UNIT NO. 1

MALE AGING

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PREVIEW

This unit covers the pathophysiology of aging, endocrinology of the aging male and rational approach to endocrine replacement in the aging male.

OBJECTIVES

At the end of this unit, the course participants should be able to describe the following:

1. Pathophysiology of aging including the basic theories of aging
2. Endocrinology of the aging male including the physiology of age-related decline in various hormones in the aging male
3. Rational approach to endocrine replacement in the aging male.

1. PATHOPHYSIOLOGY OF AGING

1.1 Why focus on aging?

Over the past few decades, aging has become a major health and policy issue throughout the world because of a rapid growth in the population of people aged 65 years and above. Humans had an average life expectation at birth of 30 years or less for more than 99.9% of the time that they have inhabited the planet. However, this has been steadily increasing over the past 4 decades and now stands between 70–80 years. The average life expectancy in Singapore has increased from 66 years in 1970 to 78 years in 1999. In 1999, 0.5% of the resident population (around 16,000 residents) in Singapore was aged 85 years and above, which is expected to increase to 0.8% in 2020 (33,600 residents), representing an average annual growth of 3.6% per annum. Thus, with this sudden increase in human longevity, research and an understanding of the meaning of 'old age', its basic causes and mechanisms and its potential consequences is increasingly becoming a social, economic and scientific challenge.

1.2 Definitions of aging

Aging is a complex process that is not well understood and difficult to define. Biologists consider aging to be a continuous process that starts at conception and continues until death. Others regard it as a degenerative process, causing progressive loss in function and an increase in risk of death. Still others define it as a failure to maintain homeostasis under conditions of physiological stress, leading to decreased viability and increased vulnerability of the individual.

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There are two fundamental parameters of aging:

1. Maximum life span: Represents the longest-lived member(s) of the population. The maximum life span potential has remained approximately constant for humans at around 90 – 100 years. Only a few reach 100 years and no human being has been recorded to live beyond 122 years.

2. Average life span: Also known as life expectancy. This is represented by the age at which 50% of a given population survives.

The two most popular definitions of aging are:

i) Chronological age

This is the most popular method of defining age. It is defined as the passage of time from birth onwards and is easy to measure.

ii) Biological age

This definition is based on the presence or absence of pathological processes and is thus a disease-oriented approach. Biological age is a more potent indicator of health status than chronological age.

1.3 Theories of aging

The remarkable process of aging remains a mystery to date and explains the existence of a large number of theories of aging. These theories can be classified as aging due to intrinsic causes (developmental-genetic) or due to extrinsic causes (stochastic). The theories of aging could also be classified as:

1.31 Cellular theories of aging

1.31a Programmed cell death

In culture, normal diploid cells exhibit a finite number of population doublings. This theory suggests that an in-built cellular clock controls the aging process.

1.31b Waste product theory

With age, many cell systems accumulate the pigment lipofuscin. However, the exact role and mechanism by which lipofuscin can lead to cellular aging remains unclear.

1.31c Cross linkage theory

With time, irreversible covalent bonds form between macromolecules in cells, including DNA molecules, collagen and elastin fibres, leading to cellular dysfunction.

1.32 Organ based theories of aging

1.32a Immune theories of aging

With advancing age, there is a decline in both cell-mediated and humoral immunity and increase in auto-antibody production. Immunological efficiency decreases, leading to an increased incidence of illnesses.

1.32b Calorie restriction

The influence of diet on aging forms the basis of the 'rate-of-

living' theory, which states that longevity is inversely proportional to metabolic rate. It has been shown that calorie restriction increases life span in yeasts, worms, fireflies and rodents.

1.32c Neuro-endocrine theories of aging

A number of hormones decline with aging, prominent among them being growth hormone (GH), dehydroepiandrosterone (DHEA) and its sulphate (DHEAS) and estrogen in women and testosterone in men. It has been suggested that this decline leads to aging.

1.33 Genetic theories of aging

1.33a Programmed theories of aging

These theories propose that aging is the result of a pre-written programme that leads to the development of an organism to a fertile adult, which is followed by a decline in reproductive capability and then senescence. These include:

Modifier genes: This theory proposes that there exist a group of genes that suppress any deleterious effects of the genome until the achievement of reproductive potential. Thereafter, such genes are no longer required and senescence is thus allowed to occur.

Pleiotropic genes: This theory proposes that genes that are beneficial in early life become harmful later in the lifespan. This idea of a trade-off between early life benefits at the cost of late life deleterious effects forms the basis of the 'disposable soma' theory.

Gene redundancy: According to this theory, aging could be considered as a prevailing loss of unique, non-repeated information from the genome.

1.33b Unprogrammed theories of aging

These theories suggest that environmental insults cause genetic damage and mutation, outpacing repair mechanisms, such that these random errors lead to accumulation of abnormal substances leading to cellular dysfunction and death.

Somatic mutation: Genetic damage from background radiation accumulates with time leading to cellular dysfunction and death.

DNA repair: This theory suggests that it is not the somatic mutations that determines aging, but the inability to repair such mutations.

Error catastrophe: This theory suggests that during protein synthesis, random errors occur leading eventually to accumulation of defective DNA and enzymes.

Free radicals: It is suggested that the free radicals, produced during normal aerobic metabolism, cause progressive accumulation of cellular damage, via damage to DNA, lipids and proteins.

Telomeres: Telomeres are short, non-coding repetitive DNA sequences found at both ends of chromosomes. With each division of the cell, there is gradual shortening of telomere length. Eventually the telomere is too short to permit further division thereby promoting senescence.

2. ENDOCRINOLOGY OF THE AGING MALE

In this section, age related changes in endocrine function are highlighted. The focus shall primarily be upon changes in the levels of serum testosterone, GH, IGF-1 and adrenal androgens.

However, clinically, the two most important changes in endocrine activity with aging are in the pancreas and the thyroid that leads to clinically defined disease states. Approximately 40% of individuals aged 65–74 years and 50% of those aged 80 years and above have impaired glucose tolerance or diabetes mellitus. Almost half of the elderly diabetics remain undiagnosed. Recognizing this fact, the Singapore Ministry of Health's Clinical Practice Guidelines on diabetes mellitus recommends screening of all individuals aged 40 years and above and if normal, to repeat the screening at minimum 3 yearly intervals.

Age-related thyroid dysfunction is common in the elderly. The prevalence of primary hypothyroidism is higher in elderly women, seen in 5–10% of them. Both hyperthyroidism and hypothyroidism are common in the elderly and can be missed because of paucity of symptoms and signs.

2.1 Decline in gonadal androgens with aging in men

In men, serum testosterone levels are high at birth and then drop to low levels in infancy to peak along with the onset of puberty. From third decade onwards, there is a steady decline in total serum testosterone levels at a rate of 0.5–1% per year. There is an age associated increase in Sex Hormone Binding Globulin (SHBG), resulting in relatively lower levels of free testosterone and bio-available testosterone (free testosterone + albumin bound testosterone). Overall, there is a decrease of approximately 35% of total testosterone and 50% of free testosterone levels between the ages of 20 to 80 years.

This steady and continuous decline is gradual, and unlike women, where the reduction in serum estrogen is rapid, elderly men do not present with acute symptoms. Serum testosterone values not only show considerable inter-individual variability but also get readily depressed in the presence of associated systemic illnesses and medications, often present in the elderly. Thus, the lower limit of cut-off below which elderly men could be defined hypogonadal remains unclear. If one were to use a total testosterone value of ı 325 ng/dL (11.3 nmol/L), the lower limit of normal in young men, then almost half of the healthy elderly men between the ages of 60–80 years will have total testosterone concentrations in the hypogonadal range.

Many investigators describe this gradual decline in serum testosterone levels with aging as a syndrome of partial androgen deficiency of aging males (PADAM) or "andropause". However, unlike menopause in women, men do not experience a rapid decline of gonadal function or irreversible arrest of reproductive capacity with aging and hence the term "andropause" is probably not appropriate.

2.2 Decline in adrenal androgens (DHEA and DHEAS) with aging in men

DHEA and DHEAS are the main androgens of adrenal origin. These hormones are at their highest levels at birth, decreasing to almost undetectable levels by the first year of life. The levels begin to rise approximately 2 years prior to the onset of puberty (adrenarche) to reach a peak at around the age of 20–30 years, followed by gradual decline at a rate of approximately 2% per year. At age 85, DHEAS levels are one-fifth that at age 30 years. Some authors have described this gradual decline in the levels of DHEA and DHEAS as 'adrenopause'. However, like testosterone, DHEA and DHEAS values show marked inter-individual variability and therefore it is difficult to define a lower cut off value for a deficiency state of these hormones.

2.3 Decline in GH – IGF1 axis with aging in men

There is a steady decline in the level of serum growth hormone with aging, a condition described by some as "somatopause". GH secretion peaks around the time of pubertal growth spurt and then declines steadily. After 40 years of age, GH production decreases gradually at a rate of approximately 14% per decade. GH concentrations relative to pre-pubertal years are 130–210% in late puberty, 60% in the third decade, 35–50% in the fourth to sixth decades and 25–40% in the seventh decade and thereafter.

This is associated with a decline in serum IGF1 levels, with serum IGF1 levels increasing two-three folds at puberty compared to pre-pubertal levels, falling to adult levels in the third decade and from then on progressively declining with advancing age.

2.4 Link between age-related hormonal decline and changes seen with aging

Aging in men is typically associated with a decrease in lean body mass including bone mass. This decrease is mostly a result of decrease in skeletal muscle mass, which decreases approximately by 35–40% between 20–80 years of age. There is also an increase in total amount of fat, especially visceral fat. Similar changes in body composition are also seen in young hypogonadal men and in adults with acquired severe organic growth hormone deficiency. Moreover, similar to older men, young androgen-deficient men report decrease in strength and vitality, decreased virility, libido and sexual activity, increased erectile dysfunction and general decrease in well-being.

These similarities have led to the speculation that changes in body composition seen with aging could be due to age-related decline in serum testosterone and GH levels. However, it is unknown whether the decline in these hormones with aging is a cause of aging or whether such decline is an effect of aging, having beneficial and protective effects on some of the many age-associated diseases including cancer. Of particular interest in this context are the recent findings of prolongation of life in worms, flies and rodents who have either deficient GH-IGF-1 signaling or deficiency of GH.

3. RATIONAL APPROACH TO ENDOCRINE REPLACEMENT IN THE AGING MALE

3.1 Testosterone replacement in healthy aging men

Testosterone therapy in young men with primary or secondary hypogonadism increases lean body mass, muscle size and strength, improves bone density and reduces fat mass. These observations led to the speculation that age-related changes in body composition could be related to the declining levels of serum testosterone with aging.

However, the small number of studies conducted to date, including a small number of healthy elderly men with low or low-normal testosterone levels, have not been able to demonstrate all the expected beneficial effects of testosterone administration as seen in truly hypogondal young men. Testosterone administration in healthy elderly men has been shown to result in an increase in lean body mass and a reduction in fat mass. However, the effect of the increase in muscle bulk, incidentally more marked in the upper half of the body, on muscle strength remains unclear. Moreover, clinically relevant outcomes such as an improved ability to live independently have not been studied. Although some studies have suggested a positive effect on bone turnover, the effect on bone mineral density remains unclear and there is at present no data on the effect of testosterone replacement in healthy elderly men on the incidence of osteoporotic fractures.

The other difficulty in considering treatment with testosterone in healthy elderly men is with regards to the definition of hypogonadism in this age group. The lower normal limit for serum total testosterone in healthy elderly men has been variably defined as 6 nmol/L (173 ng/dL), 8 nmol/L (230 ng/dL) and 11.3 nmol/L (325 ng/dL). Some authors insist on a value of 7 nmol/L (200 ng/dl), claiming that values of 10 (290 ng/dL) or 11 nmol/L (317 ng/dL) misclassify a large proportion of elderly men as hypogonadal when they actually represent normality.

One could argue that long-term data would be available with time and meanwhile, why not administer testosterone to all healthy elderly men with borderline low serum testosterone levels given the benefits seen in body composition. However, testosterone replacement therapy is not uniformly safe and is associated with a few severe potential adverse effects. Testosterone controls the growth and differentiation of the prostate. Whether it results in prostatic hypertrophy is a matter of debate. Many elderly men harbour in-situ carcinoma of the prostate. The long-term effect of testosterone replacement on these lesions remains unclear. Most studies have shown a slight but significant rise in serum prostatic specific antigen levels with testosterone therapy. Testosterone replacement is therefore currently contraindicated in men with prostate cancer and obstructive benign prostatic hyperplasia. Testosterone therapy in elderly men has also been shown to increase the haematocrit in a fair proportion of patients. The long-term consequences of this rise in haematocrit on stroke frequency remain unclear. The effect of testosterone administration on

the serum lipid concentrations in healthy elderly men is a matter of debate and its effect on the cardiovascular system remains uncertain.

Thus, in the absence of proven severe androgen deficiency, testosterone replacement should not be offered routinely to healthy elderly men in the hope of reversing age related changes in the body composition. Longer term studies, including much larger number subjects, with clinically relevant end points such as fracture rates, falls and cardiovascular mortality rates, are necessary before deciding on the future of testosterone replacement in healthy elderly men. The research questions that need answering are the criteria for identification of elderly men who would benefit the most from replacement dose including the lower normal limit for total serum testosterone in the elderly, the dose, duration of treatment, possible cardiovascular effects and effects on the prostate gland. A very important lesson to learn is from our initial enthusiasm in administering hormone replacement therapy in post-menopausal women that had been studied, discussed and practiced for years. It is only recently that studies have conclusively demonstrated that HRT in post-menopausal women is associated with increased risk of breast cancer and cardiovascular disease and routine HRT is no longer recommended in post-menopausal women.

3.2 DHEA replacement in healthy aging men

The interest in DHEA as an anti-aging hormone stems largely from its beneficial effects seen in animals. DHEA has been shown to prevent diabetes, obesity, cancer and heart disease and improve immune function in rodents. However, there are two points that need careful attention while interpreting these results and extending them to human beings. First, rodents, unlike humans and other primates, naturally have very low levels of DHEA. Second, these beneficial effects have been seen after the administration of supraphysiological doses of DHEA.

Studies of DHEA replacement in women with adrenal insufficiency, the ideal pathophysiological model of DHEA deficiency, have demonstrated significant improvements in well-being, mood, and sexuality. However, it is not possible to extend these findings to healthy aging men as it is unclear whether the physiological decline in serum DHEA with aging has the same effect as pathological, premature loss of DHEA production in patients with adrenal insufficiency. The effect of DHEA administration on body composition and muscle strength in healthy elderly men are conflicting largely due to small number of subjects studied for very short periods of time. There has been no documented benefit of DHEA administration on markers of bone turnover or bone mineral density. The claims that DHEA can prevent memory loss and slow the progression of age-related conditions, such as Alzheimer's and Parkinson's diseases, are not supported by available scientific evidence.

The link between DHEA and human cancer is at best unclear as is its role in cardioprotection and atherosclerosis. DHEA administration in large doses in animals results in adverse effects such as stimulation of prostate cancer and liver dysfunction. DHEA administration in humans in physiological doses of 50–100 mg per day results in modest elevation of androgens with the same concerns as noted above regarding the long-term safety of administering testosterone. DHEA administration results in a drop in HDL cholesterol and its long-term impact remains unclear.

Thus, overall, there is insufficient data not only with regards to the beneficial effects of administration of DHEA in healthy elderly men but also regarding its potential long-term adverse effects on cancer and cardiovascular risks. Further long term data, obtained from well conducted randomized controlled trials, are necessary before deciding on the future of routine use of DHEA replacement in healthy elderly men.

3.3 GH replacement in healthy aging men

The interest in GH as an anti-aging hormone stems from the many similarities seen in the body composition of healthy aging men and those described over the past decade in young adults with severe GHD such as decreased lean body mass, decreased muscle strength, decreased bone mass and increased fat mass. Moreover, it has been now been demonstrated that GH replacement in young adults with severe GHD results in a reversal of a number of these changes in body composition. The success of these studies led to a number of studies of using GH in normal healthy elderly persons. One of the first and most widely quoted studies dates back to 1990 that reported an increase in lean body mass and decrease in fat mass following 6 months of GH administration in 12 men over 60 years of age. Although, this and a few other studies in healthy aging men have confirmed the beneficial effects of GH administration on body composition, this was not associated with clinically significant changes in either muscle strength or endurance capacity. The effects of GH replacement in healthy elderly men on bone mineral density is controversial with a few studies suggesting an improvement and others not.

On the other hand, GH administration leads to dose related side effects including water retention causing lower limb edema, arthralgias and carpal tunnel syndrome. Gynaecomastia is a frequently observed side effect. The effect of long term GH administration on cancer risk in healthy elderly men is unclear. It could be that age-related decline in GH levels is probably an adaptive response to aging and has beneficial effects and protects the individual from the development of age-related increase in cancer. Recent studies have demonstrated an association between circulating serum IGF-1 levels in the upper quartile of the normal range and the development of prostate and breast cancer. Thus, the administration of GH to raise the serum IGF-1 levels in elderly men to those found in younger men aged 30–40 years may not be safe and more information is urgently awaited on this critical question.

Thus, even though GH administration in healthy elderly

men has been shown to improve their body composition, such change has not been shown to improve muscle strength and its effect on clinically relevant outcomes such as independent living is unclear. All the studies to date have been of short duration, have included healthy elderly rather than frail old subjects and had withdrawal of large number of subjects from the study protocols because of side effects consequent upon use of rather high doses of GH. Thus whilst it has now become clear that GH replacement is certainly not the answer to reversing the many effects of old age and for restoring the youthful looks and vigour, there is still hope that it might be of benefit in carefully selected elderly persons, and further research is certainly required in this area.

RECOMMENDED READING

1. Balcombe NR, Sinclair A. Ageing: definitions, mechanisms and the magnitude of the problem. Best Practice & Research Clinical Gastroenterology. 2001; 15:835-49.
2. Lamberts SW, van den Beld AW, van der Lely AJ. The Endocrinology of aging. Science. 1997; 278(5337):419-24.
3. Anawalt BD, Merriam GR. Neuroendocrine aging in men. Andropause and Somatopause. Endocrinology and Metabolism Clinics of North America. 2001; 30:647-69.

LEARNING POINTS

- Among many other organ systems, there is a gradual decline in the function of a number of endocrine glands with aging
- Of these, the decline in pancreatic and thyroid function leads to clinically defined disease states that need proper diagnosis and treatment
- The causative role of the decline in the serum levels of testosterone, DHEA, DHEAS, GH and IGF-1 in the changes seen in body composition with aging is far from clear
- It is indeed unknown whether the decline in these hormones with aging is a cause or effect of aging
- Hormone replacement strategies have been recommended by some for the aging male but remain highly controversial. Increasing serum hormone levels in aging men to those seen in young adults has not been uniformly proven to be of benefit or safe
- At present, the administration of testosterone, DHEA, DHEAS and GH as anti-aging hormones in normal healthy men is not recommended. Any such administration should be considered only under proper research protocols. We need to await the results of long term trials involving large number of elderly men that demonstrate not only the beneficial effects of the administration of these hormones in healthy aging men but more importantly, clearly demonstrate the safety of such administration
- It is possible that the administration of some of these hormones might be of benefit in a subgroup of elderly males with age-related problems including frailty characterized by generalized weakness, impaired mobility and balance and poor endurance; however, we need to await results from large, randomized trials with clinically relevant end points, in these subgroups of elderly males, before recommending such use.