with the preservation of regular, mostly ovulatory cycles. Finally, when follicle availability becomes insufficient, cycle irregularity (>7 days longer than their previous cycles) occurs, which signals the onset of the early phase of menopausal transition, at a mean age of 46 years (range 34–54). The lengthening of cycle duration (ie, delayed dominant follicle growth or anovulatory bleeding), missed periods, and prolonged (≥ 60 days) intervals of amenorrhoea signal the passage to the late menopausal transition phase, ending with near total exhaustion of the ovarian follicles and the final menstrual period (after 12 months of amenorrhoea retrospectively identified as menopause) around age 51 years (range 40–60). The age at which these successive events occur varies considerably, and is influenced by body composition, ethnicity, genetics, and lifestyle-related factors.⁵⁶

As menopausal transition progresses, cycles are more often anovulatory. Conversely, in ovulatory cycles, luteal phase duration and hormone concentrations remain stable throughout reproductive life and menopausal transition, with the exception of slowly declining mean progesterone concentrations. Changes in gonadotropin secretion throughout menopausal transition and after menopause, characterised by increased luteinising hormone (LH) and FSH pulse amplitude and loss of pre-ovulatory gonadotropin surges, are caused by altered feedback resulting from the intrinsically determined ovarian decline in sex steroids, inhibin A, and inhibin B production.^{57,58,60} The existence of direct age-related neuroendocrine changes, as revealed by the progressive decline of gonadotropin concentrations with advancing age after menopause, appears to be less physiologically relevant than the intrinsic ovarian changes.^{56,61} Throughout reproductive life and menopausal transition, there is an age-related decreasing trend of adrenal production of DHEA and DHEAS, and of mixed adrenal and ovarian production of testosterone and androstenedione. However, the LH-stimulated theca cells in the postmenopausal ovaries still contribute to circulating testosterone concentrations for up to 10 years.^{62,63} The multi-organ clinical consequences of the hormonal changes that occur during menopausal transition and after menopause, such as altered vasomotor regulation, bone metabolism, or urogenital status, result primarily from changes in oestrogen production. In this regard, the concentration of late postmenopausal oestrogens originating from androgen aromatisation in the

peripheral tissues, although generally low compared with their concentration during the reproductive period, is still of clinical significance, as illustrated by their association with clinical correlates such as bone fractures and breast cancer, and by the occurrence of vasomotor and articular symptoms, and the increased fracture risk during pharmacological aromatase inhibition in postmenopausal women.⁶⁴

Oestrogen replacement therapy can effectively inhibit the undesirable effects of menopause, such as hot flushes, accelerated bone loss, and vaginal dryness. However, the long-term risk–benefit balance remains to be determined.⁶⁵

Ageing of the male reproductive system

Since many men have a well preserved sex hormone production and fertility until old age, men do not undergo an equivalent of the menopause. Nevertheless, ageing does affect the male reproductive system.^{66,67} Testicular volume in men older than 75 years is decreased by 30%, and the number of Sertoli cells is reduced, as reflected by a modest increase in FSH concentrations and a decrease in the ratio of serum inhibin B to FSH.⁶⁸ Changes in sperm quality are limited to a modest decrease in ejaculate volume and suboptimal spermatozoa motility and morphology; an increase in DNA damage also contributes to the age-related decrease in fertility.^{67,69} However, although these changes are attributed to ageing, they might be confounded by other factors, including increased intervals between ejaculations and health-related factors, such as obesity.

In healthy ageing men, a slow and progressive decline in morning serum testosterone concentrations of 25% takes place between age 25 and 75 years, and this is a net effect of a decreased testosterone production that is not fully compensated by reduced metabolic clearance. Additionally, sex hormone-binding globulin (SHBG) concentrations increase by about 1% per year, which causes the concentration of testosterone that is not bound to SHBG, in particular the approximately 2% of biologically active free testosterone, to more rapidly decline than total testosterone serum concentrations by approximately 50% between the ages of 25 and 75 years (figure 3).^{67,70} Normal serum (free) testosterone circadian rhythmicity, which includes higher concentrations of testosterone in the morning, is blunted. The concentration of free and total testosterone varies greatly between individuals, although approximately 20% of men aged 65 years or older have testosterone concentrations below the normal range for young men; this proportion increases with advancing age, and is greater for free testosterone than for total testosterone.^{66,67}

Other male hormone concentrations also decrease with age, including total and free serum dihydrotestosterone concentrations (20% of which is produced in the testes, and 80% of which is converted from testosterone by

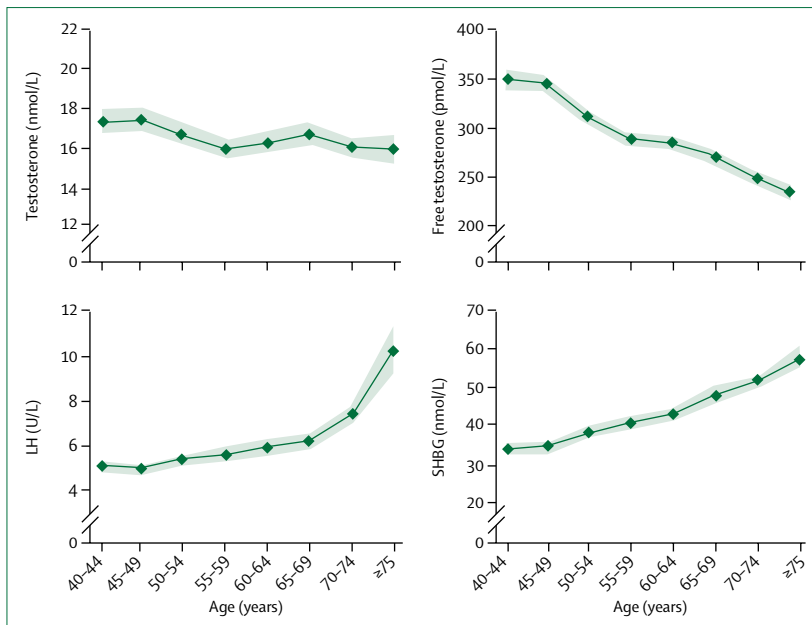


Figure 3: Relationship between age and hormones

Mean hormone concentrations (datapoints) with 95% CIs (shaded area) are presented in 5 year age bands for a cohort of 3220 men living in Europe.⁷⁰ Mean hormone concentrations with increasing age were interpolated to approximate the age trend. Total testosterone and free testosterone were significantly lower ($p < 0.001$), and the concentrations of LH and SHBG were significantly higher ($p < 0.001$) in the older age groups. The concentration of LH increased substantially at around age 70 years. Reproduced from Wu and colleagues,⁷⁰ by permission of Oxford University Press. LH=luteinising hormone. SHBG=sex hormone-binding globulin.

5 α -reductase type 2 in the peripheral tissues), and serum testosterone precursor androstenedione (produced both in the testes and adrenal glands).⁶⁶ Further, excretion of the urinary metabolite androstenediol glucuronide (70% of which is converted from testosterone, and 30% of which is converted from DHEAS) is also decreased. However, serum concentrations of oestradiol, produced by the aromatisation of testosterone and androstenedione in peripheral tissues such as fat and striated muscles, do not decrease with ageing, although serum free oestradiol concentrations might decrease.^{66,71}

Different mechanisms contribute to the decline in serum free and total testosterone concentrations, including a progressive, although small, increase in LH and FSH concentrations, a diminished testosterone response to exogenous LH and human chorionic gonadotropin, and a reduced number of Leydig cells, all of which point towards primary testicular changes. The inadequate increase in LH concentrations in response to the reduction in free and total testosterone in many older men reveals additional changes in gonadotropin secretion, characterised by the decreased frequency of larger amplitude LH pulses, presumably resulting from the decreased hypothalamic secretion of gonadotropin-releasing hormone, since the pituitary response to exogenous gonadotropin-releasing hormone is preserved. The independent increase of hepatic SHBG production is a third factor, and is possibly the

consequence of declining somatotrophic axis activity.^{66,67} Additionally, adiposity has major confounding effects, because being overweight (BMI 25–29 kg/m²) is associated primarily with lower SHBG and total serum testosterone concentrations than is being a healthy weight, and in obesity (BMI ≥ 30 kg/m²) both total and free testosterone concentrations are decreased as a result of additional hypothalamic dysfunction.⁷⁰

The relative contribution of ageing and both clinical and subclinical comorbidities to the changes in reproductive hormones in older men remains a matter of debate.^{66,70} Although many clinical features of ageing in older men are reminiscent of hypogonadism in young men, their association with sex steroid concentrations are mostly weak, with causality being difficult to demonstrate. Moreover, clinical changes may in part be the cause rather than the consequence of changed sex steroid levels;^{66,67} low testosterone in older people is a marker of poor health, and has been linked to an increased risk of death.^{70,72} Sexual dysfunction is consistently associated with low serum testosterone, and even more closely associated with low serum free testosterone. The cutoff levels for the occurrence of symptoms, such as decreased libido and erectile dysfunction, are located at the lower limit of the normal range of young men—ie, total testosterone concentrations below 320 ng/dL (11 nmol/L), and free testosterone concentrations below 6.4 ng/dL (0.22 nmol/L).^{66,73} Of increasingly recognised importance is the role of testosterone as a precursor for oestradiol, which has important physiological effects in men, such as effects on bone homeostasis.⁷⁴ The reported beneficial effects of testosterone treatment on muscle, bone, sexual function, and wellbeing are essentially limited to older men who initially had low testosterone concentrations. However, these benefits appear to be modest, and long-term data on issues of concern such as prostate and cardiovascular safety are scarce. Therefore, testosterone administration to older men is controversial outside the context of an established organic cause of hypogonadism.^{73,75}

Calcium and bone homeostasis

Advancing age represents a major risk factor for low bone mass and strength and a decline in muscle mass and function, leading to an increased risk of falls and fractures. Osteoporosis is caused by an imbalance between bone-forming osteoblasts and bone-resorbing osteoclasts, the processes of which are normally coupled and influenced by signals from osteocytes, which are embedded in mineralised bone and function as sensors of mechanical loading.⁷⁶ Traditionally, oestrogen deficiency at menopause or loss of both oestrogens and androgens in older men are considered to be the main endocrine factors contributing to the development of osteoporosis. Increasing evidence now suggests, especially from studies in rodents, that fundamental intracellular processes in the bone, such as

increased oxidative stress, cell senescence, inflammation, osteocyte apoptosis, DNA damage, formation of advanced glycation end products, and a decrease in autophagy, mitochondria biogenesis, vascularity, hydration of bone, and alterations in musculoskeletal progenitor cells also play important roles in the development of osteoporosis and fragility fractures with ageing.^{77–79}

These age-related intrinsic mechanisms are coupled with changes in endocrine systems during ageing, and a higher incidence of endocrine diseases with age, including type 2 diabetes. We focus here on the major endocrine changes influencing bone.

Sex steroids

Oestrogens and androgens play important roles in the growth and maintenance of tissue mass and function in bones and muscles. Their actions on the bone result predominantly from the binding of ligands to classic sex steroid receptors, including the oestrogen receptor α and β and the androgen receptor.⁷⁴ For detailed information about the molecular and cellular mechanisms of action of oestrogens and androgens on bone and the contribution of oestrogen or androgen deficiency, we refer to a comprehensive review.⁸⁰ The imbalance between bone formation and resorption with oestrogen deficiency affects both trabecular bone, with loss of connectivity, and cortical bone, with cortical thinning and porosity. An increase in osteocyte apoptosis occurs following the loss of ovarian or testicular function, which is mainly due to an increase in oxidative stress.⁷⁷ Sex steroid deficiency could contribute to age-related bone loss, at least in part, by increasing oxidative stress and influencing the immune system. Additionally, hypogonadism is associated with the increased formation of advanced glycation end products and inflammation, thus contributing to intrinsic causes of osteoporosis that occur with ageing. In women, the potential roles of changes in progesterone, androgen, inhibins, and FSH concentrations in enhancing the effects of oestrogen deficiency on bone loss during the perimenopausal period remain to be further defined.⁸¹ In older men, oestrogen is the dominant sex steroid regulating bone resorption, and both oestrogen and testosterone are important for the maintenance of bone formation.⁸² In men, low serum oestradiol predicted incident fractures, but the highest risk occurred in men with additionally low testosterone and high SHBG concentrations.⁸³

Sex steroids are also considered to be important in the changes in calcium and phosphate homeostasis that occur with ageing. Postmenopausal women have higher serum phosphate concentrations than men of similar ages, and some studies have found higher serum calcium concentrations in older women than in older men, suggesting a sexual dimorphism in calcium and phosphate homeostasis after menopause, and a potential association with sex hormone concentrations. Oestrogen has been shown to induce renal phosphate wasting and

hypophosphataemia,⁸⁴ to reduce renal calcium excretion, and to increase intestinal calcium absorption.⁸⁵

Glucocorticoids

Osteoporosis and fractures are important side-effects of the use or an excess of glucocorticoids, and are caused by effects of glucocorticoids on bone and muscle strength.⁸⁶ The generation of systemic and locally produced glucocorticoids and the sensitivity of bone cells to glucocorticoids increase with age.⁸⁷ Glucocorticoids are strong inhibitors of bone formation that function, at least in part, by stimulating osteoblast and osteocyte apoptosis,⁸⁸ and by suppressing the generation of new osteoblasts through the attenuation of Wnt signalling. They also increase bone resorption by promoting osteoclast survival. These combined effects can contribute to the age-related decline in bone mineral density, cortical porosity, and bone strength, and the increase in fractures.⁸⁷

Vitamin D, parathyroid hormone, fibroblast growth factor 23, and Klotho

Vitamin D and its metabolites and parathyroid hormone are crucial parts of the endocrine system that control whole body calcium and phosphate homeostasis.⁸⁹ Serum vitamin D concentrations are well known to decrease with age, which can result in decreased intestinal calcium absorption and the development of secondary hyperparathyroidism.⁹⁰ Circulating parathyroid hormone concentrations also appear to increase with age, independent of 25-hydroxyvitamin D, ionised calcium, phosphate, and renal function.⁹¹ Primary hyperparathyroidism, a disease most prevalent in postmenopausal women, is a well known cause of decreased bone mineral density and fractures, and is more prominent at sites with cortical bone. Secondary hyperparathyroidism can also increase fracture risk,⁹⁰ as does the decline in kidney function that occurs with ageing. A previous study showed that older men and women, even without overt kidney disease, have an increased fracture risk with increasing serum phosphate concentrations, even when these are within the normal range, and independently of bone mineral density.⁹² Whether this increased fracture risk is directly related to serum phosphate concentration or to underlying changes in phosphate-regulating hormones, such as osteocyte-derived FGF23, α -Klotho, parathyroid hormone, or 1,25-hydroxyvitamin D, remains unknown. FGF23 is a hormone secreted by osteocytes in the bone, which together with its co-factor α -Klotho inhibits phosphate reabsorption and 1,25-hydroxyvitamin D production in the kidney. Defects in either α -Klotho or FGF23 gene expression cause phosphate retention and premature ageing syndrome in mice. FGF23 already begins to increase during the early stages of chronic kidney disease in response to decreased phosphate excretion, but other age-related changes in this

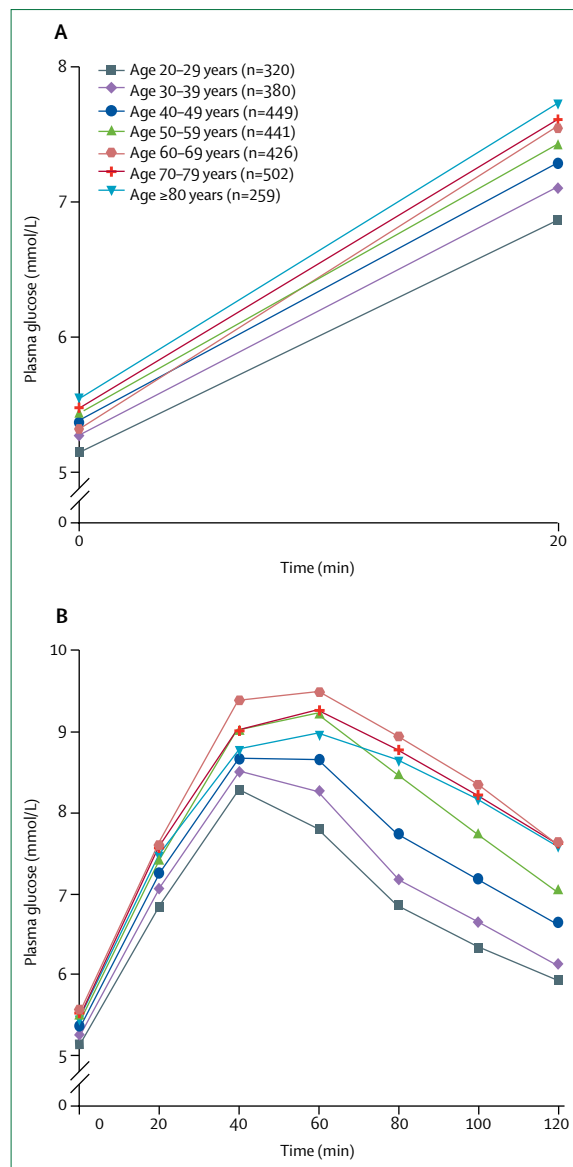


Figure 4: Concentrations of fasting plasma glucose and plasma glucose after oral glucose administration over time in non-diabetic individuals. The concentrations of fasting plasma glucose (A) and plasma glucose (B) after the administration of 75 g oral glucose (oral glucose tolerance test) were measured over time in non-diabetic individuals. Data are means from the Baltimore Longitudinal Study of Aging (BLSA), from participants aged 20–89 years who were receiving no anti-hyperglycaemic medications. Oral glucose tolerance tests were done in all individuals at their first visit to the BLSA. The individuals presenting for their first visit were healthy with no known active disease, and were therefore not representative of the general population. Josephine M Egan, unpublished data.

bone–kidney endocrine system have not been well studied in human beings.⁹³

Growth hormone and IGF-1

Growth hormone and its downstream mediator, IGF-1, are major determinants of peak bone mass. Declining concentrations of growth hormone and IGF-1 during

ageing are associated with bone loss. Between the ages of 20 and 60 years, the IGF-1 content in human bones declines by 60%.⁹⁴ A decline in IGF-1 and IGF-binding protein-3 content in the bone matrix is associated with an age-related decrease in bone mineral density, and a risk of hip fractures.⁹⁵

Hormone replacement therapy has been shown to decrease bone loss and fracture risk in women, but the increased risk of breast cancer and cardiovascular disease reported in the Women's Health Initiative study⁹⁶ has resulted in a substantial decrease in its use. The risks of side-effects appear to depend on many factors, such as type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used, which has led to recommendations on individualised therapy.⁹⁷ No large randomised controlled trials have been done to investigate the effect of growth hormone-increasing therapies or testosterone supplementation on fracture rates in men.

Glucose homeostasis

Glucose homeostasis is maintained by a balance between glucose ingestion, utilisation, and production, and is under tight hormonal control by insulin. Glucose homeostasis tends towards disequilibrium with increasing chronological age.^{98,99} Fasting plasma glucose rises by approximately 0.055 mmol/L per decade, beginning as early as the fourth decade of life, and glucose concentrations 2 h after a 75 g oral glucose tolerance test also gradually increase (Egan JM, unpublished; figure 4). No data have been shown to support alterations in glucose ingestion with age. Another important consideration is that impairment of cerebral glucose metabolism might precede histological findings in Alzheimer's disease, and probably exacerbates its pathology.

Reduced pulsatility and decreased insulin action

Insulin is secreted in a pulsatile manner comprising two stereotypical pulses: high frequency pulses with a pulse interval of about 6 min, and ultradian pulses with a pulse interval of approximately 90 min.^{100–102} Pulsatile secretion accounts for at least 70% of secreted insulin.¹⁰³ Total and pulsatile insulin secretion is abnormal in people with type 2 diabetes, being both deficient and chaotic.¹⁰⁴ However, even healthy older individuals have disordered insulin secretion with a characteristic reduction in both amplitude and number of high frequency pulses, and a reduced frequency of ultradian pulses in both the basal and stimulated state.^{105,106}

The liver is exposed to insulin pulses from the islets directly through the portal vein. Insulin is subject to degradation during first pass, thereby dampening the amplitude of the pulses arriving at peripheral tissues. Insulin receptor trafficking upon activation is dynamic, and dephosphorylated insulin receptor is recycled to the cell surface, a process that is synchronous with

the pulsatility of insulin secretion.¹⁰⁷ Consequently, insulin is less effective in suppressing hepatic glucose production when it is delivered to the liver in a disordered manner than when delivered normally. Additionally, insulin clearance in the liver is said to be increased in older people.¹⁰⁸

Effect of age on glucose disposal

Whether ageing is responsible for the gradual deterioration in glucose disposal across the human lifespan (figure 4B) is a matter of ongoing debate because of confounding physical changes that occur in the body over time. In humans beings, the majority of the glucose in an oral glucose load is disposed into muscle, glucose concentrations after glucose ingestion gradually rise with age (figure 4), and glucose disposal becomes slower over the course of a lifetime. Studies using hyperglycaemic clamps show that this slowing in glucose disposal is probably not due to diminished total insulin secretion in response to the rising glucose.¹⁰⁹

The progressive decline in insulin action with age can be attributed largely to gradual increases in the percentage of total body, especially visceral, fat, and to the changing ratio of fat to lean muscle mass. The degree of relative obesity and the site of fat deposition appear to be the crucial variables determining the efficacy of insulin action.^{110,111} These factors are in turn influenced by total caloric intake, decreasing physical activity, medications, and illnesses.¹¹² However, although exercise improves insulin action and slows the onset of diabetes, no evidence shows that exercise reverses age-related changes occurring in β cells.

Diabetes in older people

There is a continuum of risk for the development of diabetes, coupled with underlying genetic and environmental factors unique to each individual, although the risk of developing diabetes seems to reach a plateau or even decline after age 85 years.¹¹³ In older people, β -cell dysfunction and deficiency play a greater role in the pathophysiology of diabetes than in younger adults, and insulin resistance in muscle increases even in the absence of obesity in some individuals.^{114,115} The prevalence of diabetes varies depending on the criteria used. At least 25% of people older than 65 years have diabetes,^{116,117} which can be detected only on the basis of a 2 h oral glucose tolerance test (≥ 11.1 mmol/L) in 58% of people.^{118,119} However, an oral glucose tolerance test is not the standard recommendation for diabetes screening. HbA_{1c} concentration testing, which is recommended due to ease of testing (12 h fasting not required), can detect 14.5% of undiagnosed cases ($\geq 6.5\%$ [48 mmol/mol]),¹²⁰ but the addition of fasting plasma glucose concentration (≥ 7 mmol/L) testing to HbA_{1c} increases detection to 42% of undiagnosed cases. Therefore, even when using both HbA_{1c} and fasting plasma glucose to diagnose diabetes, the majority of people with diabetes who are aged

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase from their inception up until Nov 14, 2017. We used the search terms “pituitary”, “thyroid”, “adrenal”, “growth hormone”, “IGF-I”, “receptor sensitivity”, “testosterone”, “oestradiol”, “glucose”, and “insulin” in combination with the term “aging”. Additionally, we used the terms “osteoporosis” or “skeletal aging” or “bone-aging” in combination with the terms “endocrinology” or “hormones”. The search was restricted to articles that were published in English. We largely selected publications from the past 5 years, but also included commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. We have cited review articles to provide readers with more details and references than this paper has room for. Our reference list was modified on the basis of comments from peer reviewers.

65 years and older will remain undiagnosed. The low detection in older people with these easily available diagnostic tests mean that the prevention of diabetes progression and complications due to glucose disequilibrium is often delayed. Additionally, because the pathophysiology of diabetes can be different in younger patients compared with those who are older—eg, severe insulin resistance with obesity can be a more prominent factor in younger patients—increased attention to treatment individualisation is required given the heterogeneity of the older population and their underlying conditions. Most clinicians would agree that healthy older people, similarly to younger people, should have diabetes screening, and if prediabetes is uncovered, lifestyle intervention tailored to the patient could prevent the development of diabetes with its accompanying microvascular and macrovascular complications, given the presumed increased in life expectancy for all populations.¹²¹ Similar screening would not apply to someone with severe functional limitations or Alzheimer’s disease.

Conclusions

Changes in the activities of various endocrine systems occur during ageing, including altered hormonal secretory patterns and modulation of feedback sensitivity, summarised in figure 1. These physiological changes should be considered when interpreting hormone concentrations in older individuals with and without endocrine disease. However, the magnitude of these changes varies considerably between individuals, and reference values for hormone concentrations at older ages should be established. Differentiating whether these changes are due to the ageing process, or whether they are related to other processes, such as intercurrent chronic diseases, inflammation, nutritional status, or a combination of these, is difficult. The effect

of these age-related changes on body composition, physical function, emotional wellbeing, morbidity, and finally mortality is only partly known. Some of the changes could be a beneficial adaptation to ageing, whereas others are not. Future studies should aim to explore whether endocrine alterations are maladaptive or adaptive to ageing.

Contributors

AWvdB contributed to the abstract, introduction, sections on the thyroid axis and the adrenal axis, and conclusion. J-MK contributed to the gonadal axis section. MCZ contributed to the section on bone and calcium homeostasis. SWJL contributed to the abstract, introduction, and conclusion, and revised the manuscript. JME contributed to the section on glucose homeostasis. AJvdL contributed to the section on the somatotrophic axis.

Declaration of interests

We declare no competing interests.

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