

Sharing Pathological Mechanisms of Insomnia and Osteoporosis, and a New Perspective on Safe Drug Choice

Sun Shin Yi¹, Soo-Ho Chung², Pan Soo Kim³

¹Department of Biomedical Laboratory Science, College of Medical Sciences, Soonchunhyang University, Asan, Korea, ²Department of Obstetrics and Gynecology, Soonchunhyang University College of Medicine, Bucheon, Korea, ³Bio-Center, Gyeonggido Business and Science Accelerator, Suwon, Korea

Lack of adequate sleep has become increasingly common in our 24/7 modern society. Reduced sleep has significant health consequences including metabolic and cardiovascular disorders, and mental problems including depression. In addition, although the increase in life expectancy has provided a dream of longevity to humans, the occurrence of osteoporosis is a big obstacle to this dream for both male and female. It is known that insomnia and bone health problems, which are very critical conditions in human life, interestingly, share a lot of pathogenesis in recent decades. Nevertheless, due to another side effects of the synthetic drugs being taken for the treatment of insomnia and osteoporosis, patients have substantial anxiety for the safety of drugs with therapeutic expectation. This review examines the pathogenesis shared by sleep and osteoporosis together and herbal medicine, which has recently been shown to be safe and efficacious in the treatment of both diseases other than synthetic drugs. We suggest how to treat osteoporosis. These efforts will be the first step toward enabling patients to have comfortable and safe prescriptions through a wide selection of therapeutic agents in the future. (**J Menopausal Med 2018;24:143-149**)

Key Words: Herbal medicine · Osteoporosis · Safety · Sleep

The Link between Sleep and Osteoporosis

A typical example of sleep deprivation is insomnia. In recent decades, there have been an increasing number of patients who are claiming insomnia regardless of age, and the causes are not limited, however, daily influencing life environments such as smartphone use, light noise, overwork, and the presence of absence of diseases can be cited.^{1,2} Chronic sleep loss is associated with deficits in attention, cognition, immune function, metabolism, mood, and cardiovascular function and hormonal disturbances.^{2,3} In addition, it is not easily to say which symptom is first, but

it is known that sleep deprivation and depression are also closely related.^{4,5} Even depression is recognized as a kind of disability in the United States, and some studies report that depression is an important risk factor for osteoporosis.^{5,6} Therefore, sleep quality is a very important factor for physical and mental health in human. In particular, postmenopausal women are under the influence of multiparity and prolonged lactation, severe hormonal changes by estrogen deficient condition, and osteoporosis is a major disease that occurs.⁷ Interestingly, osteoporosis is increasingly prevalent in men as well as women in recent years with hormonal disturbances.^{8,9} In male, eating behavior, appetite related hormone changes such as leptin, insulin and ghrelin, body

Received: October 21, 2018 Revised: November 8, 2018 Accepted: November 16, 2018

Address for Correspondence: Pan Soo Kim, Bio-Center, Gyeonggido Business and Science Accelerator, 107 Gwanggyo-ro, Yeongtong-gu, Suwon 16229, Korea

Tel: +82-31-888-6940, Fax: +82-31-888-6983, E-mail: pan@gbsa.or.kr

Copyright © 2018 by The Korean Society of Menopause

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).

mass index, sex hormone, and chronic consumptive disease such as pulmonary diseases are the major causes of osteoporosis.¹⁰⁻¹⁴ Thus, the cause of osteoporosis in women may be slightly different with in men, however, the quality of sleep is an important factor in the development of osteoporosis.^{15,16} Certainly, it is expected that there are hidden important links between sleep and osteoporosis, and there are effective mechanisms that can break the vicious cycle between the 2.

Possible Causative Factors of Bone Mass Deficit in Subjects with Insomnia

1. Hypothalamo-pituitary-adrenal (HPA) axis regulation

Stressors are imminent or perceived challenges to homeostasis in human. Our body is trying to restore the non-stressed homeostatic set point from any specific stress factors. Monoamine, cytokines, glutamate, γ -aminobutyric acid (GABA) and other central mediators have main roles in the normal stress response. In this context, corticotropin-releasing factor (CRF)/HPA axis and the sympathomedullary systems play a very important role in the regulation of the physical and psychological balance in body. Since HPA axis regulation is based on the principle of negative feedback system, it reacts by stress condition like insomnia, it secretes adrenal hormone to relieve this stress and reduces the secretion again when the cause is removed. However, if insomnia persists and stress factors are not removed, the secretion of adrenal hormone persists and body homeostasis is greatly affected. A research study demonstrated that sleep deprivation could increase cortisol concentration, which might decrease bone formation and bone mineral density (BMD).¹⁷ Moreover, there have reported that short sleep or long regulated in elevated pro-inflammatory cytokines, which subsequently increased osteoclast activity that insomnia is related to osteoporosis.¹⁸⁻²²

2. Sympathetic system

Stress is the disturbance of the complex dynamic equilibrium that all organisms must maintain, and is associ-

ated with activation of the stress system comprising of the HPA axis and the arousal/sympathetic nervous systems.²³ As mentioned earlier, the stress system functions on a baseline circadian fashion and interacts with other systems in the organism to regulate diverse behaviors, endocrine, metabolic, immune and cardiovascular functions, and this chronic stress condition may lead to several psychopathologic conditions, metabolic syndrome, and osteoporosis.²³ In mice experiment, mice were exposed to various severe stressors for 2 weeks, and the mice showed bone loss mediated by catecholaminergic system, as it could be improved by β -blocker.²⁴

Thus, chronic tension conditions lead to abnormal cortisol secretion, which can have an additional impact on cognitive and emotional development, puberty and timing of the final key even in children and adolescence. To prevent distraction during stressful situations, the capacity to seek and experience pleasure is reduced, food intake is diminished and sexual activity and sleep are held in abeyance.²⁵ Monoamines, cytokines, glutamate, GABA and other central mediators have key roles in the normal stress response. Many central loci are involved. The subgenual prefrontal cortex restrains the amygdala, the CRF/HPA axis and the sympathomedullary system.^{4,25,26} The function of the subgenual prefrontal cortex is moderately diminished during general stress to disinhibit these loci. This disinhibition enhances anxiety and physiological hyperarousal, while diminishing appetite and sleep.^{25,27} In addition, Kuriyama et al.²⁸ have directly confirmed that short sleep was closely associated with a decline in cortical bone thickness by enhanced bone resorption and sympathetic nervous system hyperactivity in the middle-aged group.

3. Sleep and hormones

(1) Orexin

Orexin-A and -B (also known as hypocretin-1 and -2) are neuropeptides secreted in the lateral hypothalamus that stimulate wakefulness, feeding, thermogenesis, and reward behaviors.^{29,30} Orexin deficiency in humans causes behavior abnormalities including sleep and mood disorders.³¹ Orexin deficiency and sleep disorders are also frequently related with major mood disorders such as depression.^{32,33} They

function through 2 receptors: Orexin-1R and Orexin-2R. It has known orexin deficiency in human and mice leads to narcolepsy, hypophagia, and obesity.^{34~36} Thus, there is tremendous pharmacological interest in developing orexin-targeting small molecules for the medications of sleep and metabolic disorders such as insomnia,³⁷ obesity, and diabetes,^{36,38,39} some of which has completed phase III clinical trials.³¹

(2) Ghrelin

It has known that ghrelin is a recently discovered brain-gut peptide with 2 main physiological actions such as growth hormone secretagogue activity and food intake inducer. In addition, ghrelin also plays the role of control of energy metabolism, regulation of gastric and pancreatic activity, and cardiovascular and hemodynamic activities, modulation of bone homeostasis, sleep and behavioral influences.⁴⁰ In same context, ghrelin and estrogen levels in plasma in women were significantly associated with according to Nouh et al.'s report⁴¹.

It has reported that Orexin-1R inhibits osteoblast differentiation by reducing osseous ghrelin expression without changing circulating ghrelin levels, suggesting that distinct mechanisms may account for the regulation of ghrelin expression in bone and stomach.³¹ Ghrelin siRNA knockdown experiments and previous pharmacological experiments show that ghrelin promotes osteoblastogenesis.^{42~44} Although ghrelin has yet to be clarified more clearly about the relationship between ghrelin and sleep and bone metabolism, various functions of ghrelin need to pay attention to the relationship between sleep and bone for a therapeutic approach.

(3) Leptin

Although many observations of leptin's cyclical pattern over the 24-hour day, relatively few studies have examined how the circadian rhythm of leptin may be essential to leptin signaling and health yet.⁴⁵ A circadian misalignment between behavior and circadian timing is known to lead to lower overall leptin levels suggesting that leptin responds to the endogenous circadian clock independently of some behaviors like feeding.^{45,46} It is also reported bone density, fertility and body weight regulation by leptin level. As described

in the sympathetic system section, leptin may influence the interactions between central and peripheral signals. In case of hypoleptinemia disturbed control of appetite and hormonal dysfunction as well as has implications for the hypothalamo-pituitary-gonadal axis, BMD and physical hyperactivity. Since leptin and orexin are very associated with sleep, eating, and bone density,^{31,47} it is necessary to further study about the sharing signaling to medicate the symptoms.

(4) Serotonin

The amino acid tryptophan is the precursor of several important product such as serotonin and melatonin. The relationship between serotonin and melatonin has been actively studied for understanding mechanisms for insomnia, particularly, in aged sleep-wake cycle function.⁴⁸ Serotonin metabolized to melatonin through the enzymes like aromatic L-amino acid decarboxylase and hydroxyindole-O-methyltransferase. This way can explain the reason why impaired the biosynthesis of serotonin led to states of total insomnia.⁴⁸

(5) Melatonin

Melatonin has widely known to have beneficial actions through anti-inflammatory, anti-oxidative stress, and bone-preserving effects. In addition, melatonin is known to be relatively safe than other sleeping aids and is widely used in patients with insomnia.⁴⁹ Melatonin treatment enhanced mesenchymal stem cells by upregulation of AMPK, FOXO3a, and RUNX2 responsible for the mechanistic link between oxidative stress and osteogenic phenotype.⁵⁰ Also, melatonin promoted osteoblast differentiation in primary bone marrow mesenchymal stem cells from ovariectomized (OVX) mice. It also reduced activation of NLRP3 inflammasome in femoral bone protein and in induced osteoblasts stimulated by OVX.⁵¹ The intake of anti-inflammatory and antioxidant melatonin is thought to be beneficial not only for induction of sleep but for bone metabolism, and should be studied for more mechanisms.

4. Alternative medicines for sleep and osteoporosis

Although the markets for sleeping pills and anti-osteoporosis drugs are enormous, many patients suffer additional pain due to various side effects of drugs, abnormal behaviors, and high irritability to gastrointestinal tract.⁵²

According to Jung's report⁵³, zolpidem overdose and patient suicide with benefits and disadvantages of pharmacotherapy. Adverse effects concerning the central nervous system, including delirium and hallucination, as well as abnormal behavior during sleep, are commonly reported among patients who have taken zolpidem for more than 1 year. Therefore, long-term prescriptions to medication of these chemical drugs for sleep induction can be serious problems in cardiovascular system, cognitive, unrecognizing abnormal behaviors. Benzodiazepines and other sedative-hypnotic drugs are frequently claimed with adverse outcomes includes their anti-cholinergic effects and increased risks of falls and hip fractures in the old patients.⁵⁴ In recent, oriental herbal pharmacy has been got attention as alternative medications for treating insomnia that can help relieved hypertension, cognitive function and improve sleep induction for seeking to increase safety and efficiency. *Passiflora incarnate L.*, *Rosmarinus officinalis L.*, *Violet oil from Viola odrata*, *Ziziphus spinose*, *Poria cocos*, *Gycyrrhiza uralensis* are recently introduced for sedative effect for well sleep.^{55,56} These herbal medicine is known to act through GABA or GABA-A receptor.⁵⁶ Since the mechanisms of these herbal medicines are thought to activate expression of Orexin-A, Orexin receptor, Leptin and Leptin receptor, therefore, we can confirm that all the mechanisms and principles of sleep therapy and bone metabolism mentioned earlier at "Possible causative factors of bone mass deficit in subjects with insomnia" also apply to herbal medicines. In particular, effect of *Passiflora spp.* extract recently reported they have possibility to use as sleep inducer and anti-osteoporosis substance.^{55,57} In recent, *Passiflora incarnate L.* has been introduced safe and promising effects on sedative, inducing sleep and anti-anxiety functions.^{55,58-60} This serotonin and melatonin driving effects have been expected to have anabolic effect in bone. Compared to the side effects and risks of synthetic medicines, the ability to treat sleep and bone health using traditional plant-derived medicinal herbs, which are safe, offers benefits to many people, while providing opportunities for a sizable pharmacy market.

Conclusion

For modern people, the dream of longevity through quality of sleep and bone health is very tempting. However, due to the increasing differentiation rate and various stresses of modern society, people live with chronic insomnia as well as the problem of bone health. These metabolic causes are closely related to various diseases such as obesity, hypertension, chronic consumptive disease, abnormal behaviors and diverse depressions, so prevention and management of such diseases will be critical. As noted above, sudden changes in hormones after postmenopausal in female can be a major cause in many cases, however, it has been found that the inability to treat stressors is a very important reason for sleep and osteoporosis. Even in the case of currently prescribed synthetic drugs, there is a risk of various side effects that cannot be predicted, so more attention is required when physicians treat them. For this reason, it seems necessary to have a very effective adjuvant to alleviate the stress on the human body, such as the control of autonomic nervous system, hormonal control, and the effect on the appetite center. These stress factors are not only the stresses of everyday life but various inflammatory factors.

It is anticipated that the number of patients experiencing sleep deprivation and osteoporosis at a time should be tremendous, and herbal medicine originated from plant-derived herbal medicine, which has been proven safe for treatment, will play an alternative medical role. It is being actively introduced into the market as a supplementary nutritional food preparation. Concentrating and encouraging the review and management of these products at the national agency with a supervisory obligation would open the way for a comfortable treatment for patients with sleep and osteoporosis who rely on synthetic drug prescriptions now.

Acknowledgement

This work was supported by Korea Institute of Planning and Evaluation for Technology in Food, Agriculture, Forestry and Fisheries (IPET) through High Value-added Food Technology Development Program funded by Ministry of Agriculture, Food and Rural Affairs (MAFRA) (115044-03-

3–HD020), Republic of Korea.

Conflict of Interest

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

References

- Te Lindert BHW, Itzhacki J, van der Meijden WP, Kringelbach ML, Mendoza J, Van Someren EJW. Bright environmental light ameliorates deficient subjective 'liking' in insomnia: an experience sampling study. *Sleep* 2018 <http://dx.doi.org/10.1093/sleep/zsy022>
- Passos GS, Poyares D, Santana MG, Teixeira AA, Lira FS, Youngstedt SD, et al. Exercise improves immune function, antidepressive response, and sleep quality in patients with chronic primary insomnia. *Biomed Res Int* 2014; 2014: 498961.
- Fifel K, Meijer JH, Deboer T. Long-term effects of sleep deprivation on neuronal activity in four hypothalamic areas. *Neurobiol Dis* 2018; 109: 54–63.
- Cizza G, Primma S, Csako G. Depression as a risk factor for osteoporosis. *Trends Endocrinol Metab* 2009; 20: 367–73.
- Cizza G, Ravn P, Chrousos GP, Gold PW. Depression: a major, unrecognized risk factor for osteoporosis? *Trends Endocrinol Metab* 2001; 12: 198–203.
- North American Menopause Society. Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. *Menopause* 2006; 13: 340–67.
- Sharma N, Natung T, Barooah R, Ahanthem SS. Effect of multiparity and prolonged lactation on bone mineral density. *J Menopausal Med* 2016; 22: 161–6.
- Choi CJ, Choi WS, Kim CM, Lee SY, Kim KS. Risk of sarcopenia and osteoporosis in male tuberculosis survivors: Korea National Health and Nutrition Examination Survey. *Sci Rep* 2017; 7: 13127.
- McCabe IC, Fedorko A, Myers MG, Jr., Leininger G, Scheller E, McCabe LR. Novel leptin receptor signaling mutants identify location and sex-dependent modulation of bone density, adiposity, and growth. *J Cell Biochem* 2018 <http://dx.doi.org/10.1002/jcb.27726>
- Thadani SR, Ristow B, Blackwell T, Mehra R, Stone KL, Marcus GM, et al. Relationship of bisphosphonate therapy and atrial fibrillation/flutter: Outcomes of sleep disorders in older men (MrOS Sleep) study. *Chest* 2016; 149: 1173–80.
- Schmid SM, Hallschmid M, Schultes B. The metabolic burden of sleep loss. *Lancet Diabetes Endocrinol* 2015; 3: 52–62.
- Fink JE, Hackney AC, Matsumoto M, Maekawa T, Horie S. Mobility and biomechanical functions in the aging male: Testosterone and the locomotive syndrome. *Aging Male* 2018 <http://dx.doi.org/10.1080/13685538.2018.1504914>
- Biver E, Salliot C, Combescure C, Gossec L, Hardouin P, Legroux-Gerot I, et al. Influence of adipokines and ghrelin on bone mineral density and fracture risk: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; 96: 2703–13.
- Munhoz da Rocha Lemos Costa T, Costa FM, Hoffman Jonasson T, Aguiar Moreira C, Boguszewski CL, Cunha Borges JL, et al. Bone mineral density and vertebral fractures and their relationship with pulmonary dysfunction in patients with chronic obstructive pulmonary disease. *Osteoporos Int* 2018; 29: 2537–43.
- Sasaki N, Fujiwara S, Yamashita H, Ozono R, Teramen K, Kihara Y. Impact of sleep on osteoporosis: sleep quality is associated with bone stiffness index. *Sleep Med* 2016; 25: 73–7.
- Davis SR, Jane F. Drugs for the treatment of menopausal symptoms. *Expert Opin Pharmacother* 2010; 11: 1329–41.
- Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998; 102: 274–82.
- Braun T, Schett G. Pathways for bone loss in inflammatory disease. *Curr Osteoporos Rep* 2012 <http://dx.doi.org/10.1007/s11914-012-0104-5>
- Dowd JB, Goldman N, Weinstein M. Sleep duration, sleep quality, and biomarkers of inflammation in a Taiwanese population. *Ann Epidemiol* 2011; 21: 799–806.
- Ferrie JE, Kivimäki M, Akbaraly TN, Singh-Manoux A, Miller MA, Gimeno D, et al. Associations between change in sleep duration and inflammation: findings on C-reactive protein and interleukin 6 in the Whitehall II Study. *Am J Epidemiol* 2013; 178: 956–61.
- McLean RR. Proinflammatory cytokines and osteoporosis. *Curr Osteoporos Rep* 2009; 7: 134–9.
- Tong Q, Wu W, Wu Q, Yu Y, Lv X, Wang B, et al. Sleep onset latency is related with reduced bone mineral density in elderly people with insomnia: a retrospective study. *Clin Interv Aging* 2018; 13: 1525–30.
- Pervanidou P, Chrousos GP. Stress and obesity/metabolic

- syndrome in childhood and adolescence. *Int J Pediatr Obes* 2011; 6 Suppl 1: 21–8.
24. Yirmiya R, Goshen I, Bajayo A, Kreisel T, Feldman S, Tam J, et al. Depression induces bone loss through stimulation of the sympathetic nervous system. *Proc Natl Acad Sci U S A* 2006; 103: 16876–81.
25. Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry* 2015; 20: 32–47.
26. Eskandari F, Martinez PE, Torvik S, Phillips TM, Sternberg EM, Mistry S, et al. Low bone mass in premenopausal women with depression. *Arch Intern Med* 2007; 167: 2329–36.
27. Weston CS. Posttraumatic stress disorder: a theoretical model of the hyperarousal subtype. *Front Psychiatry* 2014; 5: 37.
28. Kuriyama N, Inaba M, Ozaki E, Yoneda Y, Matsui D, Hashiguchi K, et al. Association between loss of bone mass due to short sleep and leptin–sympathetic nervous system activity. *Arch Gerontol Geriatr* 2017; 70: 201–8.
29. Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci* 2007; 8: 171–81.
30. Sakurai T, Mieda M. Connectomics of orexin–producing neurons: interface of systems of emotion, energy homeostasis and arousal. *Trends Pharmacol Sci* 2011; 32: 451–62.
31. Wei W, Motoike T, Krzeszinski JY, Jin Z, Xie XJ, Dechow PC, et al. Orexin regulates bone remodeling via a dominant positive central action and a subordinate negative peripheral action. *Cell Metab* 2014; 19: 927–40.
32. Allard JS, Tizabi Y, Shaffery JP, Trough CO, Manaye K. Stereological analysis of the hypothalamic hypocretin/orexin neurons in an animal model of depression. *Neuropeptides* 2004; 38: 311–5.
33. Brundin L, Björkqvist M, Petersén A, Träskman–Bendz L. Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. *Eur Neuropsychopharmacol* 2007; 17: 573–9.
34. Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 1999; 98: 437–51.
35. Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron* 2001; 30: 345–54.
36. Sellayah D, Bharaj P, Sikder D. Orexin is required for brown adipose tissue development, differentiation, and function. *Cell Metab* 2011; 14: 478–90.
37. Brisbare–Roch C, Dingemans J, Koberstein R, Hoever P, Aissaoui H, Flores S, et al. Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nat Med* 2007; 13: 150–5.
38. Funato H, Tsai AL, Willie JT, Kisanuki Y, Williams SC, Sakurai T, et al. Enhanced orexin receptor–2 signaling prevents diet–induced obesity and improves leptin sensitivity. *Cell Metab* 2009; 9: 64–76.
39. Kotz C, Nixon J, Butterick T, Perez–Leighton C, Teske J, Billington C. Brain orexin promotes obesity resistance. *Ann N Y Acad Sci* 2012; 1264: 72–86.
40. Lago F, Gonzalez–Juanatey JR, Casanueva FF, Gómez–Reino J, Dieguez C, Gualillo O. Ghrelin, the same peptide for different functions: player or bystander? *Vitam Horm* 2005; 71: 405–32.
41. Nouh O, Abd Elfattah MM, Hassouna AA. Association between ghrelin levels and BMD: a cross sectional trial. *Gynecol Endocrinol* 2012; 28: 570–2.
42. Kim SW, Her SJ, Park SJ, Kim D, Park KS, Lee HK, et al. Ghrelin stimulates proliferation and differentiation and inhibits apoptosis in osteoblastic MC3T3–E1 cells. *Bone* 2005; 37: 359–69.
43. Delhanty PJ, van der Eerden BC, van der Velde M, Gauna C, Pols HA, Jahr H, et al. Ghrelin and unacylated ghrelin stimulate human osteoblast growth via mitogen–activated protein kinase (MAPK)/phosphoinositide 3–kinase (PI3K) pathways in the absence of GHS–R1a. *J Endocrinol* 2006; 188: 37–47.
44. Fukushima N, Hanada R, Teranishi H, Fukue Y, Tachibana T, Ishikawa H, et al. Ghrelin directly regulates bone formation. *J Bone Miner Res* 2005; 20: 790–8.
45. Arble DM, Vitaterna MH, Turek FW. Rhythmic leptin is required for weight gain from circadian desynchronized feeding in the mouse. *PLoS One* 2011; 6: e25079.
46. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A* 2009; 106: 4453–8.
47. Baranowska B, Baranowska–Bik A, Bik W, Martynska L. The role of leptin and orexins in the dysfunction of hypothalamo–pituitary–gonadal regulation and in the mechanism of hyperactivity in patients with anorexia nervosa. *Neuro Endocrinol Lett* 2008; 29: 37–40.
48. Paredes SD, Barriga C, Reiter RJ, Rodriguez AB. Assessment of the potential role of tryptophan as the precursor of serotonin and melatonin for the aged sleep–wake cycle and immune function: *Streptopelia risoria* as a model. *Int J Tryptophan Res* 2009; 2: 23–36.
49. Frase L, Nissen C, Riemann D, Spiegelhalder K. Making sleep easier: pharmacological interventions for insomnia.

- Expert Opin Pharmacother 2018; 19: 1465–73.
50. Lee S, Le NH, Kang D. Melatonin alleviates oxidative stress–inhibited osteogenesis of human bone marrow–derived mesenchymal stem cells through AMPK activation. *Int J Med Sci* 2018; 15: 1083–91.
51. Xu L, Zhang L, Wang Z, Li C, Li S, Li L, et al. Melatonin suppresses estrogen deficiency–induced osteoporosis and promotes osteoblastogenesis by inactivating the NLRP3 inflammasome. *Calcif Tissue Int* 2018; 103: 400–10.
52. Um MJ, Cho EA, Jung H. Combination therapy of raloxifene and alendronate for treatment of osteoporosis in elderly women. *J Menopausal Med* 2017; 23: 56–62.
53. Jung M. Zolpidem overdose: A dilemma in mental health. *Health Care Manag (Frederick)* 2018; 37: 86–9.
54. Kwon CY, Lee B, Chung SY, Kim JW, Kim SH. Oriental herbal medicine for insomnia in the elderly with hypertension: A systematic review protocol. *Medicine (Baltimore)* 2018; 97: e12200.
55. Kim M, Lim HS, Lee HH, Kim TH. Role identification of *Passiflora incarnata* Linnaeus: A mini review. *J Menopausal Med* 2017; 23: 156–9.
56. Singh A, Zhao K. Treatment of insomnia with traditional Chinese herbal medicine. *Int Rev Neurobiol* 2017; 135: 97–115.
57. Ahmad N, Chillara R, Kushwaha P, Khedgikar V, Karvande A, Choudhary D, et al. Evaluation of anti–osteoporotic activity of butanolic fraction from *Passiflora foetida* in ovariectomy–induced bone loss in mice. *Biomed Pharmacother* 2017; 88: 804–13.
58. Ngan A, Conduit R. A double–blind, placebo–controlled investigation of the effects of *Passiflora incarnata* (passion–flower) herbal tea on subjective sleep quality. *Phytother Res* 2011; 25: 1153–9.
59. Jawna–Zboińska K, Blecharz–Klin K, Joniec–Maciejak I, Wawer A, Pyrzanowska J, Piechal A, et al. *Passiflora incarnata* L. improves spatial memory, reduces stress, and affects neurotransmission in rats. *Phytother Res* 2016; 30: 781–9.
60. Aoyagi N, Kimura R, Murata T. Studies on *passiflora incarnata* dry extract. I. Isolation of maltol and pharmacological action of maltol and ethyl maltol. *Chem Pharm Bull (Tokyo)* 1974; 22: 1008–13.