Chronic Psychological Stress as a Risk Factor of Osteoporosis

Kagaku AZUMA1*, Yasuhiro ADACHI1, Haruki HAYASHI1 and Kin-Ya KUBO2

1 Department of Anatomy, School of Medicine, University of Occupational and Environmental Health, Japan. Yahatanishi-ku, Kitakyushu 807-8555, Japan
2 Seijoh University Graduate School of Health Care Studies, 2-172 Fukinodai, Tokai 476-8588, Japan

Abstract: Osteoporosis, the most common metabolic skeletal disease, is characterized by decreased bone mass and deteriorated bone quality, leading to increased fracture risk. With the aging of the population, osteoporotic fracture is an important public health issue. Organisms are constantly exposed to various stressful stimuli that affect physiological processes. Recent studies showed that chronic psychological stress is a risk factor for osteoporosis by various signaling pathways. The purpose of this article is to review the recent progress of the association between chronic psychological stress and osteoporosis. Increasing evidence confirms the physiological importance of the central nervous system, especially the hypothalamus, in the regulation of bone metabolism. Both animal and human studies indicate that chronic psychological stress induces a decrease of bone mass and deterioration of bone quality by influencing the hypothalamic-pituitary-adrenocortical (HPA) axis, sympathetic nervous system, and other endocrine, immune factors. Active mastication, proven to be an effective stress-coping behavior, can attenuate stress-induced neuroendocrine responses and ameliorate stress-induced bone loss. Therefore, active mastication may represent a useful approach in preventing and/or treating chronic stress-associated osteoporosis. We also discuss several potential mechanisms involved in the interaction between chronic stress, mastication and osteoporosis. Chronic stress activates the HPA axis and sympathetic nervous system, suppresses the secretion of gonadal hormone and growth hormone, and increases inflammatory cytokines, eventually leading to bone loss by inhibiting bone formation and stimulating bone resorption.

Keywords: chronic psychological stress, hypothalamus, mastication, osteoporosis, sympathetic nervous system.

(Received September 14, 2015, accepted November 2, 2015)

Introduction

Osteoporosis is a chronic skeletal metabolic disease characterized by loss of bone mass and deterioration of bone quality, resulting in an increased susceptibility to fracture [1, 2]. With the aging population, osteoporosis has received increasing attention as a major health and socioeconomic problem worldwide. Osteoporosis has a complex pathogenesis and multifactorial etiology, including genetic and environmental components. Several risk factors, including menopause, smoking, low levels of physical activity, and corticosteroid therapy have been implicated in the development of osteoporosis [3]. Stress is a physiological and psychological response to environmental changes and noxious stimuli. Stress responses involve the neuroendocrine, autonomic nervous system, and behavioral changes to promote effective coping with the actual or potential threatened...
homeostasis. The stressor triggers activation of the sympathetic nervous system, which promotes the release of adrenaline and noradrenaline from the adrenal medulla [4]. Adrenaline and noradrenaline will increase respiratory rate, heart beat, blood concentration of glucose and the blood flow to skeletal muscles. This fast response is primarily related to survival.

The hypothalamic-pituitary-adrenocortical (HPA) axis is one of the most important neuroendocrine regulatory systems involved in the adaptive responses of the mammalian organism to external and internal threatening stimuli [5]. Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), originating from the hypothalamus, act as the main signals to transfer information within the HPA axis. Internal and external stressors trigger the hypothalamus to release CRH and AVP, which act synergistically on the anterior pituitary to stimulate the synthesis and secretion of adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal cortex to promote the production and release of glucocorticoid (GC) from the adrenal cortex [6].

GC includes cortisol, the predominant GC in humans and corticosterone in rodents. The physiologic and pharmacologic action of GC is mediated by the glucocorticoid receptor, a member of the nuclear receptor superfamily of ligand-dependent transcription factors [7]. Consistent with the pleiotropic actions of GC, the glucocorticoid receptor is expressed in nearly every cell of the body. GC mobilizes energy to cope with the energy demands triggered by behavioral response to stressors [8]. Therefore, stress responses are critical for the survival of the individual. However, adverse effects of repeated or chronic exposure to stress are widely known to have deleterious physical and mental effects on health, ultimately inducing various diseases.

Chronic psychological stress is a major health concern worldwide, as it affects multiple physiologic systems. Stress is a risk factor for several different diseases, including inflammatory disease, hypertension, cardiovascular disease, obesity, diabetes, atherosclerosis, and cancer, as well as neurodegenerative diseases [9, 10]. Recently, the association between chronic psychological stress and osteoporosis has been the subject of a growing body of research. The published literature, especially recent animal and human studies, showed that chronic psychological stress is a risk factor for developing osteoporosis [11–15]. In the present review, we aim to provide the current understanding of the relationship between chronic psychological stress and osteoporosis. We also discuss the possible implications for active mastication as a stress-coping behavior to prevent and/or treat chronic stress-related osteoporosis.

**Bone homeostasis regulated by the central nervous system**

Bone tissue undergoes continuous remodeling, in which old bone is removed by osteoclasts and new bone is formed by osteoblasts. Both osteoblasts and osteoclasts function in concert, which requires intimate cross talk with osteocytes [16]. When the remodeling balance becomes negative, it causes a decrease of bone mass and deterioration of bone quality, leading to osteoporosis. Osteoporosis is the most common bone disorder of the elderly with an increased fracture risk. As the proportion of elderly persons has increased substantially and will continue to do so, osteoporotic fracture is a serious global health problem. Osteoporotic fractures might affect body movement, inducing disability, limiting daily activities and affecting the quality of life [2, 17].

Osteoporosis is caused by a failure of bone homeostasis, but the precise molecular mechanisms controlling bone homeostasis are largely unknown. A large body of evidence that the central nervous system is intimately involved in bone remodeling has shed light on a novel regulatory mechanism for bone homeostasis. Recent studies have provided strong evidence of interactions between the nervous system and bone remodeling. Bone remodeling, like other homeostatic functions, is under the control of the brain, especially the hypothalamus (Fig. 1).

The hypothalamus is the part of the brain that maintains homeostasis, including the regulation of the autonomic nervous system. A key input to the hypothalamus is leptin, a peptide hormone that is synthesized by adipocytes to influence food intake, body weight and the neuroendocrine systems. Recent studies showed that leptin also affects bone remodeling. Leptin- and leptin receptor-deficient mice display high bone mass despite hypogonadism [18, 19]. Intracerebroventricular infusion of leptin in mice completely rescued the
high bone mass [19]. The effect of leptin on bone mass through the brain involved the hypothalamus, which mediates leptin functions [20]. A chemical lesioning experiment indicated that bone homeostasis was regulated by the hypothalamus. Mice lacking the hypothalamic ventromedial nucleus had a decreased sympathetic activity and did not respond to leptin. Accordingly, the bone homeostasis regulated by leptin requires the integrity of the hypothalamus, which in turn affects sympathetic activity [18]. Consequently, the sympathetic nervous system represents an important linkage between the brain and bone [18-21].

Adrenaline and noradrenaline are the main neurotransmitters of the sympathetic nervous system. The physiologic function of adrenaline and noradrenaline is mediated by the adrenaline receptor. Osteoblasts express high levels of β2-adrenergic receptor (β2-AR), through which sympathetic tone regulates various functions in the body. Mice lacking β2-AR showed a high bone mass phenotype, with an increased bone formation. Animal studies showed that leptin infusion did not decrease bone mass in β2-AR−/− mice, while it did in WT mice. These findings indicate that leptin regulates sympathetic activity from hypothalamus, which in turn activates β2-AR on osteoblasts [18]. Several animal and human investigations showed that higher sympathetic activity was inversely correlated with bone mass and β2 agonists increased the fracture risk [22, 23]. Administration of β-blockers inhibits bone resorption, stimulates bone formation, and increases trabecular bone volume. A significant decline in the incidence of hip fractures in patients treated with β-blockers has also been reported [24, 25].

Bone homeostasis is also modulated by the hypothalamus through the HPA axis. The activation of the HPA axis results in GC secretion. The action of GC is mediated by the glucocorticoid receptor. GC is known to inhibit osteoblastic differentiation and function, and to promote the apoptosis of osteoblasts and osteocytes, thereby leading to suppression of bone formation. GC also acts directly on osteoclasts to decrease the osteoclast apoptosis [26].

Neuropeptide Y (NPY) is produced in the hypothalamus and the peripheral tissues. Over-production of the NPY inhibits bone formation and accelerates bone loss [27]. Inhibition of NPY or deletion of the NPY receptor gene increased trabecular bone mass and fracture healing [28]. Negative osteotropic effects have also been observed in neuromedin U, a neuropeptide synthesized in the hypothalamus, pituitary and small intestine [29]. Neuromedin U was reported to inhibit osteoblastic function [30]. Bone formation was accelerated in mice with deletion in the neuromedin gene. Agents that inhibit NPY and/or neuromedin U could potentially be used for treating osteoporosis.

The accumulating body of evidence confirms the physiological importance of the central nervous system, especially the hypothalamus, in the regulation of bone remodeling. The control of bone homeostasis by the brain involves a multitude of signaling pathways originating or impinging on the brain (Fig. 1). However, some questions remain to be addressed. It is necessary to determine the bone-derived signals back to the brain to regulate hypothalamic functions. Further studies are required to clarify the existence of a central network from bone to brain.

---

**Fig. 1. Bone homeostasis regulated by hypothalamus.** Hypothalamus activates sympathetic nervous system (SNS) mediated by leptin. Hypothalamic corticotropin-releasing hormone (CRH) stimulates glucocorticoid (GC) secretion via adrenocorticotropic hormone (ACTH). SNS, GC, neuromedin U (NMU), and neuropeptide Y (NPY) inhibit osteoblast proliferation, leading to low bone formation through their corresponding receptors.
Relationship between chronic psychological stress and osteoporosis

Several risk factors have been implicated in the development of osteoporosis, including low peak bone mass, age, female gender, estrogen deficiency, calcium deficiency, low levels of physical activity, glucocorticoid therapy, and several other conditions as well as smoking and drug abuse [3]. Recent studies implicated chronic stress, such as depression in bone loss and osteoporosis, showing there is a link between chronic stress and osteoporosis [11, 31–34]. Epidemiological studies indicate that depression is an important risk factor for osteoporosis [32–34]. One study compared a total of 2,327 depression patients with 21,141 non-depressed individuals to determine the relationship between depression and skeletal status [32]. The depression patients showed lower bone mineral density (BMD) and higher bone resorption markers than the non-depressed subjects. The relationship between depression and lower BMD was significant in the vertebra, proximal femur and distal radius. The depression-associated low BMD is considered to involve a multiplicity of trabecular bone sites throughout the skeleton.

Both osteoporosis and depression are about threefold more common in women than in men [32, 33]. Women are more vulnerable to depression-related low bone mass [34]. Women are more sensitive to stress, and there is a greater responsiveness of depressed women to various stressors [32]. Premenopausal women display a greater depression-associated decrease in BMD compared with postmenopausal subjects [32]. The greater depression-associated low BMD in pre- than post-menopausal subjects does not necessarily mean that depression is not associated with low BMD after menopause. However, this association in postmenopausal women may be masked by other factors contributing to low BMD, such as estrogen depletion, reduced physical activity, and drug treatments [32].

There were several studies concerning the relation between osteoporosis and depression in men [35, 36]. In a population study of 80 depression patients, including 27 men, the spine BMD was 15% lower than in the control subjects [37]. A follow-up study showed that bone loss over 24 months was significantly greater in depressed subjects than in controls. It was clinically indicated that bone mass was generally lower in depressed men compared to non-depressed men, and bone loss in depressed men was greater than in depressed women [38, 39]. A large cross-sectional study of 2,000 men aged 65 to 92 years was conducted concerning the relationship between depression and BMD in men [35]. Depression was diagnosed in 8.5% of the subjects. Depression was negatively associated with the total hip BMD, and the clinically depressed subjects had an average BMD lower than the controls. The hip BMD of these subjects was 2.1% lower than in non-depressed subjects, and depression was associated with a 1.4-fold relative risk of being diagnosed as having at least osteopenia [35].

Animal experiments with chronic psychological stress also showed the loss of bone mass and deterioration of bone quality [14, 40]. Mice were exposed to a regimen of stressors every day over a period of 4 to 5 weeks. The bone responses were evaluated using quantitative micro computed tomography, bone histomorphometry, and bone remodeling markers. The results showed that chronic psychological stress induced significant decreases in trabecular bone volume, trabecular number, and trabecular thickness both in the vertebra and femurs. The bone quality, evaluated by biomechanical testing, was also reduced in stressed mice [14].

Possible mechanisms for bone fragility induced by chronic psychological stress

A causal relationship between chronic psychological stress and osteoporosis has not been fully elucidated. The bone fragility induced by chronic stress can be mediated by several signaling pathways, including the HPA axis, sympathetic nervous system, and other factors (Fig. 2).

Hyperactivity of the HPA axis or hypercortisolemia is considered an important factor for stress-induced bone loss. Several human studies report that blood cortisol levels were elevated in depressed patients, concomitantly with low BMD [41, 42]. Animal studies also showed an elevation of the circulating corticosterone levels and adrenal weight, accompanied by lower bone quantity and bone quality in chronic stressed mice [14, 40]. Chronic stress triggers the hy-
The hypothalamus to release CRH, activates the HPA axis, and stimulates the secretion of GC. GC was proved to inhibit osteoblastic function, causing bone loss [26].

Several lines of evidence indicate the sympathetic nervous system in central regulation of bone remodeling [17, 18, 43]. Chronic stress is associated with pronounced and an enduring central and peripheral hyper-noradrenergic state [44]. Stress-related increases in noradrenaline levels, especially within bone tissue, might contribute to bone loss and osteoporosis. Elevation of noradrenaline level was confirmed in chronic stress model animals along with bone loss. Furthermore, stress-triggered bone loss can be partially ameliorated by β-adrenergic antagonist propranolol, suggesting that the sympathetic nervous system mediates stress-induced bone loss [40].

Bone remodeling is controlled by the systemic and local endocrine system, including gonadal hormones [45]. Chronic stress was reported to inhibit the secretion of gonadal hormones [46, 47]. Exposure to various chronic stressors, such as restraint, noise and sleep deprivation, induces an inhibitory effect on the hypothalamic-pituitary-gonadal axis, leading to low gonadal hormones [47]. Therefore, gonadal hormones could be involved in mediating the stress-induced bone loss process. However, some animal and human studies reported that chronic stress-related low bone mass had the same normal estrogen and testosterone levels as the controls [35, 40]. A potential interaction between gonadal hormone and stress-induced bone loss requires further investigation.

As the pathogenesis of osteoporosis is multifactorial, it has been recognized that components of the immune system have a significant impact on bone homeostasis. The effects of inflammatory cytokines on the dynamic balance of bone resorption and bone formation can partially explain the occurrence of osteoporosis in conjunction with chronic inflammatory reactions [48]. Inflammatory cytokines are also potential stimulators of the HPA axis and might contribute to hypercortisolism in depression subjects. Chronic psychological stress is associated with dysregulation of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α [48, 49]. Furthermore, oxidative stress and the generation of advanced glycation end products have emerged as links between chronic stress, inflammation and osteoporosis. Further studies are needed to identify the molecular mechanisms responsible for stress-induced bone loss mediated by inflammatory cytokines in order to promote the development of novel treatment strategies for osteoporosis.

**Fig. 2. Potential mechanisms for chronic psychological stress-associated bone loss.** Chronic stress activates the sympathetic nervous system (SNS) and induces increases in hypothalamic corticotropin-releasing hormone (CRH) release, provoking higher adrenocorticotropic hormone (ACTH) and glucocorticoid (GC) secretion. Lowered gonadotrophin-releasing hormone (GnRH) and growth hormone releasing hormone (GHRH) release from hypothalamus suppress the secretion of gonadal hormones and growth hormone (GH), respectively. CRH also stimulates catecholamine release, inducing interleukin-6 (IL-6) production. The hyperactivity of SNS, GC and IL-6, together with suppression of gonadal hormones and GH, results in decreased bone formation, leading to bone loss.
Active mastication ameliorates chronic stress-induced bone loss

Active mastication, or chewing, is important not only for food intake, but also for mental, physical, and physiologic functions of the body. Chewing is also an effective stress-coping behavior [50–52]. Recent basic and clinical investigations have shown that chewing may alleviate stress-induced responses, such as increases in noradrenaline turnover in rat hypothalamus, and impaired spatial memory due to an increase in GC receptor expression in the hippocampus [51, 52]. Chewing attenuated the stress-induced increase in GC levels. Chewing could rescue the stress-related hippocampal dysfunction. Chewing also could ameliorate sympathetic hyperactivity during stress. Our recent study showed that chronic mild psychological stress triggered bone loss by inhibiting bone formation and stimulating bone resorption in mice [13]. Chewing under chronic stress could ameliorate stress-induced bone loss by attenuating the reduced bone formation and increased bone resorption. Chewing may help to maintain bone strength by suppressing the HPA axis and sympathetic nervous system. Therefore, chewing might be an effective approach for the prevention and/or treatment of chronic stress-related osteoporosis.

Conclusion

Chronic psychological stress is a major health concern as it affects multiple physiologic systems. Chronic psychological stress activates the HPA axis and sympathetic nervous system, suppresses the secretion of the gonadal hormone and growth hormone, and increases the inflammatory cytokines, which eventually lead to net bone loss by inhibiting osteoblastic bone formation and stimulating osteoclastic bone resorption. Active mastication plays an important role in stress reaction. Active mastication during chronic stress suppresses the neuroendocrine stress responses and alleviates the suppressed bone formation and activated bone resorption induced by chronic stress. Mastication is a common behavior for animals and humans. In rodents, active mastication during exposure to various stressors can improve stress-dependent bone loss. Human studies are necessary to validate the hypothesis that active mastication is effective in preventing bone loss induced by chronic stress in older people.

Conflict of Interest

The authors declare that they have no conflict of interest.

References


35. Wong SY, Lau EM, Lynn H, Leung PC, Woo J, Cummings SR & Orwoll E (2005): Depression and bone mineral density: is there a relationship in elderly Asian men? Results from Mr. Os (Hong Kong). Os-
teoporos Int 16: 610–615
骨粗鬆症の危険因子としての慢性の精神的ストレス

東 华岳¹, 安達 泰弘¹, 林 春樹¹, 久保 金弥²

¹産業医科大学 医学部 第１解剖学講座
²星城大学大学院 健康支援学研究科

要 旨：骨粗鬆症は骨量の減少と骨質の劣化が特徴で、骨折しやすくなるもっとも一般的な代謝性骨疾患である。超高齢社会の到来を受け、骨粗鬆症は大きな社会問題になっている。一方、生体はつねにさまざまなストレスにさらされ、その生理機能に影響を及ぼしている。最近の研究によれば、慢性の精神的ストレスがさまざまなシグナル経路を介し骨粗鬆症の危険因子である。本総説では、慢性の精神的ストレスと骨粗鬆症との関連性について、最近の進展状況を概説する。中枢神経系、特に視床下部による骨代謝調節機構の存在が明らかにされてきた。ヒトおよび動物研究によると慢性の精神的ストレスが視床下部-下垂体-副腎皮質系、交感神経系、および内分泌・免疫系への影響を介して骨量を低下させ、骨質を悪化させる。咀嚼動作にはストレス緩和作用があることが証明されている。咀嚼動作は、ストレス誘発神経内分泌反応を弱め、ストレス性骨量減少を改善する。したがって、咀嚼動作は、慢性の精神的ストレスに関連する骨粗鬆症の予防・治療において、有用なアプローチになりうる。また、慢性の精神的ストレス、咀嚼動作と骨粗鬆症との相互関係についてのメカニズムも考察した。慢性の精神的ストレスは視床下部-下垂体-副腎皮質系と交感神経系を活性化させ、性ホルモンと成長ホルモンを抑制し、炎症性サイトカインを増加させ、骨形成の抑制と骨吸収の促進により最終的に骨量減少を引き起こす。

キーワード：慢性の精神的ストレス、視床下部、咀嚼動作、骨粗鬆症、交感神経系。