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Endocrinology of Aging: A Short Review

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ABSTRACT
Significant progress in health and social well-being has resulted in steady increases in life expectancy, accompanied by a growing burden of age-related health issues. The complex changes in hormonal systems that govern homeostasis and survival may contribute to the challenges faced in later life, as illustrated by the increased risk of fractures in post-menopausal women. As individuals age, there are notable changes in hormone production, metabolism, and function. With advancing age there are significant alterations in hormone production, metabolism, and action. Some of these changes may play a role in the pathophysiology of senescence, although the evidence for that is limited. The magnitude of age-related alterations is highly variable and sex dependent. While only minor adjustments are observed in pituitary function, adrenal gland activity, and thyroid performance, the alterations in glucose regulation, reproductive health, and calcium metabolism are more pronounced. In light of these findings, strategies to locally regulate hormone bioavailability by altering pre-receptor metabolism may offer greater therapeutic potential in the fight against age-related disease.This review aims to provide an overview of the aging endocrine system and its probable impact on health and disease in the elderly. Here the strategies of evaluation and management protocols appropriate for the elderly with suspected endocrine dysfunction is defined. This review also confers the possible therapies against aging and new research works in delaying aging.

Keywords: Aging, Endocrine, Hormone, Metabolism, Estrogen & Menopause, Testosterone & Andropause, Ani-aging.

1. INTRODUCTION
The average lifespan of human beings is presently between 75 to 78 years and may rise to 85 years over the next two decades. However, in India, the average lifespan is 60 to 65 years. Throughout the course of adulthood, all physiological functions progressively deteriorate. There is a reduced ability for cellular protein synthesis, a decline in immune function, an increase in fat mass, a reduction in muscle mass and strength, a decrease in bone mineral density, as well as increases in blood pressure, heart disease, diabetes, and other age-related conditions. Most elderly individuals will die from atherosclerosis, cancer, or dementia; but in an increasing number of the healthy oldest old, loss of muscle strength is the limiting factor that determines their chances of living an independent life until death. Age-related disability is characterized by generalized weakness, impaired mobility and balance, and poor endurance.[1-5]

2. AGING
"A persistent decline in the age-specific fitness components of an organism due to internal physiological degeneration."[6]

Physical signs of aging
- Wrinkles on the face and body.
- Sight, hearing, taste, and smell become less acute.
- Hair begins to thin and turn gray.
- Gain weight, particularly around the waist and hips.
- Loss of bone density over time (especially in women)
- Slower reflexes and altered gait; development of motor dysfunction
- Less acute mental agility and declining memory.
- Complex diseases associated with aging are caused by the interaction of genetic and environmental factors.

Senescence is a biological process that causes a progressive deterioration of structure and function of all organs chronologically. It is thought that senescence is a potential cause for the development of various age-related disorders such as cancer, cardiovascular and neurodegenerative disorders[4]

3. CHANGES DURING AGING

Life is a process of continual change.Age-related changes occur at many levels-

- Biological level
- Physiological level
- Psychological level
- Functional level

But we will only emphasis on Biological changes[7] and it include-

I. Cellular changes
II. Morphological changes

I. Cellular changes

Cellular changes is not observed in several organisms, including perennial plants, sponges, corals, and lobsters.The role of telomeres in cellular changes has aroused general interest.

Telomerase shortening

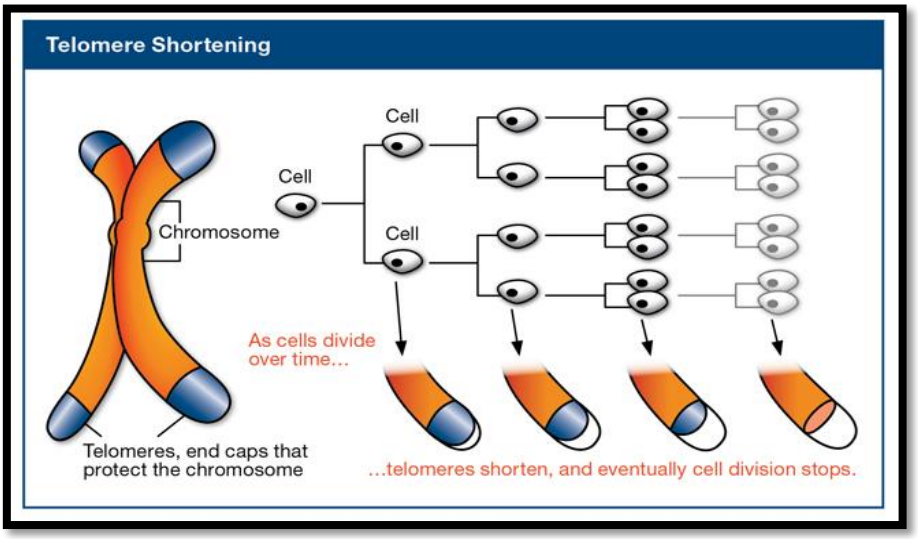

Fig. 1: Telomerase shortening

Telomere is about 10 to 15 kb in length, composed of the tandem repeat. The successive shortening of the chromosomal telomeres with each cell cycle is also believed to limit the number of divisions of the cell, thus contributing to aging. Telomeres are specialized DNA
Sequences at the end of chromosomes. They shorten with each cell division. When the telomeres become too short, the cell enters the senescence stage.The enzyme, telomerase, fills the gap by attaching bases to the end of the chromosomes. As long as the cells have enough telomerase to do the job, they keep the telomeres long enough to prevent any important information from being lost as they go through each replication.With time, telomerase levels decrease.With decreasing telomerase levels, the telomeres become shorter and shorter. Once telomeres shrink to a certain level, cells can no longer divide; hence aging commences. [8]

II. Morphological changes

Age-related reductions in muscle mass are a cause of decreased muscle strength,Disability, gait and balance problems.Between 30-75 years old, the number and size of muscle fiber progressively deceases called-sarcopenia. Blood flow to the muscles is decreased. Results in decreased endurance capacity, Capillary density decreases which makes less O_2 available during muscle work.
Neuromuscular changes-There are a decrease in the number of motor unit. The number and diameter of motor axons decreases.After 60, there is a reduction in spinal cord axonssurviving segmental neurons branch and display collateral growth. [9]

Changes in organs during aging

Skin -The skin wrinkles, loseselasticity and a decline in cellreplacement occurs. The skin tears and blisters easily.There is a loss of dermal thickness (20%), especially in sun-damaged skin.Skin neoplasms (benign and malignant) increase.Vitamin D production declines.

Eye- with aging Ptosis occur that is, wrinkling and loss of orbital fat. EyeLens grows during life span, increasing in density and weight.There is a progressive decrease in lens elasticity, with increasing age. Aqueous humor Increase intraocular pressure and lead to glaucoma[10]

4. ENDOCRINE CHANGES DURING AGING

Physical changes during aging have been considered physiologic, but there is evidence that some of these changes are related to this decline in hormonal activity. [7]

a) MENOPAUSE (Changes In women)
b) ANDROPAUSE (Changes in men)
c) Endocrine change in adrenal gland or ADRENOPAUSE
d) Changes in Growth hormone and IGF-I AXIS or SOMATOPAUSE
e) Changes in Hypothalamus-Pituitary-Thyroid Axis

a) MENOPAUSE (Changes In women)

The most dramatic and rapidly occurring change in women around the age of 50 is menopause.Estrogens hormone secreted from ovary. Cycling estradiol production during the reproductive years is replaced by very low, constant E2. In most women ovarian follicles function less well during this period, with serum.Oestradiol concentrations being lower and follicle stimulating hormone (FSH) concentrations higher than in younger women. Luteinizing hormone (LH) is unchanged [11].

The risk of cardiovascular disease in premenopausal women is lower than in men, but during the postmenopausal period the risk increases and is equal to males of equivalent age and risk factor profile.

At the time of the menopause there is rapid loss of bone, due to oestrogen withdrawal. In most women, this period of decline in estrogens is accompanied by vasomotor reactions, depressed mood and changes in skin and body composition (increase in body fat and decrease in muscle mass). In the subsequent years, the loss of estrogens is followed by a high incidence of cardiovascular disease, loss of bone mass and cognitive impairment [7].

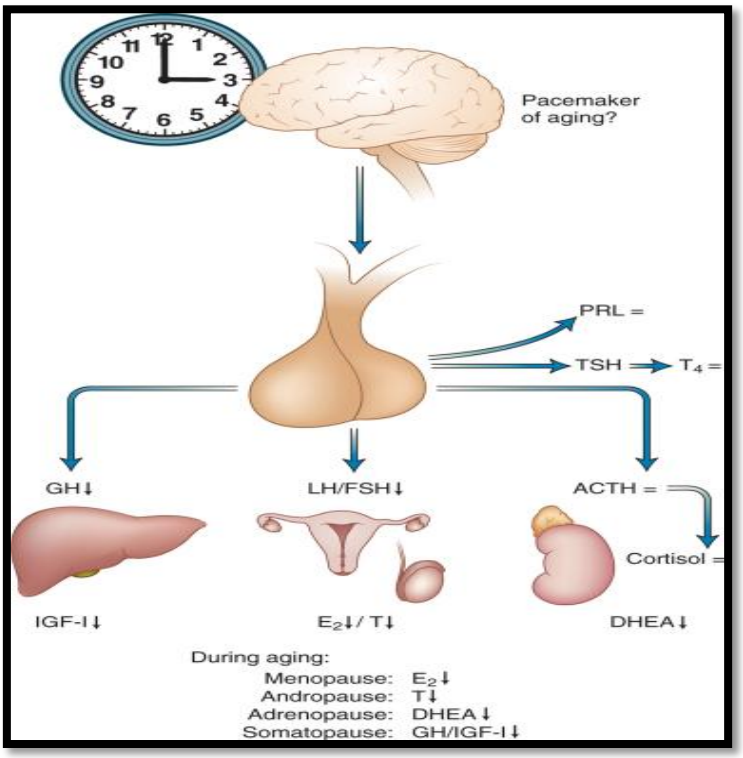

Fig.2: Endocrine changes with aging

b) ANDROPAUSE (Changes in men)

During aging, a gradual decline in serum total and free testosterone (T) levels occurs). Testosterone secreted from testis. This "Andropause" is characterized by a decrease in testicular Leydig cell numbers and in their secretory capacity, as well as by an age-related decrease in episodic and stimulated gonadotropin secretion [5]. It is generally agreed that as men age, there is a decline in serum total testosterone concentration that begins after the age of 40 years. The higher decline in free testosterone levels is related to the increase in sex hormone–

binding globulin (SHBG) levels with age. Healthy men there is a gradual but progressive age-dependent decline in testosterone levels, termed the andropause. The clinical features associated with reduced testosterone levels in aging men include increased fat mass, loss of muscle and bone mass, fatigue, depression, anaemia, poor libido, erectile deficiency, insulin resistance and higher cardiovascular risk[12].

c)Endocrine change in adrenal gland or ADRENOPAUSE

Circulating DHEAS levels in healthy adults are more than 10 times higher than those of cortisol. Second hormonal system demonstrating age-related changes is the circulating levels of dehydroepiandrosterone (DHEA) and its sulphate (DHEAS), which gradually decline with age, resulting in "adrenopause" Adrenal secretion of DHEA gradually decreases over time, whereas adrenocorticotropin (ACTH) secretion, which is physiologically linked to plasma cortical levels, remains largely unchanged[13].

In older subjects, serum cortical secretion concentrations may vary more within a 24 hours period as compared to younger subjects. No deficiency of adrenal production of corticosteroids in aging. In older females increasing levels of HPA axis activity, as measured by urinary free cortisol excretion, are associated with a decline in memory performance. There is an association between 24 h cortisol production rate and increased body fat in older men. Decline in DHEAS levels cause cardiovascular disease, breast cancer, low bone mineral density, depressed mood, type 2 diabetes and Alzheimer's disease[14].

d) Changes in Growth hormone and IGF-I AXIS or SOMATOPAUSE

The third endocrine system that gradually declines in activity during aging is the growth hormone (GH)/insulin-like growth factor I (IGF-I) axis. Elderly men and women secrete GH less frequently and at lower amplitude than do young people. The concept that this decline in GH and IGF-I secretion contributes to the decline of functional capacity in elderly people.The progressive decline in GH secretion has been termed the somatopause. Decrease in GH secretion is known to cause a reduction of protein synthesis, a decrease in lean body mass and bone mass and a decline in immune function[15].

e) Changes in Hypothalamus-Pituitary –Thyroid Axis

The hypothalmo–pituitary–thyroid axis undergoes a significant number of complex physiological alterations associated with aging[16]. Thyroid hormone clearance decreases with age, but thyroid hormone secretion is also reduced, leading to unchanged total and free serum thyroxin (T4) concentration. In contrast to thyroxin, serum total and free triiodothyronine (T3) concentrations decrease with aging. This slight decrease in plasma T3 concentration occurs largely within the broad normal range of the healthy elderly population and has not been convincingly related to functional changes during the aging process[17].

5. THERAPIES AGAINST AGING

As there are many problems that occur during aging, so to reduce it, hormonal replacement therapy has been introduced [18].

a) Estrogens/ Progestin Replacement in women

Estrogen/ progestin replacement therapy delays atherosclerosis, loss of bone mass, and loss of cognitive function [18]. Life expectancy seems not to be influenced by estrogen/progestin replacement, but atherosclerosis and bone loss are considerably delayed, apparent delay. In the onset of Alzheimer's disease in women treated with hormone replacement also have important negative effects of estrogen/progestin replacement therapy during menopause. The most compelling problem is the increased incidence of breast cancer, weight gain [19].

b) Testosterone Replacement in Men

Testosterone replacement therapy is in most instances and not effective for the treatment of impotence in elderly males [20]. Testosterone Replacement therapy in the elderly,doseduration of treatment, the identification of elderly men who might benefit most, risks to the prostate, and possible effects on the process of atherosclerosis remain subjects for study [21]. Beneficial effects of testosterone on mood and cognition, on bone and muscle, and also on heart disease but it may have possibilities to develop prostate cancer. Risks associated with testosterone replacement in elderly men include fluid retention, gynecomastia, worsening ofSleep apnea, polycythemia and acceleration of benign or malignant prostatic disease[22].

c) Dehydroepiandrosterone (DHEA)Replacement therapy

Replacement- DHEA appears to be beneficial in hypoandrogenic men as well as in postmenopausal and aging women[23]. Menopause is the event in a woman's life that induces a dramatic change in the steroid milieu, and use of DHEA as 'replacement treatment' has been reported to restore both the androgenic and estrogenic environment and reduce most of the symptoms of this change. Elderly women found no evidence of benefits from DHEA replacement [24,25].

In men with adrenal insufficiency and hypogonadism without androgen replacement, DHEA administration results in a significant increase in circulating androgens[22,27].

d) Growth Hormone (GH) Replacement

GH replacement- therapy in GH-deficient adults was shown to increase muscle mass, body mass, muscle strength, bone mass, and the quality of life. A beneficial effect on the lipid profile LDL decrease. And important decreases in fat mass were also observed (from effect of GH on older men) no effect to bone density of proximal

femur [28]. Hormone replacement strategies have been developed, but many of their aspects remain controversial and increasing blood hormone levels in aging individuals to those found during mid-adult life has not been uniformly proven to be safe and of benefit [29,30].

6. NEW RESEARCH WORKS IN DELAYING AGING

New researches are done to increase longevity or delaying aging and sustain a good life. Here are some of the more important advances in endocrinology of aging research over the past year.

a) Identification of steroidal lipids that active nuclear hormone receptors to modify lifespan in nematodes

The lifespan of C. elegans can be extended approximately 60% by removing the germline with a laser microbeam[31] or a mutation that prevents Germline development, such as glp-1[32]. This lifespan extension requires DAF-12 [31], a nuclear hormone receptor these findings suggest that germ line ablation leads tothe DAF-9-dependent synthesis of a lipophilic hormone thatActivates DAF-12, and that hormone is pregnenolone.Germline ablation triggers longevity by stimulating the synthesis of pregnenolone[33].

Genetic studies suggest that when C. elegans is grown under replete conditions, DAF-9 is involved in the biosynthesis of a hormone that promotes growth to adulthood by activating DAF-12.Recently 3-keto-4-cholestenoic acid and 3-keto-7, (5α)-cholestenoic acid were identified as endogenous hormonal ligands for DAF-12 [34].

b) Regulation of lifespan and processes associated with aging by the klotho

Klotho is a single-pass transmembrane protein that exerts its biological functions through multiple modes it is expressed in kidney and sometime Klotho protein itself or its metabolites may function as a humoral factor. Klotho is an enzyme that in humans is encoded by the KL gene (klotho gene).This gene encodes a type-I membrane protein that is related to β-glucuronidases[35]. Klotho is a new anti-aging gene This gene was named after the purported Greek goddess,Klotho, who spins the thread of life. The life-span of klotho-deficient mice is only about 5-6% of that of wild-type mice [35,36]. Klotho is a transmembrane protein that, in addition to other effects, provides some control over the sensitivity of the organism to insulin and appears to be involved in aging. The klotho protein is a novel β-glucuronidase capable of hydrolyzing steroid β-glucuronides. Genetic variants in klotho have been associated with human aging [36], and klotho protein has been shown to be a circulating factor detectable in serum that declines with age. mutations within this protein have been associated with aging and bone loss.

Several interesting papers related to the hormone klotho were published during the past year. It was recently reported by kurosu Et al.[35]. That overexpression of klotho, a newly discovered hormone, extends longevity of mice. Because klotho induces igf-1 and insulin resistance, these findings appear to contradict previous evidence for increased life span of dwarf mice with reduced igf-1 and insulin levels and enhanced insulin sensitivity. However, activation of signalling molecules downstream from igf-1 and insulin receptors is reduced in both klotho and dwarf mice, suggesting common mechanisms of delayed aging[35,37].

It was demonstrated that an overexpression of klotho in mice might extend their average life span between 19% and 31% compared to normal mice. However, the actual use of overexpressing klotho for extending life-span without side-effects is still a matter of speculation and remains to be justified by further experimentation. Klothoalso inhibits intracellular insulin and IGF1 signalling[38].

c) Melatonin administration

Pineal melatonin secretion declines with aging, whereas visceral fat, plasma insulin, and plasma leptin tend to increase.By an experiment Wolden-Hanson T, Mitton DR, McCants RL, Yellon SM, Wilkinson CW, Matsumoto AM, Rasmussen DD wanted to show that the daily melatonin administration at middle age suppressed male rat intra-abdominal visceral fat, plasma leptin, and plasma insulin to youthful levels [39]. Melatonin administration extends the lifespan of mice. The prolongation of lifespan by melatonin has been interpreted in favour of an up regulation of the immune system as well as due to anti-stress properties of melatonin acting via the brain opioid system [40].

d) Direct roles of Gonadotrophic Hormones in pathophysiology associated with menopause

Probably because the menopause-associated decline in serum estradiol levels is substantial,estradiol is associated by many as the prime factor involved in the pathophysiologic processes that occur during and after the menopausal transition. This view permeates the clinical community and is the basis for the intense interest in estrogen therapy following menopause[41,42].

However, new research is coming to light implicating the rise in gonadotropin levels, generally thought to be associated with falling estrogenic levels through feedback regulation at the hypothalamic-pituitary level, as important in their own right for menopause-associated

pathophysiologic processes in non-reproductive tissues. In addition, gondadotropins had been thought to target only reproductive tissues seeing of these effects in nonreproductive tissue particularly interesting[43]. The recent paper showing a direct effect of FSH on bone mass in mice is another piece of evidence linking the menopause-associated rise in gonadotropins to pathophysiology. [44]. (Casadesus et al. 2006) implicated the

menopause-associated rise in serum FSH a more important than declining estrogen levels in determining bone mineral density (BMD) or prevalence and frequency of vasomotor symptoms in perimenopausal women [43]. Thus menopause-associated pathophysiology and loss of cognition that previously had been attributed primarily to loss of estrogen may actually be due, at least in part, to changes in gonadotropin levels. These findings open new avenues of approach to understanding and treating menopause-associated health problems[45].

6. CONCLUSION

The discipline of endocrinology is increasingly being acknowledged within the aging research community. Previous groundbreaking discoveries indicated that a lifespan-regulating pathway in model organisms shares homology with the insulin/IGF signaling pathway, and this relationship now appears to extend to mammals. A significant aspect of this lifespan-regulating pathway, particularly in nematodes, is analogous to the steroid hormone signaling pathway found in mammals. In the past year, we have acquired more detailed insights into the specific steroidal activators involved. Furthermore, the role of sirtuins in extending lifespan in model organisms previously linked to the insulin/IGF signaling pathway and caloric restriction has now been demonstrated to influence insulin secretion in mouse pancreatic β cells. Additionally, the overexpression of Klotho has been shown to prolong lifespan in mice. Thus, in all these examples endocrine pathways seem to be closely involved in the modulation of lifespan in both mammalian and model organisms. Still plenty of work are to be done in this field in delaying aging with minimizing the side effects resulting from all the therapies.

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