

REVIEW ARTICLE

Biological Interaction of Stress and Osteoporosis

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ABSTRACT

Stress is a state of the mind, involving brain and body as well as their interactions; that alter physiological systems to produce a chronic stress burden that, in turn, is a factor in the expression of disease, impact on an individual health behavior such as diet, physical activity, sleep, and substance abuse. Hormones associated with the chronic stress burden protect the body in the short run and promote adaptation but in the long run, the burden of chronic stress causes changes in the brain and body that can lead to disease ,brain circuits are plastic and remodeled by stress to change the balance between anxiety, mood control, memory, and decision making, that has adaptive value in particular contexts, but their persistence and lack of reversibility can be maladaptive to any part of the body organ such as in bone health as bone is a dynamic structure which continuously undergo remodeling in balance to preserve bone strength ,if this balance tips toward excessive resorption, bones weaken (osteopenia) and over time,can become brittle and prone to fracture (osteoporosis),women are common victims of osteoporosis especially after menopause due to the hormonal cause equally man are also reported to be the host which get synergized and be dominant if stress is the common feature. Understanding these conditions will be helpful in discovering the effective prevention and treatment of osteoporosis, therefore this review will focus on the biological interaction between stress and bone health.

Key words: stress, fracture, osteopenia, menopause, osteoporosis.

INTRODUCTION

The activation of the HPA (hypothalamo-adrenal-pituitary) axis and the increase in release of pro inflammatory cytokines (interleukin-6 [IL-6] in particular are marker of stress, shorter and less intense exercise a form of somatic stress elevates IL-6, whereas brief peripheral IL-6 "bursts" are observed with longer and more intense exercise.^[1,2] resulting in the release of anti-inflammatory glucocorticoids from the adrenal cortex^[3] induced easy infectious which indirectly increases inflammation-induced cytokine increases interleukin-6 (IL-6) that is downstream of estrogen related to the production of osteoclast and thus osteoporosis.^[4]

Osteoblast and osteoclast communication:

Osteoclast and osteoblast lineages communicate with each other through cell to cell contact, by paracrine factors and cell-bone matrix interaction in a basic multicellular unit (BMU)^[5] begins with initiation phase in which hematopoietic precursors are recruited to the BMU that express cell surface receptors including c-Fms, RANK co-stimulatory molecules, such as osteoclast-associated receptor

(OSCAR), semaphorin 4D(an axon guidance molecule), differentiate following interactions with osteoblasts, which express or secrete ligands RANK-L and OPG^[6,7] thus, differntaite into mature osteoclast. Subsequently , bidirectional interactive signaling generated between ephrinB2 on osteoclasts and EphB4 on osteoblast precursors facilitates the transition,where osteoclast derived 'coupling factors', growth factors released from the bone matrix during resorption, or is generated from maturing osteoblasts which direct the differentiation and activation of osteoblasts in resorped lacunae to refill it with new bone ,finally in termination phase, bone remodeling is completed by osteoblastic bone formation and mineralization of bone matrix,signals derived from molecules released from the resorped bone matrix, as TGF-beta and bidirectional signaling generated by interaction between ephrinB2 on osteoclasts and EphB4 on osteoblast precursors facilitates the transition.^[7,8]

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Regulation of osteoblasts and osteoclast communication:

Bone homeostasis is a function of cellular interaction between osteoclasts and osteoblasts, specialized cells responsible for bone formation and resorption respectively, the coupling of bone resorption to bone formation that is essential for the correct function and maintenance of the skeletal system, repairing skeletal microdamage and replacing aged bone^[9].

Recent developments in bone cell biology have greatly changed the concept of regulatory mechanisms of the differentiation of osteoblasts and osteoclasts, study has shown that bone morphogenetic proteins (BMPs) plays critical role through Smad-mediated signaling with transcription factors Runx2 and Osterix, in osteoblast differentiation are essential molecules.^[10]

Receptor activator of NF- κ B ligand (RANKL)-RANK interaction play an essential role in osteoclast differentiation. RANKL a membrane-associated factor expressed by osteoblasts differentiate precursors osteoclasts that express RANK, a receptor for RANKL, recognize RANKL through the cell-cell interaction and change into mature osteoclasts, the bone-degrading a unique type of exocrine cell that dissolves bone mineral and enzymatically degrades extracellular matrix (ECM) proteins.^[11]

Osteoclast-osteoblast communication occurs in a basic multicellular unit (BMU) at the initiation, transition and termination phases of bone remodeling and is regulated in different level, binding of Sema4D to its receptor Plexin-B1 on osteoblasts resulted in the activation of the small GTPase RhoA, which inhibits bone formation by suppressing insulin-like growth factor-1 (IGF-1) signaling as IGF-1 regulates osteoclastogenesis both directly, through the IGF receptor (IGFR) present on osteoclasts, and by upregulating the crucial osteoclast differentiation factor receptor activator of nuclear factor κ B ligand (RANKL).^[11,12]

Cytokines, stress and osteoporosis:

Cytokines, signaling molecules of the immune system, have been implicated as a contributing factor for osteoporosis. Essentially, a relationship between cytokines and bone is based on the findings that proinflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor- α) and bacterial endotoxins cause osteoclast differentiation.^[13] In addition,

circulating monocytes may serve as early progenitors of osteoclasts and produce a wide variety of factors important to bone metabolism.

Three genes potentially contributing to bone metabolism, CCR3 (chemokine receptor 3), HDC (histidine decarboxylase, i.e. the histamine synthesis enzyme), and GCR (glucocorticoid receptor), In addition, significant negative correlation was observed between expression levels of the genes and BMD. These three genes and/or their products mediate monocyte chemotaxis, histamine production, and/or sensitivity to glucocorticoids suggesting a novel pathophysiological mechanism for osteoporosis that is characterized by increased recruitment of circulating monocyte into bone, enhanced monocyte differentiation into osteoclasts, as well as osteoclast stimulation via monocyte functional changes.^[14]

During stress, interleukin-1 (IL-1) is a potent activator of the corticotropin-releasing hormone (CRH) system in the hypothalamus, and it has been shown to be involved in many stress responses, acting on the brain ventral noradrenergic bundle that innervates the CRH-containing neurons in the paraventricular nucleus of the hypothalamus to enhance release of monoamines, such as norepinephrine, dopamine, and serotonin, as well as induce activation of the hypothalamo-pituitary-adrenal (HPA) leading to secretion of corticotropin-releasing hormone (CRH), the pro-inflammatory cytokine interleukin-1 (IL-1), produced following exposure to immunological and psychological stress plays an important role in activation of the hypothalamo-pituitary-adrenal axis and secretion of glucocorticoids, which mediate the detrimental effects at high levels in bone remodeling.

At physiological conditions low levels of IL-1 promote the adaptive stress responses necessary for efficient coping, under severe and chronic stress conditions blockade of IL-1 signaling can be used as a preventive and therapeutic procedure for alleviating stress-associated osteoporosis.^[15,16] as Osteoclastogenesis is induced by TNF α in the presence of IL 1 and produces bone resorption.^[17]

Stress, sympathetic regulation and osteoporosis:

Chronic isolation seems to be a stronger stressor that increases PNMT activities and mRNA levels in the adrenal medulla with highest elevation of plasma NA and A with strong activation of SAM

system.^[18,19] Clinical and experimental evidence has driven attention towards the pivotal role of the sympathetic nervous system (SNS) in bone remodeling, that is mediated by adrenergic nerves and neurotransmitters^[20]

The noradrenergic/sympatho-adreno-medullary (SAM) system maintaining homeostasis response during stress.^[21,22] release norepinephrine that act on the osteoblast cell which contain beta2-adrenergic receptor-mediated signaling in osteoblasts that inhibits bone formation and triggers RANKL-mediated osteoclastogenesis and bone resorption.^[23] β -adrenergic agonist isoproterenol decreases bone mass, beta-Adrenergic receptor antagonists (beta-blockers) propranolol increase bone formation and shows promising in the treatment of osteoporosis and fracture healing.^[24], β 1- and β 2-adrenergic signaling exert opposite effects on bone, with β 1 exerting a predominant anabolic stimulus in response to mechanical stimulation and during growth, whereas β 2-adrenergic receptor signaling mainly regulates bone resorption.^[25]

Stress, neuro endocrine regulation and osteoporosis:

Stress responses are mediated largely by overlapping circuits in the limbic forebrain, the hypothalamus and the brainstem, so that the hypothalamic-pituitary-adrenal (HPA) axis is the major endocrine stress axis of which cortisol is the final hormone^[26] that affects metabolic, cardiovascular and central nervous systems, the hippocampus, the amygdala, the prefrontal cortex and brainstem nuc mediated by^[26,27] Corticotropin-releasing hormone (CRH) which plays a central role in the regulation of the (HPA)-axis, that in turn stimulate ACTH which is strongly potentiated by vasopressin, that is co-produced in increasing amounts when the hypothalamic paraventricular neurons are chronically activated, on the contrary oxytocin inhibit it, ACTH release results in the release of corticosteroids from the adrenal cortex mainly cortisol present in higher levels in women than in men.^[28]

Stress, Glucocorticoid and Osteoporosis:

Glucocorticoids modify osteoblastic activity and cause profound effects on bone cell replication, differentiation, and function which is involved in regulation of bone remodeling by acting on the level of osteoblast gene expression, including down-regulation of type I collagen and osteocalcin, and up-regulation of interstitial collagenase, the synthesis and activity of osteoblast

growth factor such as insulin-like growth factor I (IGF-I) is modulated by glucocorticoids an important stimulator of osteoblast function, and expression of IGF-I is decreased by glucocorticoids. The activity of IGF I can be modified by IGF binding proteins (IGFBPs), and their synthesis is also regulated by glucocorticoids.^[29] Thus, glucocorticoid action on osteoblasts can be direct, by activating or repressing osteoblast gene expression, or indirect by altering the expression or activity of osteoblast growth factors.

Glucocorticoids cause bone resorption by stimulating osteoclastogenesis by increasing the expression of RANK ligand, colony-stimulating factor-1 and decreasing the expression of its decoy receptor, osteoprotegerin.. Clinically, patients with glucocorticoid-induced osteoporosis (GIOP) develop bone loss in the first few months of glucocorticoid exposure, and modest doses of glucocorticoids increase the risk of fractures of the spine and hip.^[30]

However, the most significant effect of glucocorticoids in bone is an inhibition of bone formation. This inhibition is caused by a decrease in the number of osteoblasts secondary to a shift in the differentiation of mesenchymal cells away from the osteoblastic lineage, and an increase in the death of mature osteoblasts.^[31]

Stress, gender differences in osteoporosis and fractures

stress and osteoporosis is traditionally been considered as a “woman’s disease” because the prevalence of osteoporosis and the rate of fractures are much higher in postmenopausal women than in older men which results in the syndrome of type I osteoporosis that is due to the direct skeletal consequences of estrogen deficiency, manifested by an increase in bone resorption without an adequate increase in bone formation. However, the absolute number of men affected by osteoporosis and fractures is larger^[32] despite the higher fracture risk in postmenopausal women, older men tend to have worse outcomes after fracture and poorer treatment rates as only few men receive antiresorptive treatment,^[33] excess annual mortality after hip fracture is higher in men and they are twice as likely to die after hip fracture than women^[34]

Bone mineral density (BMD) from dual-energy xray absorptiometry (DXA) scans is used to screen for and diagnose osteoporosis in both men

and women which exhibited lower levels of BMD and a higher prevalence of osteoporosis in women than men. [35]

Recent evidence indicates that even late postmenopausal bone loss (type II or 'smile' osteoporosis) in women may be due to estrogen deficiency. In particular, the late consequences of estrogen deficiency in elderly women result in abnormalities in calcium homeostasis and increases in parathyroid hormone secretion, leading to increased bone resorption and bone loss. The etiology of bone loss in aging men has remained relatively unclear [36]

Preventive measures of stress in health and disease

Reducing stress is crucial to bone health as well as to our general health.,short-term stress releases chemicals into the bloodstream, and in particular the hormone cortisol, that give the brain and the body a temporary boost. [37] Brain is a target sites of stress, and the hippocampus ,the first brain region, besides the hypothalamus a target of glucocorticoids, stress hormone therefore produce both adaptive and maladaptive effects on this brain region throughout the life course. The hippocampus, amygdala, and prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physiological responses,thus social and behavioral interventions such as regular physical activity and social support reduce the chronic stress burden and benefit brain and body health [38]

Chronic stress instead of improving certain abilities end up doing some real damage to our mental, emotional and physical health. As far as the latter is concerned, the most common symptoms are elevated blood pressure and glucose, digestive issues, cardiovascular symptoms, and even a compromised immune system in all this cortisol is the major stress hormone associate also in the bone health namely osteoporosis [38,39] can be slowed to the men below 50 years by encouraging to take calcium ,vitamin D and weight-bearing exercise should be suggested ; smoking and excessive alcohol should be avoided. in general pharmacological treatment for men older with spine or hip fractures is recommended. [40]

CONCLUSION

Stress related osteoporosis is common both in man and women dominant with advancing of age, immune system mediated effect is the route for this disorder and osteoblast apoptosis and

osteoclastogenesis is the chief cause of this problem as the estrogen deficiency lead with aging process in both sexes.. Hormones are possibly the most crucial modulators of bone formation. It is well established that estrogen, parathyroid hormone and to a lesser extent testosterone are essential for optimal bone development and maintenance. Of these, estrogen is now believed to have the most direct effect on bone cells, interacting with specific proteins, or receptors, on the surface of osteoblasts and osteoclasts, activation of autonomic system during chronic stress sets a complex chain of events , increasing osteoblast activity while at the same time ,osteoblast-osteoclast communication – one of the ironies of bone remodeling thus the osteoblasts releases factors that stimulate osteoclasts and drive bone resorption, the most effective ways to dramatically lower your stress level and get protected from stress-related physical and emotional problems is meditation that dramatically lower stress levels by reducing the amount of stress hormones the body makes, and by increasing the hormones and neurochemicals that allow us to relax also consumption calcium supplement may be helpful to slow the osteoporosis

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