



Sleep Disorders and Menopause

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Sleep disorders are one of the main symptoms of menopause. Symptoms of sleep disorders that menopausal women complain about include falling asleep, frequent awakening and/or early morning awakening. There are many possible causes of sleep disorders in postmenopausal women, including vasomotor symptoms, ovarian hormone changes, restless legs syndrome, periodic leg movement syndrome, and obstructive sleep apnea. In this review, we discuss the relationship between menopause and sleep disorders.

Key Words: Menopause, Postmenopause, Sleep wake disorders

INTRODUCTION

Sleep is composed of rapid eye movement (REM) sleep, characterized by rapid eye movement and decreased muscle tone during sleep, and non-REM (NREM) sleep. Normally, sleep level repeats at a cycle of about 90 to 120 minutes between REM and NREM sleep and occurs about 5 cycles per night. REM sleep accounts for 20% to 25% of total sleep and NREM sleep 75% to 80% [1]. Sleep is controlled by two ways: the homeostatic process, and circadian process. The longer people stay awake, the more they sleep. The desire for sleep is one of the automatically-controlled homeostatic processes and depends on the amount of prior wakefulness. The circadian process is regulated by an endogenous circadian pacemaker. The suprachiasmatic nucleus mainly controls the circadian rhythm and is controlled by hypothalamus. Complex interactions among neurotransmitters, and interconnected neurons promote or suppress sleep and wakefulness [1]. Insomnia and fatigue are the most common symptoms of postmenopausal women. The definition of menopause refers to the period after 1 year has elapsed since the last menstrual period [2]. However, changes in hormones begins to occur 7 to 10 years before menopause,

leading to a decrease in estradiol and inhibin and an increase in follicle-stimulating hormone and luteinizing hormone [3,4]. Women undergo physical and psychological changes as a result of hormonal changes, e.g., mood swing, anxiety, stress, forgetfulness, and sexual dysfunction [5,6]. Many women especially complain of sleep disorders at this time.

According to the Study of Women's Health Across the Nation (SWAN), the prevalence of sleep disorders increases with age. The prevalence of sleep disorders is variable, ranging from 16% to 42% in premenopausal women, from 39% to 47% in perimenopausal women, and from 35% to 60% in postmenopausal women [7]. Symptoms of sleep disorders that menopausal women complain about include falling asleep, frequent awakening and/or early morning awakening [8]. The etiology of sleep disorders in menopausal women isn't yet clear and seems to be different to according to the specific symptoms of sleep disorder. However potential factors include the menopause itself, aging, vasomotor symptoms, depression, anxiety, and many other medical condition, such as cardiovascular, endocrine disease, medication, and psychosocial factors [9].

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EFFECT OF MENOPAUSE ON SLEEP DISORDER AND TREATMENT

Vasomotor symptoms

Vasomotor symptoms are the most common menopausal symptoms reported by 75% to 85% of postmenopausal women. Hot flashes are defined as a sudden sense of body heat or redness around the face and neck, often accompanying sweating and tachycardia. Most symptoms last for 1 to 2 years after menopause but rarely last for more than 10 years. Although many perimenopausal and postmenopausal women experience vasomotor symptoms, the cause is not clear. However, there is evidence that vasomotor symptoms are caused by estrogen withdrawal [10]. Some herbal treatments for menopausal symptoms contain hops (*Humulus lupulus* L.) and its components which have high estrogenic potency. Although the mechanisms which hops relieves menopausal symptoms are not clearly understood, preparations based on hops have been found to decrease the severity and frequency of hot flashes [11].

In some studies, vasomotor symptoms of perimenopausal and postmenopausal women have been reported as one of the causes of sleep disturbances. A recent study has shown that vasomotor symptoms were related to poor sleep quality [12]. Other studies have supported this finding by suggesting that hormone therapy improves sleep quality [13]. However, some argue that there is no close relationship between vasomotor symptoms and sleep disorders. Young et al. [14] showed that menopause was not a strong predictor of sleep disorders, although perimenopausal and postmenopausal women have lower quality sleep than premenopausal women.

Hormone change (estrogen/progesterone)

Ovarian hormones have been reported to affect sleep disorders. Progesterone has both sedative and anxiolytic features. It stimulates the production of the NREM associated gamma-aminobutyric acid receptors by stimulating benzodiazepine receptors [15]. In addition, progesterone also acts as a respiratory stimulant and has been used to treat mild obstructive sleep apnea (OSA) [16]. The effect of estrogen on sleep structure is complex as estrogen has a wide range of effects that potentially affects sleep structure. First, it is associated with metabolism of norepinephrine, serotonin, and acetylcholine-neurotransmitters that affect sleep

pattern. Estrogen has been proved to decrease sleep latency, the number of awakening after sleep occurs, and cyclic spontaneous arousals; and increase total sleep time [17,18]. Second, estrogen has a regulating effect on body temperature. During the night, estrogen plays a role in keeping the central body temperature low [19,20]. In mammals, estrogen is a hormone that regulates the temperature of the lowest body temperature during the night. When decreased estrogen, this time shift forward and the depth of the temperature drop changes [19]. Estrogen has a direct effect on mood by affecting the norepinephrine activity and serotonin response and uptake in the brain. All of these effects mean that estrogen would have an antidepressant effect [20,21].

If we treat menopausal symptoms earlier in the menopause period with estrogen or estrogen-progesterone therapy, it will have a more beneficial effect in improving menopausal symptoms. Estrogen therapy is very effective in treating vasomotor symptoms, which improves sleep quality, and hormone replacement therapy is one of the main therapies for osteoporosis, mood disorder, and depression [22,23]. Studies have shown that estrogen replacement therapy improves sleep quality, enables falling asleep, decreases nighttime wakefulness and also reduces vasomotor symptoms [13]. Therefore, hormone replacement therapy is recommended for menopausal insomnia to improve the quality of sleep and life. For those who are starting hormone replacement therapy, use of low dose estradiol rather than conjugated estrogen is more suitable.

Melatonin

Melatonin plays a major role in circadian rhythm, especially in sleep onset and in sleep maintenance through block arousal mechanism. These effects help to keep humans sleeping at night. However, the relationship between melatonin and menopause is still unclear. Melatonin levels decline with aging process but are not always associated with menopause. Melatonin levels decrease with aging before menopause, but then increase again over the years. In some studies, melatonin levels in postmenopausal women with insomnia were lower than those in premenopausal women [24]. Recently, more potent melatonin analogs (selective melatonin-1 [MT-1] and melatonin-2 [MT-2] receptor agonists) have been developed with extended effects and slow release melatonin preparations [25,26]. The MT-1 and MT-2 melatonin receptor ramelteon [27,28]

was found to be effective in reducing total sleep time and sleep efficiency as well as reducing sleep initiation delay in patients with insomnia [29]. It has been shown that melatonergic antidepressant agomelatine, with strong MT-1 and MT-2 melatonergic agonists and relatively weak serotonin 5-hydroxytryptamine (2C) receptor antagonists [30,31], is effective in treating insomnia with insomnia. In short, melatonin compounds can be useful in the treatment of insomnia [32-40].

Mood disorders

Mood disorders such as anxiety or depression are associated with sleep disorders in postmenopausal women [41]. Difficulty in falling asleep cause to anxiety, irritability, and inadequate sleep and possibly depression [42]. One of the main causes of depression is insomnia. In addition, women with hot flushes are more likely to develop depression. Women with depression and hot flushes have a lower quality of sleep than women without depression. Consequently, depression and hot flushes may have additional effects on sleep pattern.

ASSOCIATED SLEEP DISORDER

Obstructive sleep apnea

The incidence of OSA is significantly increased in postmenopausal women. In some studies, from 47% to 67% of postmenopausal women are reported to suffer from OSA [43,44]. Women tend to gain weight after menopause. Gained weight leads to the increased neck circumference, the body mass index, and waist-hip ratio [43-46]. Thus, the upper airway changes anatomically after menopause and causes problems like OSA during sleep [15,47,48]. Therefore, it seems that the prevalence of OSA in postmenopausal women is higher than in premenopausal women [46]. However, body weight is not the only factor that causes this disease. Some studies have reported that testosterone is a factor that aggravates OSA [49]. The primary treatment for OSA is positive airway pressure. The effect of hormone therapy, such as estrogen and progesterone, is controversial. While some studies show improvement in symptoms [50,51], others do not [52].

Restless leg syndrome and periodic leg movement syndrome

The restless leg syndrome (RLS) is a disorder which that causes an urge to move the leg accompanied by an uncomfortable sensation. Although RLS is not associ-

ated with menopause and hormone therapy, it seems to increase with age [53]. The etiology is unclear but is known to be related to iron deficiency anemia, pregnancy, and uremia [46,54]. Periodic limb movement disorder (PLMD) is repetitive cramping or jerking of the legs during sleep occurring about every 20 to 40 seconds. PLMD is considered to cause to disrupt sleep and make arousal. The only reliable treatment for both diseases is dopamine agonist and also do not clearly respond to hormone therapy [55].

CONCLUSION

We have reviewed sleep disorders in postmenopausal women. We presented several factors and changes that affect women during the menopause transition and suggested the effect of these factors on sleep. However, because the etiology of sleep disorder in menopause is multifactorial, sleep disorders are simply a part of the aging. Although the cause of menopausal sleep disorder is not clear, some studies have reported that hormone therapy improves sleep quality and is considered a primary treatment if other causes are excluded. Despite of the effectiveness of hormone therapy, sleep disorders may simply be associated with limb movement syndrome, depression, anxiety and so on. Therefore, to manage effective sleep disorders in menopausal women, it is helpful to evaluate the cause. Further investigation by randomized controlled trials is needed to assess the efficacy of these treatments in postmenopausal women.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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