SLEEP DISORDERS AND AGEING RELATED DISEASE: IS IL6 OVER-PRODUCTION THE MISSING LINK?

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SLEEP PLAYS A VITAL ROLE in our health and wellbeing, similar to that exerted by nutrition, stress control, and physical activity for example. And we know today that the quality of sleep is directly related to quality of life and life expectancy.

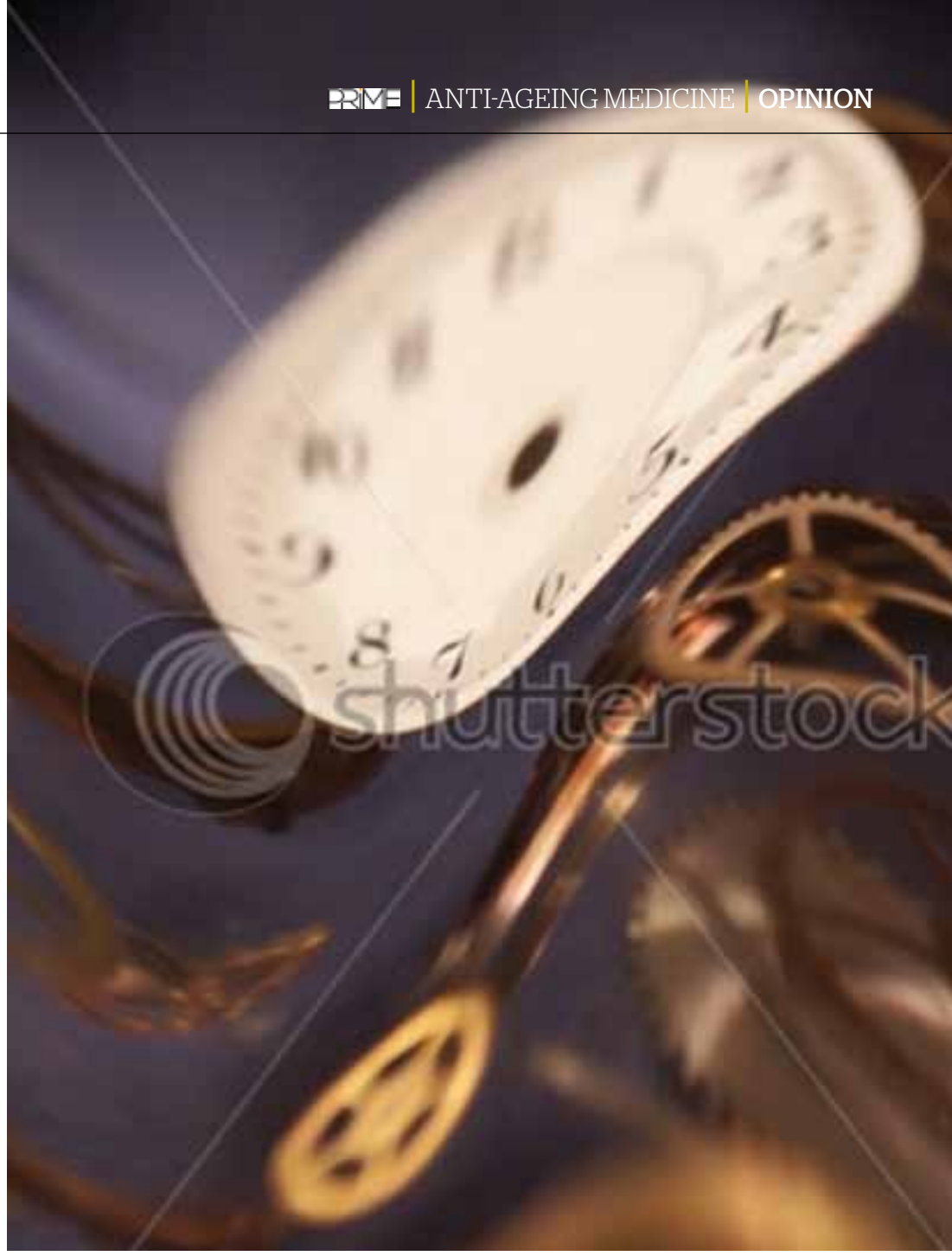
Sleep exerts different functions, the most important of which are:

- Energy conservation
- The consolidation of memory
- Hormonal and immune system regulation
- Body–mind restoration.

The immune system benefits from the effects of sleep that regulates the circadian alternation between cell-mediated immunity (Th1 immune branch), which develops mostly at night (first part of sleeping time under the influence of slow-wave sleep) and that is promoted by hormones such as melatonin and growth hormone, and humoral immunity (Th2 immune branch), which is expressed during the final part of sleeping time and during daylight hours, and that is stimulated by cortisol and vitamin D. On the other hand, sleep is influenced by the immune system; proinflammatory cytokines have a somnogenic effect while anti-inflammatory cytokines promote waking up, altering sleep. Interleukin-6 (IL-6) is a multifunctional cytokine that plays a central role in host defense owing to its wide range of immune, haematopoietic, hormonal and metabolic activities, and its potent ability to induce the acute phase response.

What is IL-6?

IL-6 is one of the main drivers of Th17 immune branch, and concomitantly regulates proinflammatory and anti-inflammatory activities, and contributes to both the development and the resolution of the acute inflammatory response. IL-6 is a cytokine that is produced by the cells of the immune system, vascular endothelial cells, adipocytes and skeletal muscle, and has shown to have anti-inflammatory as well as pro-inflammatory properties. Over-expression of IL-6 has been implicated in the pathology of a number of diseases, including multiple myeloma, rheumatoid arthritis, Chron's disease,



Castleman's disease, psoriasis, and post-menopausal osteoporosis. IL-6 overproduction is also thought to be involved in the pathogenesis of ageing and ageing-related diseases, such as diabesity, cardiovascular disease (CVD), dementia, sarcopoenia, frailty, disability, cancer, and autoimmune diseases. However, a fundamental question remains as to whether elevated levels of IL-6 are aimed at resolving an inflammatory response that is inappropriately long or whether a primary dysregulation of IL-6 production is responsible for a chronic proinflammatory state, which has a negative impact on health status.

It is possible that in some diseases, which are ageing and chronic inflammation related, IL-6 could exert a pathogenetic role. In other disorders IL-6 could be the effect of the diseases rather than a causative factor (i.e. in obesity, diabetes, metabolic syndrome); while in others it could exert a double role of cause and effect at the same time (e.g. CVD, dementia). Future studies that evaluate the effects of blocking the IL-6 signalling in older persons affected by a chronic proinflammatory state, and different patterns of comorbidity may shed light on this question.

IL-6 and sleep

In both young and older persons, the secretion of IL-6 follows a circadian rhythm with two nadirs at approximately 8am and 9pm, and two zeniths at approximately 7pm and 5am. REM sleep enhances IL-6 production through the action of catecholamines, but IL-6 is inhibited by deep sleep (stages 3–4, non-REM sleep) and by waking (through the action of cortisol). For this reason, it is produced mainly in the second part of the night when REM sleep is greatly expressed, and is inhibited during the first part of the day (under cortisol influence). On the other hand, IL-6 negatively influences deep sleep and REM sleep (in the first part of the night), while promoting sleep induction and enhancing superficial sleep (stages 1-2, non-REM sleep), REM sleep (in the second part of night) and cortisol release.

Sleep disorders that are very common among the population, such as insomnia, restless leg syndrome and obstructive sleep apnoea, may promote ageing, are cofactors in many age-related diseases, and increase the risk of mortality in a range of conditions. Among the diseases advanced by insomnia and other sleep disorders, are reportedly obesity, diabetes, and CVD. Sleep disturbances that characterise the ageing process would also be an important cofactor of cognitive disorders of varying degrees, of immunosenescence and inflammageing. A number of studies have proved that chronic insomnia can promote an increased risk of mortality for cardiovascular diseases (and in women especially).

Sleep and ageing

Sleep disorders promote ageing and ageing-related dIsease, generating a global psycho-neuroendocrine-immune imbalance. Inflammageing, or low-grade chronic inflammation, is one of the main players of this imbalance that binds sleep disorders to ageing processes and ageing-related diseases. While acute inflammation is normally tightly controlled, and is a part of the healing process, the low-grade elevation of inflammatory markers seen in older adults has been associated with a number of chronic conditions of ageing, such as CVD, diabetes, obesity, sarcopoenia, physical disability, cognitive decline, cancer and increased mortality.

A number of inflammatory markers, especially IL-6, tumour necrosis factor-alpha (TNF-α) and C-reactive ▷

protein (CRP), have the most consistent associations with age-related chronic disease and disability. Their production increases with age, and high blood levels of IL-6 in particular, checked at 8am (>4.18pg/ml) is considered an important marker of unsuccessful ageing and ageing-related disease. The exact mechanism for the increase of inflammatory cytokines with age has not been fully understood. Proposed mechanisms include the known increase in total and visceral adiposity with age (fat mass produces approximately the 15–30% of IL-6), the declining levels of sex hormones and insulin growth factor-1 (IGF-1) after menopause and andropause, malnutrition, physical inactivity, subclinical chronic infection, dysbiosis, chronic stress and chronic pain diseases.

Oxidative damage with ageing, which further invokes an inflammatory response, may be another mechanism leading to an increase in the level of these markers. The physiologic alteration of sleep architecture that characterises ageing processes and ageing-related sleep disorders, are also considered important pathogenetic factors of inflammageing.

An interesting study published in *Biological Psychiatry* (2008), has proven that sleep deprivation activates TNF gene expression through an increased adrenergic output related to stress. TNF-α is a strong activator of NF-κB, and then of IL-6 and inflammatory cascade. An enhancement of IL-6 release is also promoted by the activation of adrenergic tone. NF-κB activation is thought to contribute to the pathophysiology of diseases such as diabetes mellitus, CVD, cancer and atherosclerosis. Given the evidence that sleep disturbance is associated with each of these conditions, sleep-dependent NF-κB activation may be a common mechanism in the cumulative burden that finally leads to morbidity and mortality.

A further study published by the same university (UCLA) in 2010, showed that sleep loss promotes higher activation of inflammatory cascade in women compared with men. Whereas both females and males showed a marked increase in lipopolysaccharide (LPS)-stimulated production of IL-6 and TNF-α the morning immediately after sleep deprivation, production of these cytokines during the early and late evening was increased in females as compared with decreases in males. These results have implications for understanding the role of sleep disturbance in the differential risk profile for inflammatory disorders between the sexes and the increased cardiovascular mortality rate in women with sleep loss compared with men (women suffer from sleep disorders and chronic inflammatory diseases more than men).

Conclusions

It is possible to say, then, that old age is associated with decreased sex steroid concentration, increased proportional body fat, decreased quantity and quality of sleep, and frequent chronic pain/inflammatory conditions that promote inflammageing. Reducing the secretion of IL-6 in older patients, by administration of sex steroids, decreasing fat through diet and exercise, improving nighttime sleep, and adequately controlling chronic pain and inflammation, may improve sleep, daytime alertness, and performance (altered by the accumulation of evening cortisol and daytime IL-6 during ageing), and in turn decrease the risk of common ailments of old age (e.g. metabolic and cardiovascular problems, cognitive disorders, and osteoporosis).

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