REVIEW ARTICLE

Sleep: Is it the hidden agenda in the aging program?

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Abstract

Sleep is a basic biological function of the brain, which is essential for physical, mental, and emotional well-being. In aging, there is a progressive constriction of homeostatic reserves of the body. Many factors influence the aging process. Aging produces architectural changes in sleep that affect its quality and quantity. Sleep alterations of aging coupled with several body system changes exert their influences on the aging process. There is a close association between insomnia, sleep-disordered breathing, cytokines, insulin resistance, atherogenesis, and aging. It is important to recognize and treat sleep disorders in the elderly, as these interventions may help in retarding the aging process.

Keywords: Sleep, Aging, Obstructive sleep apnea (OSA), Cytokines.

Introduction

Aging is a natural phenomenon in which there is a complex interaction of genetics, chemistry, physiology, and behavior. The progressive constriction of homeostatic reserve of every organ system-a process termed as homeostenosis, is a major characteristic of aging.[1] Moreover, the process starts in the third decade of life.[1] There are several theories of aging, namely immune theory, neuroendocrine theory, free radical theory, cell aging theory, somatic mutation theory, and error theory.[1] Several changes happen in body systems with the advancing age. Sleep, which is an integral component of humans, must be of good quantity and quality to provide physical, mental, and emotional well-being. Modern medical science has offered a better health care but modern lifestyle has also generated several disorders including sleep disorders, which have an adverse effect on aging. Changes in sleep patterns in elderly bear a close relation with aging.

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Sleep and Aging

Human sleep is under the dual control of a circadian rhythm and of a homeostatic process relating the depth of sleep to the duration of prior wakefulness.

The society perceives aging as a decline in body functions. Retirement is a major milestone, and it affects the subject emotionally. Sleep patterns change both subjectively and objectively (polysomnography) with aging. Elderly individuals often exhibit the following incidents: (i) take a longer time to fall asleep; (ii) have reduced sleep efficiency; (iii) have frequent nocturnal and early morning awakenings, which can result in daytime napping and falls; (iv) have increased wake times after sleep onset; (v) have a reduced slow-wave sleep (SWS) but increased sleep times in stages 1 and 2; and (vi) slightly reduced rapid eye movement (REM) sleep with an increased latency to first REM period and reduced REM cyclicity.[2] The reduction in or even absence of SWS and a slight decrease in REM sleep in elderly people signifies that most of the night is spent in a lighter sleep. With these changes of reduced nocturnal

sleep in both quality and quantity associated with daytime napping, it would be wise to assume that there is redistribution of sleep in the elderly people. Alteration in sleep–wake homeostasis is an early biological marker of aging in adult men.[3]

The common sleep disorders in the elderly people are as follows: (i) insomnia, with a prevalence ranging between 19% and 38.4%[4] and an increase with the advancing age; and (ii) sleep-disordered breathing (SDB), which comprises snoring, upper airway resistance syndrome, obstructive sleep apnea, and obesity hypoventilation syndrome. Udwadia et al.[5] reported habitual snoring in 26% of the study population (middle-aged urban Indian men); the estimated prevalence of SDB was 19.5% and that of obstructive sleep apnea/hypopnea syndrome (SDB with daytime hypersomnolence) was 7.5%. In our study,[6] the prevalence of snoring in elderly people was found to be 69.5% (75.3% men and 24.7% women). Several studies show that the prevalence of SDB increases with age ranging from 5% to 15% in middle-aged adults to approximately 24% in community dwelling adults[7,8]; (iii) sleep deprivation (SD); (iv) advanced sleep phase syndrome; (v) periodic limb movement disorders and restless legs syndrome; (vi) parasomnia—REM sleep behavior disorder; and (vii) sleep disorders secondary to disorders such as backache, diabetes mellitus, depression, and others.

Insomnia and Aging

Insomnia is the most common sleep-related complaint. Insomnia generates considerable emotional stress, which can aggravate the aging process. Growth hormone (GH) secretion is affected adversely because of the reduced sleep times. Varying degrees of insulin resistance can also result. Difficulty in initiating sleep and a poor subjective quality in a healthy community cohort have been independently correlated with higher fasting insulin levels independent of confounding factors such as obesity.[9] Sleep-related difficulties are more prevalent in individuals with type 2 diabetes mellitus than those without this disorder.[10] Type 2 diabetes mellitus has been considered as a state of premature aging.[11]

Elderly are immunocompromised subjects.[1] Sleep is essential for the proper functioning of the immune system. Insomnia is often a manifestation of depression. In addition, a host of age-associated factors such as social isolation, financial insecurity, poor health, and proximity to death result in anxiety states and insomnia. Polypharmacy in elderly population carries a risk of generating sleep problems. Patients with severe OSA can present as insomnia owing to repeated respiratory arousals. Chronic insomnia has been shown to be associated with (i) enhanced secretion of tumor necrosis factor-a and interleukin (IL)-6 during the day and (ii) hypersecretion of cortisol (arousal hormone). Both these conditions lead to daytime fatigue, somnolence, and poor quality of sleep.[12] Moreover, elevated levels of IL-6 in combination with the increased activation of HPA and an elevated level of cortisol are related to poor sleep, fatigue, and sleep disturbances.[13] The relationship of IL-6 with the alteration of sleep architecture (increase of REM sleep at the expense of SWS) may have an important implication in the process of aging through related alterations of immunity.[14]

Growth hormone, cortisol, obesity, insulin resistance, and aging

GH is stimulated during sleep, and in men, 60%–70% of daily GH secretion occurs during early sleep in association with SWS. In young healthy women, SWS and GH release are less closely coupled, and daytime GH secretion is relatively more important than in men.[15] However, the hypothalamic–pituitary–adrenal (HPA) axis is acutely inhibited during early SWS.[16,17] The chronology of aging of GH secretion follows a pattern remarkably similar to that of SWS. Thus, in men, the so-called somatopause (a gradual and progressive decrease in GH secretion that occurs normally with increasing age during adult life, which is associated with an increase in adipose tissue and LDL levels and decrease in lean body mass), which occurs early in adulthood between the age range of 25 and 35 years, corresponds to the human life expectancy before the development of modern civilization and is essentially completed by the end of the fourth decade.[3]

An elevated evening cortisol levels is a hallmark of aging.[18,19] Even partial SD results in the elevation of cortisol levels the following evening.[20] An elevated evening cortisol levels in late life probably reflect an impairment of negative feedback control of the HPA axis in aging. There is an impaired ability to achieve evening quiescence following morning stimulation. Evening elevations of cortisol could facilitate the development of central and peripheral disturbances associated with glucocorticoid excess such as memory deficits insulin resistance[21,22] and further promote sleep fragmentation. Thus, decreased

SWS coupled with sleep fragmentation and sleep loss could contribute to the elevated cortisol levels. Glucocorticoid excess in addition to metabolic effects also inhibits GH secretion. Reduced amount of SWS independent of age are partly responsible for reduced GH secretion in the middle and late lives.[3] Van Cauter et al.[23] and Gronfier et al.[24] have shown that pharmacological enhancement of SWS results in increased GH release. Patients of sleep apnea treated with positive airway pressure showed an increase in GH release.[25,26]

Aging and pathological GH deficiency, glucocorticoid excess, or both occurring in elderly adults are associated with osteopenia, loss of muscle mass strength and exercise capacity, increased total and intrabdominal fat with glucose intolerance, dyslipidemia, increased fragility of skin blood vessels, poor healing connective tissue, altered immune function, and a diminished quality of life.[27] Although the clinical implications of reduced SWS are still unclear, but there seems to be a strong relation between SWS, GH, and aging.

Cauter et al.[3] stated that, although the benefits of replacement therapy with recombinant GH is being explored, it is advisable that such hormone interventions should target a younger age range (early midlife) rather than older than 65 years when peripheral tissues have been continuously exposed to very low levels of GH for at least two decades. In addition, aging, increased blood glucose, obesity, and blood free fatty acids that inhibit GH secretion. A causal relationship, therefore, exists between decreased sleep quality and reduced nocturnal GH secretion. It must also be appreciated that the use of GH in elderly has the potential to stimulate oncogenesis.

Sleep deprivation and Aging

Sleep deprivation, which is common with modern lifestyle, could also occur in sleep disorders such as SDB because of altered sleep architecture. I would like to coin the term *unconscious sleep deprivation* in such situations.

Elderly often have an advanced sleep phase syndrome but are forced to sleep late owing to societal issues, which results in *rebound sleep deprivation*.[6]

Early morning awakening around 4 a.m., *Brahma muhurta* (traditional Indian time), is considered auspicious. REM SD can result, which can cause loss of memory, increased appetite, and hypersexuality.[28] Melatonin, which has several actions including retarding aging process, also gets reduced. Meditation is often practiced by elderly subjects. I would like to comment sleep can be called as unconscious meditation and meditation as conscious sleep.

Nocturia is common in elderly and often a manifestation of OSA. Nocturia can cause sleep fragmentation and vice versa. Nocturia, therefore, can be responsible for daytime fatigue and sleepiness. Middlekoop et al.[29] listed nocturia as by far the most common explanation offered by elderly people as to the cause of inability to stay asleep.

Sleep deprivation has multiple adverse effects on the cardiovascular, metabolic, and endocrine functions.[30,31] Chronically reduced sleep times are associated with obesity.[32] Sleep-deprived subjects have daytime sleepiness and have a tendency to overeat and eat fast. Elderly subjects are often edentulous and cannot eat fast.[6] Sleep deprivation induces or aggravates snoring by increasing muscular hypotonia and delaying contractions of the dilator muscles of the pharynx.[33] OSA results in oxidative stress, which can aggravate the aging process.

Aging and Sleep Apnea

SDB, although important, has a poor awareness. Sleep apnea can be obstructive, central, or mixed. OSA is a common disorder, which is prevalent in overweight men and in the elderly people.[34] Habitual snoring and excessive daytime sleepiness are the two prominent symptoms of OSA. There is a repetitive pharyngeal collapse in sleep, resulting in cyclical hypoxemia, cyclical hypertension, and release of stress hormones and catecholamines.

It is clear that snoring increases with age at least up to the age of 70 years.[35] After the age of 80 years, snoring prevalence appears to decline. In elderly, snoring may be mild because of the reduction of SWS. Moreover, polysomnography demonstrates that obstructive events predominate rather than central or mixed events. Therefore, several elderly subjects suffer from OSA.

On the basis of data, sleep apnea appears to be present as two different disorders[36]:

1. Age related, manifesting in middle age.
2. Age dependent, manifesting in old age. (This refers to sleep apnea in elderly people, which has potential

age-dependent risk factors such as increase in body weight, decreased lung capacity, decreased ventilator control, decreased muscular endurance, decreased thyroid function, increased sleep fragmentation, and decreased SWS.)

The longer you live, the more chances of developing sleep apnea. Martin et al.[37] have demonstrated that the upper airway size decreases with increasing age in both men and women and that men have greater upper airway collapsibility in lying down at oropharyngeal junction than women.

It is now suggested that possibly sleep apnea in elderly paves the way for the development of hypertension, ischemic heart disease, stroke, type 2 diabetes mellitus, and dementia.[36]

Central obesity is a feature of aging and obesity itself may lead to increased sleepiness via the action of adipose-derived IL-6. Both IL-6 and C-reactive protein are elevated in patients with OSA syndrome, and treatment with continuous positive airway pressure (CPAP) was associated with the marked decrease of these factors.[38] Blood glucose levels increase with age.[39] A close association is observed between sleep, aging, and metabolic syndrome.[40]

Chronic systemic inflammation is an underlying cause of many seemingly unrelated age-related diseases. Aging itself results in an increase of inflammatory cytokines that contribute to the progression of many degenerative diseases. Evidences suggest that proinflammatory cytokines play an important role in aging and longevity. Salvioli et al.[41] have proposed the phenomenon of inflamm-aging.

The interactions and consequences of sleep and aging are depicted in Fig. 1.

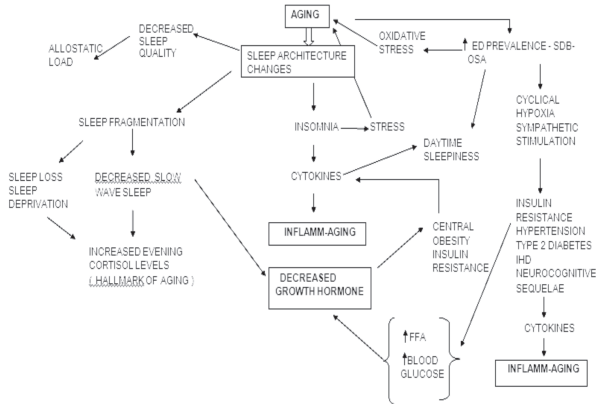

Figure 1: Sleep and aging: interactions and consequences

Posture, sleep, and health

Drawing an analogy between ancient Indian healing practices and modern medicine, it would be appropriate to mention that sleeping in supine posture maintains body chakras (energy-receiving centers) in alignment. This facilitates the smooth flow of energy in body systems and, thereby, initiates good health in all levels of existence. However, sleep disorders such as sleep apnea may force the subject to sleep on one side disturbing the alignment of body chakras. Patients using CPAP have often reported that it helps them to sleep supine.

Conclusions

It is widely accepted that the practice of elements of lifestyle, environment, and health care can provide longevity and quality of life in individuals and population groups. The secretion of GH progressively declines as the age advances possibly because of reduced sleep. Obesity and hyperglycemia of aging inhibits GH secretion. Moreover, GH deficiency causes increase in adipose tissue and decreased muscle mass. Both these are recognized features of aging. SDB prevalence is higher in elderly subjects, and SDB aggravates the aging process. There is a close association between aging, sleep, and cytokines. The issues of lifestyle such as shift work and chronic SD have their own contribution to sleep problems in the elderly people. Still waters often run deep. Sleep disorders need recognition in the elderly people. Management of sleep disorders may pave the path for retarding the aging process.

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