Brain neural effects of the 'tonifying kidney and benefiting marrow' method in the treatment of osteoporosis

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Abstract

In Traditional Chinese Medicine (TCM), the ‘tonifying kidney and benefiting marrow’ (TKBM) method is based on the theory that kidney controls bones, while marrow moistens bones. There have been abundant theoretical studies on kidney controlling bones since Huangdi’s Internal Classics. However, there are too few ones about the marrow moistening the bones. Researchers generally use the tonifying kidney method instead of the TKBM method, which causes lack of a unified standard and theoretical basis in evaluating the TKBM method. Herein, we first proposed the hypothesis that deficiency of marrow sea causes osteoporosis. Next, we prove the scientific validity of this hypothesis from the side of the TCM theory on the relationship among kidney, bone and marrow sea physiologically and pathologically. Based on this, we find that the TCM theory provides theoretical basis for deficiency of marrow sea causing osteoporosis. On the other side, Western Medicine theory holds that (a) physiologically, the brain regulates the bone mass via three pathways: the neuro-osteogenic network, neuro-endocrine-bone network, and neuropeptide-bone network; (b) pathologically, brain impacts bone mass via three major passways including the regulation of the sympathetic nervous system, secreting hormones that directly act on bone cells and regulating the synthesis and secretion of hormones in the intermediary organs, and neuropeptides such as neuropeptide Y (NPY), substance P (SP), and calcitonin gene-related peptide (CGRP). Evidences involving estrogen deficiency, sympathetitonia, or neuropeptides imbalance prove that brain-bone mass regulation plays an important role in the pathogenesis of osteoporosis. Finally, we find that kidney invigoration method can change the concentrations of central neurotransmitters of norepinephrine and glutamate to regulate neuro-osteogenic network, and promote the recovery of ovarian function and have an estrogen-like effect by regulating the hypothalamus-pituitary-ovarian axis, which thus influences bone metabolism without clinically significant estro-
gen-like side effects, and regulate NPY, CGRP and SP involved in the bone metabolism. These further support our hypothesis by revealing the brain neural mechanism of the TCM kidney invigoration method for preventing and treating osteoporosis. In the future, neuroimaging techniques may be useful in exploring its neural effects and also aid in developing new strategies for treating osteoporosis.

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Keywords: Osteoporosis; Brain (TCM); Reinforcing kidney; Kidney controlling bones; Brain-bone mass regulation

INTRODUCTION

Kidney controlling bone is proposed by Huang Di Nei Jing more than 2000 years ago which plays important role in the theory of visceral manifestation in Traditional Chinese Medicine (TCM). The ‘tonifying kidney and benefiting marrow’ (TKBM) method is based on the theory that the kidney controls the bones, the marrow moistens the bones; this theory has clinical application in osteoporosis. Many theoretical studies have discussed the kidney controlling the bones. However, there are few studies about the marrow moistening the bones, which means that the studies evaluating the TKBM method lack a unified standard and theoretical basis. The TKBM method actually involves the nervous, reproductive, and endocrine systems, and also affects the whole body at an organ, cellular, molecular, and gene level. However, researchers generally use the tonifying kidney method instead of the TKBM method, and so there is a lack of evidence connecting TCM with Western Medicine regarding the relationships between the kidney, bones, and marrow. Thus, the study results do not further the innovation and development of TCM and the improvement of its clinical curative effects.

Our hypothesis is that a deficiency of marrow sea causes osteoporosis, based on the TCM theory of the brain being the marrow sea. Herein, we discuss the brain neural mechanism via which the kidney controls the bones, and the marrow moistens the bones, based on the Western Medicine theory of brain-bone mass regulation, and emphasize the importance of the marrow-brain integration effect in modern studies of the TKBM method. In future, neuroimaging techniques may aid in the early diagnosis, effective evaluation, and innovative treatment of osteopenia.

DEFICIENCY OF MARROW SEA CAUSES OSTEOPOROSIS

The kidney generates marrow and dominates the bones

In TCM theory, one of the physiological functions of the kidney is to generate marrow and dominate the bones. The prenatal essence (referred to as jing) is needled initially to form and shape the viscera, tissues, and organs. Thereafter, the backbone develops, and blood vessels are formed. The kidneys are the storage place of true yang, and are the root of all storage in the body; they store the jing/essence Qi of the five Zang and six Fu organs, and manifest their abundance and health in the head hair. The role of the kidney is to fill the bones and marrow, which shows the importance of kidney essence in the growth and development of marrow. As stated in Su Wen-The Universal Truth, at 8 years of age the kidney energy becomes full, the permanent teeth appear, and the hair becomes long. By 56 years of age, the liver energy weakens, causing the tendons to stiffen. At 64 years of age, the Tiangui dries up and the jing is drained, resulting in kidney exhaustion, fatigue, and weakness; the flow of the menses ceases, and women are no longer able to conceive. This shows the close relationship between the kidney and the growth of bone, and that age is the main cause of deficiency of kidney essence. The depletion of kidney water/Yin results in uncontrolled fire that dries out the marrow and jing/essence. Broadly speaking, the kidney essence consists of marrow, spinal cord, and brain. The essence perfuses from the brain to Dazhu (BL 11), then enters the spinal cord, flows to the coccyx, and spreads to every bone; thus, the essence in the skull becomes the brain, the essence that flows through the spinal canal to the coccyx becomes the spinal cord, and the essence in the bone cavities becomes marrow. The true meaning of the kidney generating marrow and dominating the bones is that kidney essence improves growth and development, and bone formation.

Marrow moistening the bones

Marrow is generated from the kidney essence; it depends on the postnatal essence, and the presence of ample marrow in the bones results in a person with a powerful frame, with abundant energy and endurance. As stated in Su Wen-The Methods of Pulse Examination, the bones are the palace of the marrow. The inability to stand for prolonged periods or walk with stability suggests that the bones are about to be exhausted. Thus, the kidney, bone, and marrow are closely linked physiologically and from a pathological aspect. Tangrong Chuan proposed a new theory on sui in the Essence of Medical Classic’s about integration of Chinese and Western Medicine, and makes a distinction between sui in TCM versus Western Medicine. Western Medicine considers Sui as marrow and connective tissue, which includes the whole nervous system, while TCM considers that the kidney stores jing, and that jing becomes marrow. Thus, marrow is generated and flows from the kidney meridians through the spine, into the head, and finally becomes the brain. Therefore, in TCM theory, the brain stores marrow rather than producing it. TCM also considers that the kidney stores the essence...
The dryness and brittleness of bone and deficiency of marrow sea

In TCM, osteopenia or osteoporosis is called Guwei (bone paralysis), Guku (dryness and brittleness of bone), or Gubi (bone rheumatism). Guwei is the most appropriate of these terms. The kidney governs the bones and bone marrow. Therefore, when the kidney is attacked by heat, the jing/essence is exhausted and the marrow decreases. This leads to dry bones and spinal weakness, and the back becomes so weak that the patient cannot maintain an upright position; this is a wei condition of the bones (Guwei).13 Zhang Jingyue in the Ming dynasty considered Shen wei (hypofunction of the kidneys) as Guwei. These two expressions show that the deficiency of kidney essence results in the depletion of marrow sea, which leads to muscle relaxation and dry and brittle bones. We propose that the depletion of marrow sea is a key component causing bone dryness and brittleness. The marrow sea mentioned here refers to the brain, as the brain stores marrow and performs mental activities. Su Wen—Dysfunction of the Five Zang Viscera states that all marrow belongs to the brain, while the Compendium of Materia Media states that the brain is the house of mental activity.1617 The brain dominates the most basic life activities of growth and development, and so the condition of the marrow sea relates not only to the kidney, but also to the brain. Ling Shu said that the brain stores marrow, and marrow flows from Baihui (GV 20) to Fengfu (GV 16). An overabundant marrow sea results in an excess amount of energy and unrestrained action, while insufficient marrow sea leads to vertigo, tinnitus, dizziness, weakness of the legs, loss of vision, and difficulty in sleeping peacefully.18 When nourished by sufficient marrow sea, the brain is energetic, which results in a healthy and powerful body. Studies below show that older adults with encephalopathy conditions such as stroke, Alzheimer’s disease, depression, and Parkinson’s disease often have osteopenia or osteoporosis.1922 Stroke disrupts the balance between bone resorption and bone formation; bone resorption increases while bone formation decreases, which causes or worsens the condition of osteoporosis.1922 Patients with Parkinson’s disease have at least twice the risk of fracture compared with the general population, due to high incidences of falls and osteoporosis,2122 which indicates that patients with Parkinson’s disease have abnormal bone metabolism.23 Most patients with Alzheimer’s disease have bone resorption and/or osteoporosis.24 In addition, depression is reportedly correlated with low bone mineral density, and a meta-analysis showed that patients with depression have an increased fracture risk.2526 Taken together, these findings suggest that osteoporosis is related to deficiency of the brain and depletion of the marrow sea.

BRAIN NEURAL EVIDENCE FOR THE THEORY OF THE KIDNEY DOMINATING THE BONES

Theory of brain-bone mass regulation

As the leading regulatory organ that balances visceral activities, the brain influences the respiratory, digestive, reproductive, and immune systems. Recent studies show that the physiologic function of bone is controlled and coordinated by the brain, and that this control is closely related to the signaling process of leptin.27 The brain contains many neurotransmitters and hormones related to bone remodeling, and the neuronal circuitry in the brain plays an important role in bone remodeling. The mechanism by which the brain regulates bone mass is extremely complex.28 And the discovery of communication between the brain and bones has important implications for the treatment of osteopenia.29

Pathways of brain-bone mass regulation

The brain regulates bone mass via process integration of the signal produced by nerve nuclei or uploaded by peripheral tissues (mainly containing leptin that is produced by adipose tissue) (Figure 1). The regulation of brain-bone mass occurs via three major pathways: (a) the neuro-osteogenic network in which neuronal signaling of the brainstem-hypothalamus regulates the sympathetic nervous system (SNS); (b) the neuro-endocrine-bone network comprising the neuroendocrine signaling pathway of the hypothalamus-hypophysis; and (c) the neuropeptide-bone network in which the hypothalamus secretes neuropeptides that directly act on bone cells.1

BRAIN NEURAL EVIDENCE FOR THE THEORY OF THE KIDNEY DOMINATING THE BONES AND AFFECTING THE LOSS OF BONE MASS

Neuro-osteogenic network

In recent years, studies on the effects of the nervous system on bone regulation have focused on bone formation.2231 Sympathetic nerves provide negative feedback to bone metabolism, while parasympathetic nerves provide positive feedback.22 The negative feedback effect
of sympathetic nerves is to active β-adrenoreceptors signal acting on obese mice by leptin 5-hydroxytryptamine (5-HT), which results in a decrease in bone metabolism. Modern studies show that the bone mass loss in postmenopausal women is related not only to the lack of estrogen, but also to the increase in sympathetic activity. Low estrogen levels enhance sympathetic activity through the central nervous system to decrease bone mass. The lack of leptin also depresses sympathetic activity and promotes bone formation in rats lacking dopamine β2 hydroxylase that are unable to synthesize epinephrine and norepinephrine, thus increasing the bone content. And, women older than 50 years experience increases in bone density and a decrease in fracture risk after taking a sympathetic β2 receptor antagonist (propranolol). The mechanism may be that the β2 receptor antagonist suppresses the expression of receptors on osteoblasts and osteoclasts, promoting bone formation and increasing bone mass. Cholinergic activity favors bone mass by suppressing the SNS and promoting apoptosis by osteoclasts. Mice lacking nicotinic acetylcholine receptor in bone have low bone mass due to high osteoclast activity. The sensory nerves also play a role in skeletal biology, as low bone mass results from the conditional deletion of Sema3A (a factor necessary for sensory neuronal development via the regulation of axon guidance and growth) from neurons rather than from bone, suggesting that osteoblasts are indirectly affected via sensory nerves. Moreover, stimulation of the sensory nervous system regulates bone mass via the effects of central nerves. Although there are still only a small number of in-depth studies into the effects of the automatic nerve system, sensory system, and peripheral nerve system on the regulation of bone mass, the neuro-osteogenic network has a definite effect on osteoporosis.

**Neuro-endocrine-bone network**

The neuro-endocrine network regulates bone mass via the hypothalamus-pituitary-target gland axis (where the target gland is the gonad, adrenal gland, or thyroid) or the hormone system via the suppression or promotion of the release of different hormones to regulate bone metabolism. For example, the kidney can turn the growth hormone secreted by the pituitary into insulin-like factors that act on osteoblasts and bone cells, which results in the increased synthesis and deposition of collagen and chondroitin sulfate. Many regula-
Neuropeptide-bone network

The neuropeptides secreted by the brain are important regulating factors in the process of bone metabolism. The brain secretes regulating factors, and combines them with factors on the surface of osteoblasts, such as neuropeptide Y (NPY), substance P (SP), tyrosine hydroxylase, and calcitonin gene-related peptide (CGRP), which then activate second messengers, regulate the synthesis and secretion of active material in cells, and influence bone metabolism; the main effect is caused by the neuropeptides, while CGRP is the second-most effective factor. NPY suppresses osteoblast activity and bone formation by binding with Y1 or Y2 receptors in the central nervous system, peripheral nervous system, and bone tissues, which results in loss of bone mass and strength.42,43 One study reported that the osteoblast activity and cortical and trabecular bone mass is increased in rats with NPY deficiency, while the bone mass of rats with neuropeptide overexpression is significantly decreased.44,45 However, other studies report that rats with NPY deficiency have no change in bone mass, and that NPY promotes cell proliferation, angiogenesis, and callus formation, which aid in fracture healing.46,47 Thus, there is currently no consensus on the effect of neuropeptides on bone metabolism.

The mechanism of the effect of CGRP on bone metabolism is that CGRP affects the expression of bone formatting protein, promoting the proliferation and differentiation of mesenchymal stem cells into osteoblasts, and suppresses osteoclast activity.48 CGRP also prevents bone resorption and promotes bone formation. The expressions of CGRP and Calalinon gene-related peptide and its type 1 receptor (CGRPR1) are decreased in the bone tissue of rats with ovariectomy-induced osteoporosis.50 Rats with no CGRP have decreased bone formation, but no significant change in osteoclast ability, which shows that CGRP is a physiological factor that stimulates and promotes bone formation.51 Therefore, CGRP plays an important role in bone metabolism via a very complicated mechanism.

Brain effects of the TCM kidney invigoration method in preventing and treating osteoporosis

Broadly speaking, the theory of the kidney dominating the bones should comprise the bone microenvironment and the regulation of bone metabolism by the kidney and other factors, which emphasizes the organic link between the kidney, life essence, marrow, brain, and bone. Therefore, research evaluating the kidney invigoration method for osteoporosis prevention via brain-bone mass regulation should be comprehensive, and should be based on the effect of kidney-tonifying herbs on bone tissue, and the nervous, endocrine, and immune systems.

Kidney invigoration method effects via the neuro-ostogenic network

In osteoporotic rats with kidney deficiency, kidney-tonifying herbs significantly suppress the increase in total phospholipid and total cholesterol in the brain tissues, decrease the 5-HT concentration, and change the concentrations of central neurotransmitters, which delays the aging of brain tissue and prevents osteoporosis.52 Glutamate is an important neurotransmitter that excites the majority of synapses in the central nervous system and influences many important physiological functions of the brain, such as the proliferation, development, and survival of neuronal cells and colloid cells.53 Kidney-tonifying herbs mediate bone remodeling by regulating the signals of glutamate, thus improving the symptoms of osteoporosis in ovariectomized rats.54 Kidney-tonifying herbs also significantly increase the bone density by downregulating hypothalamic protein kinase C, bone morphogenetic protein, and its signal molecule.55,56

Another TCM treatment that increases bone mass is acupoint catgut embedding. The end products of acupoint catgut embedding are lysine, tyrosine, phenylalanine, and glycine, which suggests that acupoint catgut embedding may regulate bone mass via the hypothalamic-bone mass regulation network that involves leptin, 5-HT, the hypothalamus, and sympathetic nerves.57 Acupoint catgut embedding exerts an analgesic effect by regulating phenylalanine and glycine.57

Kidney invigoration method effects via the neuro-endocrine-bone network

The kidney invigoration method regulates bone mass via the hypothalamus-pituitary-target gland axis. The modern biological mechanism of the kidney-marrow-bone system includes variations in the hypothalamic-pituitary-target gland axis, anomalies of various growth factors and their signal transduction, and meta-
bolic disturbances of intestinal calcium-bone calcium.\textsuperscript{32} Kidney-tonifying herbs promote the recovery of ovar-ian function and have an estrogen-like effect that im-proves the estrogen levels in postmenopausal women by regulating the hypothalamus-pituitary-ovarian axis, which thus influences bone metabolism.\textsuperscript{32,39} Estrogen plays an important regulatory role in the bal-ance of bone metabolism. Estrogen suppresses the se-cretion of tumor necrosis factor-α (TNF-α) and interleukin-6 from osteoblasts to reduce the activity of osteo-clasts, thus retarding the process of osteoporosis.\textsuperscript{45} Ovariectomized rats that are unable to secrete estrogen lose control of the secretion of TNF-α, interleukin-1β, and interleukin-6, which results in significant increases in the concentrations of these factors, enhances the ac-tivity of osteoclasts, speeds up the process of bone resorp-tion, and causes osteoporosis.\textsuperscript{49} The estrogen in TCM invigorating herbs combines with estrogen receptors in bone cells, downregulates TNFα and interleu-kin-6, prevents bone destruction and absorption, and increases bone mineral density.\textsuperscript{66} Furthermore, kid-ney-tonifying herbs have no clinically significantestro-gen-like side effects, and so are easily accepted by pa-tients.\textsuperscript{62-64} For example, the administration of a classical prescription for kidney invigoration called Yougui pills resulted in a significantly higher testosterone level in rats with kidney yang deficiency than in the control group, which shows that kidney-tonifying herbs in-crease the serum testosterone level and regulate the hy-pothalamus-pituitary-gonad axis.\textsuperscript{66} Additionally, exter-nal or internal administration of a prescription for kid-ney invigoration raised the levels of estrogen, calcium/parathyroid hormone, thyrotropin, three iodine thyrold, and thyroxine in a rat model of osteoporosis, which shows that the kidney invigoration method pre-vents hypofunction of the pituitary-thyroid axis and improves thyroid function, thus decreasing the bone re-sorption by osteoblasts and increasing the bone forma-tion by osteoblasts, which results in an increase in bone density.\textsuperscript{66} Moreover, an experimental study of a rat model of osteoporosis showed that kidney-tonifying herbs suppress the activity of bone resorption activat-ing factors (mainly interleukin-1 and -6) through the regu-lation and protection of the hypothalamus-pitu-itary-adrenal axis, which suppresses the formation and development of osteoporosis.\textsuperscript{66} The effects of acupoint catgut embedding using the TKBM method on tyro-sine and phenylalanine show that acupoint catgut em-bedding may regulate the hypothalamic arcuate nucleus via monoamine neurotransmitters to make it secrete gonadotropin-releasing hormone, growth hormone-re-leasing hormone, and thyrotropin-releasing hormone to regulate neuroendocrine function, including the bone mass regulation of the hypothalamus-pituitary-adrenal axis, hypothalamus-pituitary-thyroid axis, and hypo-thalamus-pituitary-liver axis.\textsuperscript{66} The kidney invigoration method affects bone metabolism by comprehen-sive multi-link, multi-channel, and multi-target regula-tion via the neuro-endocrine network.

**Kidney invigoration method effects via the neuropeptide-bone network**

Rats with ovariectomy-induced osteoporosis have sig-nificantly decreased nerve supply and CGRP, SP, and NPY concentrations in bone tissue, but these concen-trations significantly increase after the administration of Zuogui pills or Yougui pills; this suggests that ad-ministering kidney-tonifying herbs upregulates the ex-pression of neuropeptide genes, which regulates bone metabolism.\textsuperscript{47} Tonifying the kidney and activating the blood also prevents osteoporosis by regulating the ex-pressions of NPY and mRNA in blood and bone tissue.\textsuperscript{66} Furthermore, the administration of a kidney in-vigoration prescription for 12 weeks in ovariectomy-in-duced osteoporotic rats caused significant increases in the levels of CGRP and SP in blood and bone tissue, and significant increases in bone density.\textsuperscript{66} Overall, this evidence shows that neuropeptides are involved in the bone metabolism process of osteoporosis, and that kid-ney-tonifying herbs disrupt the process of osteoporosis by influencing neuropeptides.

**CONCLUSION**

The hypothesis that a deficiency of marrow sea causes osteoporosis is based on the TCM theory of the kidney controlling the bones, the marrow moistening the bones, and the relationship between the dryness and brittleness of bone and the deficiency of marrow sea. The hypothesis agrees with the Western Medicine theo-ry of the brain regulating bone mass, which shows that the TCM theory of the kidney controlling the bones is supported by specific brain neural correlations. In addi-tion, the hypothesis is further proved by studies showing that the kidney tonifying method prevents osteoporosis. The theory of the kidney controlling the bones from the aspect of brain-bone mass regulation fits the holis-tic TCM concept rather than the Western Medicine way of thinking about the kidneys affecting bone, bone affecting the kidneys, and the metaphysics of bone and marrow,\textsuperscript{66} which reflects the holism of the kid-ney-bone-marrow system (brain). Neuroraming tech-niques may aid in exploring the neural effects of the TKBM method for the prevention and treatment of os-teoporosis, and in the development of new therapies for osteoporosis.

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