

The impact of postmenopause on sleep and sleep disorders: The current state of the art

O impacto da pós-menopausa no sono e nos distúrbios do sono: O estado atual da arte

El impacto de la posmenopausia sobre el sueño y los trastornos del sueño: Estado actual de la cuestión

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Abstract

Sleep disorders in postmenopausal women are important symptoms that demonstrate the impact of the hormonal changes that have begun since menopause. Hormonal changes during the transition to postmenopause play a crucial role in sleep disorders, contributing to symptoms such as insomnia, hot flashes, obstructive sleep apnea and restless legs syndrome. Such disorders impact on women's quality of life, increasing the risks of developing chronic and psychological health conditions, including depression, anxiety and cardiovascular disease. In addition, Hormone Replacement Therapy (HRT) in the treatment of menopausal symptoms is the most widely used pharmacological therapy, although its effectiveness in improving sleep quality is still uncertain due to the heterogeneous nature of the results. Sleep hygiene, together with Cognitive-Behavioral Therapy for Insomnia (CBT), has emerged as a promising non-pharmacological approach to the management of sleep disorders in postmenopausal women. The management of sleep disorders in postmenopausal women should be analyzed taking into account the physical, psychological and hormonal aspects of the patients.

Keywords: Sleep wake disorders; Menopause; Hormone replacement therapy.

Resumo

Os distúrbios do sono em mulheres na pós-menopausa são sintomas importantes que demonstram o impacto das alterações hormonais que começaram desde a menopausa. As alterações hormonais durante a transição para a pós-menopausa desempenham um papel crucial nos distúrbios do sono, contribuindo para sintomas como insônia, ondas de

calor, apneia obstrutiva do sono e síndrome das pernas inquietas. Esses distúrbios afetam a qualidade de vida das mulheres, aumentando os riscos de desenvolvimento de problemas de saúde crônicos e psicológicos, inclusive depressão, ansiedade e doenças cardiovasculares. Além disso, a Terapia de Reposição Hormonal (TRH) no tratamento dos sintomas da menopausa é a terapia farmacológica mais usada, embora sua eficácia na melhoria da qualidade do sono ainda seja incerta devido à natureza heterogênea dos resultados. A higiene do sono, juntamente com a Terapia Cognitivo-Comportamental para Insônia (TCC), surgiu como uma abordagem não farmacológica promissora para o tratamento de distúrbios do sono em mulheres na pós-menopausa. O tratamento dos distúrbios do sono em mulheres na pós-menopausa deve ser analisado levando-se em conta os aspectos físicos, psicológicos e hormonais das pacientes.

Palavras-chave: Distúrbios do sono e vigília; Menopausa; Terapia de reposição hormonal.

Resumen

Los trastornos del sueño en las mujeres posmenopáusicas son síntomas importantes que demuestran el impacto de los cambios hormonales iniciados desde la menopausia. Los cambios hormonales durante la transición a la posmenopausa desempeñan un papel crucial en los trastornos del sueño, contribuyendo a síntomas como el insomnio, los sofocos, la apnea obstructiva del sueño y el síndrome de las piernas inquietas. Estos trastornos repercuten en la calidad de vida de las mujeres y aumentan el riesgo de desarrollar enfermedades crónicas y psicológicas, como depresión, ansiedad y enfermedades cardiovasculares. Además, la Terapia Hormonal Sustitutiva (THS) en el tratamiento de los síntomas menopáusicos es la terapia farmacológica más utilizada, aunque su eficacia en la mejora de la calidad del sueño es aún incierta debido a la heterogeneidad de los resultados. La higiene del sueño, junto con la terapia cognitivo-conductual para el insomnio (TCC), ha surgido como un enfoque no farmacológico prometedor para el tratamiento de los trastornos del sueño en mujeres posmenopáusicas. El tratamiento de los trastornos del sueño en las mujeres posmenopáusicas debe analizarse teniendo en cuenta los aspectos físicos, psicológicos y hormonales de las pacientes.

Palabras clave: Trastornos del sueño; Menopausia; Terapia hormonal sustitutiva.

1. Introduction

Sleep is a physiological process of functional recovery of the brain and is described as a fundamental mechanism that occurs in most species (Lefter et al., 2022). Sleep has numerous functions for the body, from the development and regulation of affective brain function to the processing and consolidation of memories (Atrooz et al., 2020; Klizing et al., 2019). Inadequate sleep regulation impairs the regulation of various systems, such as metabolism, the cardiovascular system (Chellappa et al., 2019) and even affects the functional connectivity between neurons (Mason et al., 2021).

Sleep disorders, such as insomnia, are very prevalent in postmenopausal women and can lead to various illnesses, such as depression. Symptoms of sleep disorders, such as daytime fatigue, excessive sleepiness and low energy, worsen productivity at work and reduce quality of life (Kalmbach et al., 2019). The post-menopausal decline in estrogen and progesterone contributes to sleep disorders in women; timely treatment with these hormones can improve sleep quality and, consequently, general well-being (Haufe et al., 2022).

The perimenopause can be described as the deterioration of ovarian function which leads to endocrine changes, in a non-linear and gradual way. It is an event related to the aging process and occurs naturally between the ages of 50 and 53 (Grisotto et al., 2022). The menopause, therefore, is the end of the reproductive period, described as the last cycle of the menstrual period (Marjoribanks et al., 2017). Women enter the postmenopausal period when menstruation ceases for a period of 1 year, and a variety of symptoms are related to this period (Grisotto et al., 2022).

Sleep disorders are mainly related to perimenopause, menopause and postmenopause, with severity varying depending on culture and ethnicity (Xu et al., 2014). The symptoms of menopause appear and among them, sleep dysfunctions are observed and tend to vary from 24% to 50% of women, causing changes in the quality of life of this population (Khadivzadeh et al., 2018). Sleep disorders are related to changes in the sleep process, whether it's going to sleep or waking up, as well as unsatisfactory sleep, nocturnal awakenings and waking up before the usual time (Cintron et al., 2017).

Hormonal changes resulting from the menopause, such as a reduction in estrogen levels, can contribute to the appearance of hot flushes with a sudden sensation of body heat around the face and neck, usually accompanied by sweating and tachycardia (Lee et al., 2019), as well as sleep disorders such as obstructive sleep apnoea and insomnia (Laudisio et al., 2021).

Therefore, due to a longer life expectancy and consequently more time in the postmenopausal period, the hormonal changes that occur in this period lead to dysfunctions in the functional connectivity of brain areas related to the ascending inhibition system. Therefore, the aim of this review is to analyze and describe how hormonal changes in the post-menopause alter sleep variability, leading to sleep disorders.

2. Method

This article presents a narrative literature review based on the analysis of scientific articles published from 2013 to 2023, in PubMed and ScienceDirect, about insomnia in women during menopause. In the application of the first set of criteria, titles that did not mention the theme “insomnia and postmenopause and sleep” were excluded, as well as articles that were not included in the research period from 2013 to 2023 and articles that were not found in English. The second set of criteria was applied, from which were excluded the abstracts that did not address sleep disorders in postmenopause. In the PubMed database, 414 articles were found through the keywords (Postmenopause) AND (Sleep Disorders), 42 were selected following the first exclusion criteria. In the Science Direct database, 128 articles were found using the keywords (Postmenopause) AND (Sleep Disorders) AND (Endocrine System), of which only 9 studies. The second set of criteria was applied, from which abstracts that did not address the topic of hormonal fluctuations and sleep disorders were excluded, which led to the exclusion of 7 articles in the pubmed database and 4 articles in the Science Direct database. Among the remaining articles, 1 were duplicates, covering the pubmed and science direct databases. In total, 35 articles originally in English remained.

3. Discussion

3.1 Sleep in perimenopause and postmenopause

The menopause is a defining chapter in women's lives, characterized by hormonal, physical and psychological transformations, and this turn of events can trigger disturbances in sleep patterns (Kolesnikova et al., 2013).

The menopause, marked by the end of menstrual cycles, usually occurs around a woman's 52nd birthday. During the perimenopause, which covers a period of seven to ten years before the menopause, the ovaries gradually reduce their production of the hormones estrogen and progesterone. These hormonal changes play a crucial role in sleep problems, which often persist into the post-menopause, the period following the menopause (Lee et al., 2019).

On average, around 12% of women face sleep-related challenges. However, as women advance through the age range from late 40s to early 50s, this statistic jumps significantly, affecting around 40% of them. Sleep problems become more prominent and worsen during the perimenopause, which is the period leading up to the menopause and extending into the postmenopause, when women usually report the greatest difficulties sleeping (Lee et al., 2019).

Women in the transition to menopause generally complain of poor sleep quality, insufficient sleep, nocturnal awakenings and apnea. Sleep difficulties usually begin during the menopausal transition and their prevalence increases in postmenopausal life with rates of self-reported sleep problems ranging from 40% to 56%, compared to premenopausal women in their late reproductive stage reporting rates of 31% (Monteleone et al., 2018).

Sleep deprivation is a known risk factor for cardiovascular disease, diabetes, obesity and neurobehavioral dysfunction and can lead to increased health costs and reduced quality of life and work performance. Sleep disorders can be classified into three groups: difficulty falling asleep, waking up several times and waking up early. An eight-year longitudinal analysis of data from more than 3,000 women in the Nationwide Women's Health Study showed that waking up during the night was the most common type of sleep problem (Baker et al., 2018; Korostovtseva et al., 2021).

As a consequence, there are symptoms of depressed mood, anxiety, irritability and hostility. Thus, these disorders can occur due to the emotional symptoms that are very common during this period (Kalmbach et al., 2019). Furthermore, during

this period many women complain of negative changes in memory, such as difficulty with words, forgetfulness and "brain fog", which suggests the idea that hormonal changes related to the menopause are responsible for cognitive deficits. However, there is insufficient longitudinal data on the relationship between the menopause transition and cognitive deficits (Moreno-Frías et al., 2014).

It is important to note that certain depressive consequences related to sleep deprivation can be avoided with Cognitive Behavioral Therapy and Sleep Reduction Therapy. In addition, problems related to somatic hyperexcitation, characterized by anxiety and difficulty relaxing, one of the causes of difficulty falling asleep, as mentioned above, can be treated with significant responses with Cognitive Behavioural Therapy (Kalmbach et al., 2019).

3.2 Postmenopause and sleep disorders

The changes in hormone levels resulting from the peri-menopause become one of the risk factors associated with the development of sleep disorders. Difficulty initiating sleep and manifestations of nocturnal hot flashes stand out as the most frequent symptoms among women in the transition from menopause to postmenopause. These symptoms have the potential to establish a cycle of compromised quality of life in this population, since chronic sleep disorders are a cardiovascular risk factor (Zolfaghari et al., 2020).

On average, sleep problems in post-menopausal women affect 35% to 40% of the population, but over the years this figure can reach 60%. Sleep disorders are related to the physiological changes associated with the natural aging process, high levels of stress, depression, anxiety and other chronic health conditions. The most commonly reported disorders are hot flashes, insomnia, obstructive sleep apnea and restless legs syndrome (Caretto et al., 2019).

In addition, hot flashes should be studied because, being a relevant marker of sleep dissatisfaction, in their form associated with sweating and therefore known under the umbrella term of vasomotor symptoms, they affect up to 80% of women during the menopause transition (Baker et al., 2018). To explain this symptom, one must take into account the increase in core body temperature in a very narrow thermoneutral zone, as well as changes in sex steroids and gonadotropins (with GnRH being a hypothalamic link between pituitary gonadotropins, hot flashes and insomnia) during the menopause transition and in the first years of postmenopause. As for the frequency and severity of hot flashes, there is an association between this and the severity of insomnia symptoms and objective measures of nocturnal wakefulness and sleep fragmentation: there is no one-to-one relationship between hot flashes and nocturnal awakening, as what occurs is an underlying disturbance in the autonomic nervous system or another process occurring in women with vasomotor symptoms (Guthrie et al., 2018; Valiensi et al., 2019).

Depressive symptoms are associated with hot flashes, so these two symptoms are related to sleep disorders, manifested precisely as frequent awakenings and depression associated with difficulty falling asleep and waking up earlier than desired. In addition, the more severe the hot flashes, the more likely the woman is to suffer from chronic insomnia (Baker et al., 2018). In addition, the combination of hot flashes and insomnia with other frequent symptoms, such as pain and depressed mood, can make sleep disorders even worse, since a cycle of insomnia can be concatenated in the process of the woman, who is already awake and aroused, and who will also have difficulty falling back asleep and ruminating thoughts, resulting in compensatory napping behaviors that prolong time in bed (Guthrie et al., 2018).

Hormone replacement therapy (HRT), consisting of estrogen combined with progestin and estrogen alone, is the most effective treatment for menopausal symptoms. In cases where TH is contraindicated, serotonin/serotonin and noradrenaline reuptake inhibitors could be prescribed, such as paroxetine - approved by the FDA in the USA to treat moderate to severe hot flashes related to the menopause - or gabapentin, but the former only has limited reach and potency in reducing hot flashes and insomnia when present alongside this symptom, and the latter only has evidence from one trial showing its benefits (Baker et al., 2018).

Women transitioning from peri-menopause and menopause to post-menopause often experience difficulty initiating sleep or staying asleep throughout the night. These insomnia symptoms directly affect total sleep duration and sleep efficiency. Thus, these symptoms have been directly and negatively associated with the postmenopausal state due to the hormonal dysfunctions that begin in the peri-menopausal phase (Moreno-Frías et al., 2014).

Obstructive sleep apnea (OSA) is one of the most common disorders found in postmenopausal women. This condition consists of repetitive episodes of complete or partial obstruction of the upper airways resulting in a temporary decrease in oxygen saturation and brief nocturnal awakenings (Galvan et al., 2017). Although the incidence of OSA is higher in men, due to an increase in life expectancy, hormonal changes and even obesity, the incidence in women has increased significantly, as these factors contribute to the development of obstructive sleep apnea (Huang et al., 2018; Naufel et al., 2018).

During the menopause and post-menopause transition, sleep disorders can arise in association with restless legs syndrome (RLS), the cause of which is probably more related to ageing than to hormonal changes (Baker et al., 2018). Thus, RLS itself is a specific sleep disorder with distinct etiological causes (Caretto et al., 2019, 10) and is a prominent predictor of objective sleep efficiency in polysomnography, being the cause of sleep problems in 18.5% of patients (Valiensi et al., 2019).

A challenge for periodic limb movement disorder (Baker et al., 2018) is that it can be an exclusion criterion in patient selection in studies on menopause and sleep problems because it is a specific disorder and therefore remains a factor which, although it is part of menopause symptoms, is sometimes not quantified and discussed (Toffol et al., 2014). Despite this challenge, it is of the utmost importance to identify patients' morbidities and comorbidities, analyzing the interaction of these factors and assessing their impact on their sleep (Caretto et al., 2019). In order to qualify PIS, aspects such as sensation in the legs, the need to move the lower limbs while sitting or lying down and whether these symptoms worsen in the afternoon or at night and disappear when active should be asked (Zolfaghari et al., 2020).

3.3 Efficacy of hormone replacement therapy on sleep in postmenopausal women

The use of HT should be based on "joint decision-making" between doctor and patient, taking into account the risks and benefits. The choice of HT should take into account the type of hormonal use, the dose, the formulation, the route of administration, the time of initiation, the duration of use and whether progesterone should be included. Personalized treatment should consider the relationship between benefits and risks, with periodic reassessments or the possibility of discontinuing treatment (Cintron et al., 2017).

HT shows a more favorable risk-benefit ratio when started in the early stages of menopause. In addition, the symptomatic benefits of HT seem to outweigh the risks of side effects when the therapy is used for up to five years (Stute et al., 2023). HT is recommended as the most effective treatment for menopausal symptoms, including sleep disorders (Cintron et al., 2017).

A recent systematic review with meta-analysis found no significant improvements in sleep parameters in the group of women receiving HT, including total sleep time, sleep latency, sleep efficiency and number of awakenings. However, the quality of this evidence is considered low due to the limited number of participants in the studies. When assessed by subgroups, 12 studies investigating self-reported sleep outcomes showed a significant improvement in sleep quality among women receiving HT. However, this evidence is also considered low quality due to the methodology of the studies evaluated. Other subgroup analyses, considering the sample size and duration of the studies, have indicated improvements in sleep quality with HRT in postmenopausal women. In addition, when evaluating different types of estrogen and progesterone as part of HT, some improvements were shown in sleep quality, while others showed no positive impact (Pan et al., 2022).

HT seems to have a beneficial effect on sleep disorders to a certain extent. The formulations and routes of administration of the hormonal agents, the patient's genotype, age, adipose tissue composition, the presence of comorbidities and the use of

other medications can influence the size of this effect, affecting the methodological approach of the studies and exerting an influence on the results (Pan et al., 2023; Pan et al., 2022).

Unfortunately, there is currently no completely satisfactory therapy available. Therefore, the search for better options becomes essential. The new perspectives on HT for sleep treatment seek to evaluate the most recent studies and promote adequate training for physicians. In addition, more comparative randomized clinical trials with larger, multicentre samples are needed to assess the effects of different routes of administration and formulations of HT on sleep quality in order to provide better evidence (Pop et al., 2023).

3.4 Sleep hygiene and post-menopause

Insomnia is a common symptom in postmenopausal women, increasing the risk of depression in this group, which is already at high risk of developing psychiatric conditions. Although many patients report symptoms of insomnia such as nocturnal awakenings and an inability to return to and/or maintain sleep, not all of them meet the requirements for a formal diagnosis; these symptoms are related by patients to sensations of nocturnal hot flushes and night sweats - vasomotor symptoms (Guthrie et al., 2018).

It is known that vasomotor symptoms are associated with changes in sex steroids and a rise in body temperature, and the intensity of insomnia symptoms is directly proportional to the intensity of hormonal changes and a rise in body temperature, although it has not been possible to establish a causal relationship between them. The study (Kolesnikova et al., 2013) also showed an association between sleep disorders, including insomnia, and decreased melatonin secretion in postmenopausal women during the day and night when compared to perimenopausal women who showed a change in the time when melatonin secretion became more intense.

When we think about sleep hygiene in menopausal patients, we must first question whether they have adequate and sufficient knowledge on the subject and whether they are actually being effectively assisted and educated by the health teams that are accompanying them. The study (Viçeta et al., 2013) showed that of the 72 women seen by the Climacteric Outpatient Clinic and the Sleep Disorders Outpatient Clinic at the Federal University of São Paulo Teaching Hospital, linked to the Unified Health System (SUS), only 20.8% of them understood the term "sleep hygiene" despite recognizing some of the measures encompassed by this definition.

Sleep hygiene is made up of general guidelines given to the patient in order to preserve the integrity of the sleep-wake cycle, such as: a suitable environment (room with low light, adequate temperature and low noise levels), following bedtime and wake-up times, avoiding stimulating substances such as caffeine, nicotine, alcohol, stimulating drugs, exhausting physical activity and eating caloric foods close to bedtime (Granados et al., 2018; Castro-Santos et al., 2023).

The aim of sleep hygiene, in addition to maintaining the sleep-wake cycle, is to reduce the sleep latency period in order to increase total sleep time and improve the quality of sleep and quality of life of patients, enabling them to carry out routine activities (Granados et al., 2018; Castro-Santos et al., 2023).

Recent studies indicate Cognitive Behavioral Therapy for Insomnia (CBT/CIBT) as the first line of non-pharmacological therapy for these patients. CTBI has been shown to be the non-pharmacological therapy with the greatest reduction in insomnia symptoms, but with little influence on cognitive arousal in the pre-sleep period, rumination of thoughts and anxious thoughts (Kalmbach et al., 2019).

The MsFLASH trials tested 7 interventions on approximately 1,000 female patients who reported vasomotor symptoms and insomnia symptoms ranging in severity from mild to moderate. Among the interventions evaluated were: Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin-Norepinephrine Reuptake Inhibitor (SNRI), low-dose estrogen replacement, yoga, aerobic exercise, omega-3 fatty acid supplementation and Cognitive Behavioral Therapy for Insomnia (Guthrie et al., 2018).

4. Conclusion

Therefore, as a result of advances in medicine and increased life expectancy, especially in the female population, a higher prevalence of sleep disorders can be observed, not only in the menopause, but also in the post-menopause period. In this review, we analyze how hormonal changes from the menopause to the post-menopause affect sleep quality in women and which are the most current therapies for treating these disorders. Thus, this study will contribute to a better understanding of sleep disorders in postmenopausal women and the most up-to-date treatments.

Conflict of interest

The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

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