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Review

The impact of sleep on age-related sarcopenia: Possible connections and clinical implications

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ABSTRACT

Sarcopenia is a geriatric condition that comprises declined skeletal muscle mass, strength and function, leading to the risk of multiple adverse outcomes, including death. Its pathophysiology involves neuroendocrine and inflammatory factors, unfavorable nutritional habits and low physical activity.

Sleep may play a role in muscle protein metabolism, although this hypothesis has not been studied extensively. Reductions in duration and quality of sleep and increases in prevalence of circadian rhythm and sleep disorders with age favor proteolysis, modify body composition and increase the risk of insulin resistance, all of which have been associated with sarcopenia.

Data on the effects of age-related slow-wave sleep decline, circadian rhythm disruptions and obstructive sleep apnea (OSA) on hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG), somatotropic axes, and glucose metabolism indicate that sleep disorder interventions may affect muscle loss. Recent research associating OSA with the risk of conditions closely related to the sarcopenia process, such as frailty and sleep quality impairment, indirectly suggest that sleep can influence skeletal muscle decline in the elderly.

Several protein synthesis and degradation pathways are mediated by growth hormone (GH), insulin-like growth factor-1 (IGF-1), testosterone, cortisol and insulin, which act on the cellular and molecular levels to increase or reestablish muscle fiber, strength and function. Age-related sleep problems potentially interfere intracellularly by inhibiting anabolic hormone cascades and enhancing catabolic pathways in the skeletal muscle.

Specific physical exercises combined or not with nutritional recommendations are the current treatment options for sarcopenia. Clinical studies testing exogenous administration of anabolic hormones have not yielded adequate safety profiles. Therapeutic approaches targeting sleep disturbances to normalize circadian rhythms and sleep homeostasis may represent a novel strategy to preserve or recover muscle health in older adults. Promising research results regarding the associations between sleep variables and sarcopenia biomarkers and clinical parameters are required to confirm this hypothesis.

Contents

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1. Introduction

Aging is an inexorable process that involves complex interactions among endogenous, environmental and lifestyle factors. This process commonly leads to increased morbidity and mortality risks due to declining physiological and functional reserves. The multi-systemic nature of aging and its interactions with diverse chronic diseases suggest that geriatric syndromes, such as sarcopenia, have an intricate multifactorial pathophysiology (Rosenberg, 1997).

Skeletal muscle loss advances with age (Brady et al., 2014). Muscle tissue is essential not only for motor function but also for metabolic processes (Iizuka et al., 2014). Muscle mass interacts bidirectionally with systemic hormonal and inflammatory factors, and muscle loss is associated with the development of other geriatric syndromes, such as frailty (Roubenoff, 2000). In 1989, the term "sarcopenia" was proposed to describe the continuous and progressive age-related decline in skeletal muscle mass and muscle strength and, as a result, the loss of functional capacity (Rosenberg, 1989). Sarcopenia is associated with greater health costs, morbidity and mortality (Chumlea et al., 2011). Seniors between 70 and 80 years of age who are in the lowest quartile of muscle density have a 51% increase in the risk of hospitalization compared with seniors who are in the highest quartile (Abellan Van Kan et al., 2011).

Sarcopenia has been defined as a morphological and functional decline in lean body mass. Its operational diagnostic criteria are evolving, and no gold standard exists. Increasing evidence indicates that lean body mass is not the single factor related to reduced strength and impaired function (Visser et al., 2000). This parameter needs to be combined with poor strength or low gait speed to establish a sarcopenia diagnosis (Fielding et al., 2011). However, clinically relevant thresholds for these 3 sarcopenia dimensions are still being researched. More studies are required to clearly define the aspects that impact the body composition throughout the aging process, such as socio-demographic factors and clinical characteristics, and how to operationalize them into a broad and practical assessment method for the diagnosis of this condition (Spira et al., 2015).

Additional aspects of physiological regulation change with advancing age. Specifically, the deterioration of sleep parameters with age has been carefully studied. It is well documented that sleep architecture changes during adulthood and that sleep disorders are more common in the elderly population (Ohayon et al., 2004). Therefore, we propose that age-related sleep patterns and sleep disturbances contribute to skeletal muscle decline leading to sarcopenia. This novel hypothesis builds upon evidence linking polysomnography changes, insufficient sleep and sleep disturbances as they occur in older adults with the dysregulation of somatotropic, gonadal and corticotropic activity, as well as glucose metabolism, which disrupt the secretory pattern of hormones involved in muscle metabolism (Veldhuis and Iranmanesh, 1996; Van Cauter et al., 2004).

2. Influence of hormonal pathways on age-related muscle metabolism imbalance

GH and testosterone lead to nitrogen retention and protein synthesis, which promote muscle anabolism (Salomon et al., 1989; Bhasin et al., 1996). Consequently, GH, IGF-1 (an anabolic hormone secreted in response to GH secretion) and testosterone reductions can contribute to deteriorations in muscle mass and physical function. GH deficiency syndrome and hypogonadism at a young age lead to decline in body composition, muscle strength and physical performance, resembling those found in healthy aged individuals (Cuneo et al., 1990; Katznelson et al., 1996).

Similarly, anabolic hormonal pathways deteriorate with age, thus contributing to the development of sarcopenia (Veldhuis et al., 1995; Harman et al., 2001), and GH and/or testosterone replacement could reverse muscle mass deterioration related to aging (Rudman et al., 1990; Snyder et al., 1999). A reported 6-month intervention with GH or testosterone alone produced increases in whole body protein turnover and protein synthesis in healthy elderly men (Giannoulis et al., 2012). Other previous research found similar increases in muscle mass and strength with GH replacement with or without combined sexual steroid therapy in aged men and women (Blackman et al., 2002). However, the risks related to GH therapy, such as cancer development, lead to safety concerns (Swerdlow et al., 2002). Similar concerns were found for testosterone therapy. Moreover, as recently reported (Vigen et al., 2013; Finkle et al., 2014), men receiving testosterone replacement therapy may develop a higher risk of cardiovascular disease.

Additionally, cortisol is related to muscle catabolism in aging, and sarcopenic subjects have elevated cortisol levels (Waters et al., 2008). Muscle weakness and wasting were strongly correlated with hypercortisolism. Regardless of age, patients with Cushing syndrome present body composition changes similar to sarcopenia in older adults (Miller et al., 2011).

3. Sleep in advanced age

Age-related changes in sleep/wake cycle are broadly documented and may be due to an interaction among circadian, homeostatic processes and comorbidities (Crowley, 2011). Studies have demonstrated marked changes in sleep structure with aging, including a decrease in total sleep time and sleep efficiency, a decrease in the amount and intensity of slow-wave sleep (SWS), also named stage N3 non-REM sleep, and an increase in wake time after sleep onset (WASO) (Moraes et al., 2014). Complaints of sleep difficulties are more common among older people. Approximately 50% of the elderly report sleep problems (Neikrug and Ancoli-Israel, 2010a). Sleep disorders can lead to increased morbidity and mortality in this population (Morimoto et al., 2012; Martinez-Garcia et al., 2012; Birkbak et al., 2014; Su et al., 2014). However, reverse causality is also frequent, and comorbidities may contribute to sleep problems (Neikrug and Ancoli-Israel, 2010a). The relationship between chronic diseases and sleep disorders, whether direct or indirect, can progress in the form of a vicious cycle in which