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Wang, S-J, Yue, W, Rahman, K, Xin, H-L, Zhang, Q-Y, Qin, L-P and Zhang, H (2016) Mechanism of Treatment of Kidney Deficiency and Osteoporosis is Similar by Traditional Chinese Medicine. Current Pharmaceutical Design, 22 (3). pp. 312-320. ISSN 1381-6128

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Mechanism of treatment of kidney deficiency and osteoporosis is similar by Traditional Chinese Medicine

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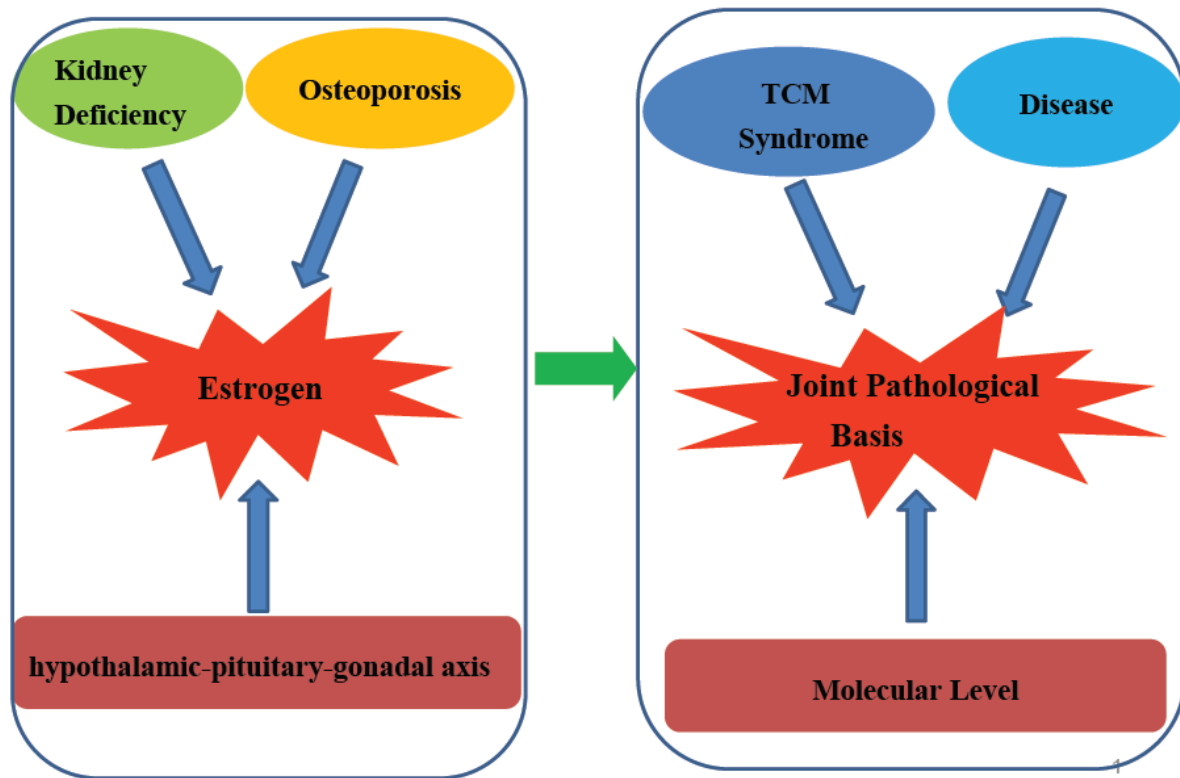
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Abstract

Traditional Chinese medicine (TCM) is a theoretical based system and is completely different from western medicine and states that numerous diseases, especially chronic diseases, are cured or relieved. “Zheng” (syndrome) is a summarization of the pathological changes which take place during the different stages of the development of a disease, including its location, cause and nature as well as the state of both Xie-qi (pathogenic factors) and Zheng-qi (healthy energy). Compared to a single symptom, syndrome can demonstrate the nature of a disease more extensively, completely and correctly. However, it is difficult to compare “Zheng” to the western medicine theory, which is based on scientific evidence for the diagnosis and treatment of a specific disease. Estrogen deficiency is a major pathogenetic factor in bone loss after menopause and oophorectomy with the subsequent risk of developing osteoporosis. According to TCM theory, the kidney stores essence and this can transform into bone marrow to nourish the bones, strengthen the skeleton by promoting growth and repair. The kidney deficiency can decrease the estrogen level adjusted by the gonadal axis, causing osteoporosis. Traditional Chinese medicines tonifying the kidney can significantly enhance the level of estrogen to alleviate osteoporosis. In combination with other evidence, we further deduce that the syndrome as defined within TCM has a similar pathological mechanism to that defined by western medicine. If TCM theory is to be understood and accepted, and further fused with the western medicine theory, the micro pathological basis of TCM syndrome must be investigated extensively, which will lead to bridging the two theories together. The fusion of TCM with western medicine will pay more attention to analyzing the common nature and difference of disease and syndrome. This paper reviews the way forward for new translational advances.

Keywords: Traditional Chinese medicine; Western medicine; Syndrome; Disease; Pathological basis

Graphical abstract



Introduction

Traditional Chinese medicine (TCM) believes that the human body is composed of viscera, meridians, five sensory organs, nine orifices, four limbs and skeletal parts. These different tissues and organs are united into five functional systems according to their interdependency in structure, physiology and pathology, this includes the heart, liver, spleen, lung and the kidney system. On one hand, human beings depend on nature to provide them with various necessities, such as sunlight, air and water whilst on the other hand, various changes taking place in nature can affect human bodies directly or indirectly and cause corresponding physiological or pathological responses.

Bian-Zheng-Lun-Zhi (syndrome differentiation and treatment) is a basic principle of TCM and is based on analyzing, inducing, synthesizing, judging and summarizing the clinical data of symptoms and signs collected with four diagnostic methods (namely inspection, listening and smelling, inquiry, taking pulse and palpation) into a certain syndrome, and then a therapeutic method is chosen according to the results of syndrome differentiation. “Zheng” (syndrome) is a summarization of the pathological changes at a certain stage during the course of development of a disease, including the location, cause and nature of the disease as well as the state of Xie (pathogenic factors) and Zheng (healthy qi). Compared to a single symptom, syndrome can demonstrate the nature of a disease more extensively, completely and correctly.

Clinically, syndrome-differentiation (Bian-Zheng) and disease-differentiation (Bian-Bing) are intrinsically interrelated although significantly different from each other. It is generally thought that disease includes the whole pathological course while syndrome is just a summarization of the pathological changes at a certain development stage of a disease. A syndrome (Zheng) may appear in different diseases, while different diseases may reveal the same syndrome (Zheng) in their development which is the basis of Bian-Zheng-Lun-Zhi. The essence of Bian-Zheng-Lun-Zhi is that the same syndrome is treated with the same therapy while the different syndromes are treated with the different methods. Therefore in TCM, understanding and treatment of disease mainly focuses on differentiating syndromes and analyzing the common nature or difference of syndromes in the course of differentiating disease.

The organ kidney is located in the waist, which is the house of the kidney according to Huang-Di-Nei-Jing (a famous monograph on traditional Chinese medicine theory). The kidney stores essence (jing), which is transformed into qi to leading to the production of blood. The kidney is also the source of genuine yin (zhen-yin) and genuine yang (zhen-yang). Therefore the kidney is closely related with the essence, qi, blood, yin and yang. Since the kidney-essence (shen-jing) comes from

parents and is the primary substance for constituting human body and conceiving new life, TCM regards the kidney as “the prenatal basis of life”. The kidney has several important physiological functions, one of which is the regulation of the bone. It means that the development and function of the bone depends on the kidney-essence, which contains the kidney yin and kidney yang. The kidney stores essence and the essence can transform into bone marrow to nourish the bone, promote the growth and repair of the skeleton and strengthen the skeleton. If kidney-essence is deficient, it will affect the production of bone marrow, leading to flaccidity of the skeleton and hypoevolutism in infants as well as brittleness of the bone and susceptibility to fracture in the aged [1]. These symptoms are regarded as indicators of kidney deficiency syndrome in TCM, which is the most important cause of osteoporosis.

Osteoporosis is a common skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue with increased fracture susceptibility [2]. The strong and dense bone results from a balance between bone breakdown (resorption) and bone formation. A disruption in the interplay between bone-building osteoblasts and bone-degrading osteoclasts can lead to osteoporosis [3]. One-second women and one-fifth men over the age of 50 years will suffer a fracture due to osteoporosis during their lifetime and demographic changes in the next few decades will result in at least a doubling in the number of these fractures[4]. Despite the increasing public awareness of this disorder, the control rate of osteoporosis remains unsatisfactory, and a substantial proportion of people under treatment do not achieve the effective control recommended by current guidelines. Suboptimal bone growth in childhood and adolescence is as important as later in life bone loss in the development of osteoporosis [5]. In 2001, the NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy suggested that both men and women experience an age-related decline in BMD starting in midlife. Women experience more rapid bone loss in years following menopause, which places them at earlier risk of fractures Whilst in men, hypogonadism is also an important risk factor [5]. Estrogen deficiency is a major pathogenetic factor of bone loss after menopause and oophorectomy with the subsequent risk of developing osteoporosis. Endogenous and exogenous estrogens play an important role in skeletal function at molecular, cellular and tissue levels via genomic and nongenomic actions [6]. After binding to ER- α and ER- β in bone cells, they can facilitate osteoblast formation by regulation of cytokines, such as IL-6 and IL-11 and they also increase osteoclast apoptosis [7]. In TCM, “osteoporosis” does not exist but in view of pathogenesis and clinical manifestations, it is largely associated with “atrophic debility of the bone” [8].

In the 1950s, Shen Ziyin, an academician, discovered that the value of urinary 17-hydroxy is generally down-regulated in patients with kidney-yang deficiency and following this extensive research was undertaken to verify the reliability of this result. Subsequently, Shen first put forward

that TCM syndrome possesses material foundation [9]. The advance aging in hypothalamic-pituitary-gonadal axis function is considered to be one of the essences of kidney-yang deficiency[10]. Consolidating the renal essence can ameliorate the symptoms in elderly male, and this method is relatively specific for the gonads [11]. Chen also recorded that there is an interconnection between gonad and kidney deficiency in TCM [12].

Estrogen deficiency is a major pathogenetic factor for the development of osteoporosis, while kidney deficiency has an intimate connection with the gonads. Accordingly, one has to address the questions if there is any essential association between kidney deficiency and osteoporosis development? What is the essential association? In recent years, the interest in the further development of herbal or botanical drug products derived from traditional preparations has increased significantly. A large number of new drugs from TCM are used in clinical and folk medicine and their effectiveness based on the extensive human use has been confirmed. Therefore, searching for the appropriate fusion between TCM syndrome and modern medicine is a promising channel to find new treatment methods and to guide the development and clinic use of medicines that stem from TCM theory and modern medicine technique. Successful implementation of this principle into the development programs for anti-osteoporosis drugs will substantially contribute to the clinically successful applications of anti-osteoporosis drugs in the future. In this article, we describe the current regulatory environment of osteoporosis treatment development in TCM, and summarize our regulatory experiences and delineated the scientific and regulatory issues involved. We hope that an introduction to the relationship between kidney deficiency and osteoporosis will stimulate more research leading to the development of new treatments based on TCM.

Osteoporosis and estrogen deficiency

The use of gonadal steroids (estrogens and progestogens) is a logical intervention in the prevention of osteoporosis [13] since these are important determinants of peak and lifetime bone mass in men, women, and children [5]. A great deal of evidence indicates that gonadal steroids, particularly estrogens and androgenic progestogens, induce small increments in skeletal mass which are not followed by a progressive decrease in bone density. Thus, dose-appropriate estrogens prevent bone loss, irrespective of whether these are given in the immediate menopausal period or when bone loss is established [13]. In 1996s, JAMA reported postmenopausal women assigned to placebo demonstrated decreased BMD at the spine and hip, whereas women assigned to estrogen therapy increased BMD during a 36-month period. These findings demonstrate that estrogen replacement therapy increases BMD at clinically important sites [14]. Also, the use of estrogen in these postmenopausal women significantly decreased the risk of osteoporosis and subsequent fracture, as reported in a large double-blind randomized clinical trial, the Women's Health Initiative (WHI) in

2002 [15]. Hormone replacement therapy (HRT) is an established approach for osteoporosis treatment and prevention. Observational studies have indicated a significant reduction in the occurrence of hip fracture in cohorts of women who maintain HRT therapy.

Kidney deficiency and estrogen deficiency

The research by Shen Ziyin has proved that TCM Zheng (syndrome) has a material foundation, and there is substantial evidence supporting a crucial role of hypothalamus in deficiency of the kidney [16]. The age-related changes elicited by gonadal axis are very similar to symptoms induced by deficiency of the kidney. The hypothalamic-pituitary-gonadal axis displays premature aging to a certain degree ie one of the essences of kidney deficiencyis areproductive endocrine dysfunction. Meanwhile, it has been confirmed that reinforcing the kidney can improve gonadal axis function by way of “proved syndrome by medicines” (mentioned in Table 2). These investigations indicate that within the context of TCM, “kidney” is linked to the function of reproductive endocrine in modern medicine as the sexual hormones levels also decrease in the female with kidney deficiency [17]. On the other hand, most animal experiments have substantiated that kidney-tonifying Chinese medicines can improve the function of hypothalamic-pituitary-gonadal axis in the animal models of kidney deficiency. These findings are consistent with the results of modern medical research for osteoporosis, indicating that estrogen deficiency is probably a joint pathological basis of kidney deficiency and osteoporosis.

Kidney deficiency and osteoporosis

The TCM theory believes that the kidney plays a central role in human health, and is regarded as “the prenatal base of life”. Governing the bones is one of the most important functions of the kidney in TCM and according to its theory the essence (jing) stored in the kidney can transform into bone marrow to nourish the bones, strengthen the skeleton by promoting its growth and repair. The deficiency of kidney-essence can affect the production of bonemarrow, leading to flaccidity of skeleton [18]. As a corollary, kidney deficiency would be a permissive requirement for sustaining chronic reductions of bone. In addition, the association of kidney deficiency with osteoporosis risk is cited as supporting a key contribution of kidney deficiency to the pathogenesis of osteoporosis. Moreover, estrogen agents are a cornerstone of current anti-osteoporosis therapy, which have an anti-resorptive effect on bone by acting as an inhibitor of osteoclast function and by stimulation of osteoclast apoptosis [19]. It is suggested that estrogen deficiency up-regulates osteoclastogenesis through increasing the production of pro-osteoclastogenic cytokines TNF- α and RANKL. A previous investigation also demonstrated that menopausal women, who have an increase in the number of osteoclastogenesis, suffer from post-menopausal osteoporosis more easily than those matched for the same period [20]. Meanwhile, the Women’s Health Initiative (WHI) study presented the first

evidence in a large randomized controlled trial that HRT or oestrogen alone (ORT) reduces the risk of all osteoporosis-related fractures, even in patients at low risk of fracture [19]. These studies suggest that kidney deficiency and osteoporosis have a common pathological basis, that is, disorder of gonadal axis and/ (or) reduction of estrogen levels.

Diagnosis

Until the first fracture occurs, osteoporosis is a silent disease without any symptoms or increased morbidity. Once the first fracture occurs, the risk of subsequent fractures will double with every new fracture, with a resultant increase in morbidity and mortality [19]. The main symptom of osteoporosis is pain and particular complications may arise from fractures of the spine and hip. The treatment of osteoporosis, therefore, aims to reduce the fracture rate by means of increasing bone strength, a parameter driven by bone mineral density (BMD) and bone quality. BMD, frequently used as a proxy measure, accounts for approximately 70% of bone strength (a surrogate endpoint in many clinical trials for osteoporosis), which is generally measured by dual energy X-ray absorptiometry (DXA). It has been regarded as a good predictor for fracture risk [21], nevertheless, there are currently no accurate methods of measurement for overall bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 SDs below the mean for young white adult women. It is not clear how this diagnostic criterion can be applied to men and children, or across ethnic groups [5]. The monitoring of treatment by serial measurement of BMD has serious pitfalls such as individual variations in precision of operators and devices.

Kidney deficiency can cause osteoporosis and based on the TCM theory, the kidney governs the bones, including its development and function and as such the essence of kidney is yin and yang. Clinically, kidney-yin deficiency or kidney-yang deficiency can lead to osteoporosis. Er-Zhi-Wan (EZW), a famous traditional Chinese medicine formulation, has been developed as a restorative preparation for hundreds of years, which is composed of two herbs viz. the aerial part of *Eclipta prostrata* L. and the fruit of *Ligustrum lucidum* Ait. EZW is widely used to prevent and treat various kidney diseases due to its efficacy for nourishing the kidney yin and strengthening tendon and bones [18]. You-Gui-Wan (YGW), another famous traditional Chinese medicine formulation, possesses the actions of warming and enriching kidney-yang, and replenishing essence and marrow. This recipe can be used for the treatment of kidney-yang deficiency syndrome and is applicable to nephritic syndrome and senile osteoporosis, etc [22].

Diagnostically, the criteria in accordance with the TCM theory is:

a. Deficiency of the kidney-yin

Vertigo, soreness of the waist and knees, seminal emission or spermatorrhea, night sweat, spontaneous perspiration, dry mouth and tongue, reddened tongue with little fur, thread pulse.

b. Deficiency of the kidney-yang

Qi deficiency and mental fatigue from senility or protracted disease, aversion to cold and cold limbs, soreness and weakness of the waist and knees, pale tongue with whitish fur, deep and slow pulse.

For example, the following symptoms occur in the experimental model of rats with kidney-yang deficiency induced by hydrocortisone. On the first five day, the rats gradually display vertical hair, body curled up, convergence, half blind eyes, more urination, etc. From 11 to 14 days, the symptoms of kidney-yang deficiency are more obvious, including loss of weight, dry hair and relaxation, cold limb, dull eyes, unresponsive, decreased spontaneous activity, squinting or closed eyes, leaden feet, low and weak cry, reductions in diet and water intake, increased urination and urine volume, etc. It is very similar to TCM characteristic symptoms of kidney-yang deficiency [23]. Accordingly, You-Gui-Wan (YGW) reverses these symptoms and evidently protects rats from kidney-yang deficiency. It coincides with “principle-method-recipe-medicines” of the syndrome of kidney-yang deficiency [23,24]. Although the animal models do not recapitulate all of the features of human osteoporosis elicited by kidney deficiency, they have nevertheless provided useful insights that have proved relevant to human disorders based on the TCM theory.

Current treatment and the unmet need

Current pharmacological treatments of osteoporosis (hormone therapy, selective estrogen receptor modulators, bisphosphonates, strontium ranelate, denosumab, etc.) are largely palliative (rather than curative) and some may result in nonspecific immunosuppression. This may be associated with a range of complications including breast secretions, gynecomastia, vasodilation, abdominal pain, headache, disturbances of consciousness, etc. For these reasons, there is renewed enthusiasm for strategies aiming to find more effective drugs and (or) treatment guideline. Due to osteoporosis being a chronic condition, it takes longer to show treatment effects of drugs, thus requiring longer and larger studies.

Therapeutic strategies should be designed to include the combined use of drugs with distinct but convergent mechanisms that can amplify treatment efficacies and diminish adverse effects. Although prevalent in postmenopausal women, osteoporosis also occurs in all populations and at all ages and has significant physical, psychosocial, and financial consequences. Clinical risk factors have an important but poorly effective role in determining who should receive BMD measurement, in assessing fracture risk, and in determining who should be treated. Both concept of holism and syndrome differentiation and treatment are the two basic characteristics of TCM in understanding human physiology and pathology as well as diagnosis, treatment and prevention of disease. The

application of TCM prescription went through the process from experience to theory. At first people chose prescriptions and drugs in the light of syndrome only but with the increasing prescriptions and long-term clinical practices, they gradually summarized some regularity of the prescriptions, and then the therapeutic theory came into being. The different syndromes have different principles of treatment. For instance, osteoporosis induced by deficiency of kidney-yang should be treated by warming and activating kidney-yang and replenishing kidney essence. Osteoporosis induced by deficiency of kidney-yin should be treated by nourishing yin and invigorating the kidney. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis.

Postmenopause estrogen replacement therapy is an established treatment for the prevention of osteoporosis in healthy women [25]. The etiology of estrogen deficiency cannot be determined in the vast majority of individuals with ‘essential’ osteoporosis in the TCM theory. Thus, it has proved difficult to develop precise profiles of individual patients for the purposes of identifying optimal therapies and predicting prognosis. Consequently, choices of anti-osteoporosis therapy are typically empirical and are based on broad epidemiological categories such as age, race and the presence of coexisting disorders such as spleen or liver deficiency. Accordingly, developing a more precise understanding of the molecular pathogenesis of osteoporosis remains a pressing priority for both TCM and modern medicine researchers in the field.

Although it is possible to initiate expanded clinical trials on some well-characterized and widely used botanical preparations without the support of nonclinical toxicity data, additional animal studies may be needed for final marketing approval. Although these animal models (deficiency of kidney-yin and deficiency of kidney-yang) do not fully recapitulate all of the features of human kidney deficiency, they have nevertheless provided useful insights that have proved relevant to human disorders. In this review, we have cited and discussed the work using these models as well as studies in humans and animals to illustrate recent progress in the treatment of osteoporosis.

New drugs in development

Before the early 1990s, fewer than ten botanical INDs had been submitted to the FDA. As the FDA initiated its plan to draft botanical guidelines in the mid-1990s, interest in developing botanical drugs escalated [26]. Unlike most small-molecule drugs that comprise a single chemical compound, Veregen, an extract of green tea leaves, contains a mixture of known and possibly active compounds. It is the first new botanical prescription drug approved since the publication of the FDA’s industry guidelines for botanical drug products in June 2004 [26]. It indicates a growing interest over therapeutic needed in rigorous clinical evaluation of botanical drugs, with a focus on indications where there is a clear medical need for new treatments. However, the efficacies of traditional Chinese

medicines have been verified by prior human experience and availability as dietary supplements before thousands of years when approved as drugs. Therefore, nonclinical toxicity studies to support the initial human trials were waived for most botanical applications. The common serious deficiencies resulting in clinical hold include previous human experiences and/or existing animal toxicity data, which are inadequate to support the safety of the proposed clinical trial. However, for many botanical preparations, extensive human experience can provide some degree of comfort in their safety, but the past human experience has rarely been documented rigorously. In this regard, these are either withdrawn by the sponsors or remain on clinical hold, and interpretation of the experience has been a problem in designing clinical trials.

Conclusions and future perspectives

Concept of holism (Zheng-Ti-Guan) and syndrome differentiation and treatment (Bian-Zheng-Lun-Zhi) are the two most basic characteristics of TCM in understanding human physiology and pathology as well as diagnosis, treatment and prevention of disease. Holistic conception guides syndrome analysis of all aspects and conditions of disease, which refers to different constitutions of disease. Treatment according to syndrome differentiation improves local pathological changes through regulating holistic function, which is the practical application of holistic conception. Researchers' inability to distinguish the causes of osteoporosis in individual people is a major obstacle for developing more personalized and effective approaches to clinical management. For example, one disease may demonstrate different syndromes which should be treated by different therapies due to differences in constitution, onset of disease, geographic conditions, or stage of development. Therefore, treatment decisions should be individualized and a general guideline should consider individual difference in pharmacological therapy. The decision, of when to begin and what type of treatment to use, should be made on the basis of the need to reduce fracture risk. Furthermore the agent used (estrogen, SERM, bisphosphonates) may vary over a woman's life time. Based on the theoretical study and clinical practice made by the previous generations and with the adoption of modern scientific theory and technology, TCM will fuse with modern scientific theory and technology reasonably and effectively.

Osteoporosis generally does not present symptoms until clinically significant bone fracture occurs. Despite reflection of bone turnover, the changes in bone mineral density (BMD) and in biochemical markers of bone metabolism do not measure bone quality [27]. The numerous investigations indicate that estrogen deficiency is a joint pathological basis of both kidney deficiency and osteoporosis. Meanwhile estrogen significantly decreases the risk of osteoporosis and subsequent fracture arising in postmenopausal women. According to evidence presented, we deduce that TCM syndrome (Zheng) and modern disease probably have a common material basis (Figure 1). TCM

could be fused with modern scientific theory and technology; however, some unmet points still exist in present research.

TCM theory believes that set prescriptions can be modified according to the actual requirements. The efficacies of Chinese traditional medicines are summarized through long-term clinical observations and repetitive practice, gradually developing into a theory. However, in alternative medicine, the definitions for diagnoses, symptoms and treatment-related adverse events are often vague and difficult to understand or do not correlate with Western medical terminology. Furthermore, the variability and complexity of natural chemical constituents will make it extremely difficult in most cases to establish a definition for ‘equivalence’ between botanical drugs and to prove that two ‘similar’ products are pharmacologically identical or therapeutically interchangeable, as many botanical products and traditional medicines are traditionally used on the basis of the theory and practice of alternative medicine. It will be a technical challenge to define botanical new drugs consistent with both TCM theory and modern medicine. The combination of clinical information collection and BMD testing with syndrome differentiation and treatment (Bian-Zheng-Lun-Zhi) may be available for determination who has a risk for development of fractures, osteoporosis or other diseases. Prospectively, we may be able to improve on this risk assessment by using advanced imaging techniques and methods based on TCM theory and modern medicine for assessing human disease. This will depend on indications, the kinds of study (placebo control or comparison of batches) and other factors. Although not all of the above approaches will be necessary for every case, the combination of some of these will be usually effective.

Syndrome is established generally by analysis, induction, synthesis, judgment and summarization of the clinical data of symptoms and signs collected by the four diagnostic methods (namely inspection, listening and smelling, inquiry, taking pulse and palpation). However, as diagnostic criteria largely depend on doctors’ clinical experience, the syndrome is affected for its reliability and accuracy. In recent years, the research for syndrome material foundation relates to the ultrastructure, physiology and biochemistry. Nevertheless, each TCM syndrome contains not only several physical and chemical indicators, but also the network link between the multi-level indices. The corresponding level inconsistency between physical and chemical indicators and syndrome determines that a single indicator or simple superposition of indicators cannot explain all aspects of TCM syndrome. Based on the concept of holism, the essence research of syndrome does not look for specific substance from body, but should investigate the body physiological material, pathological basis and their spatial and temporal distribution.

In physiology, viscera perform various functions by cooperation with each other. In pathology, morbid changes in any part of the body will affect other viscera and tissues or even the whole body.

Similarly, general pathological changes of the body will affect the function of the local viscera. Kidney-yin deficiency and kidney-yang deficiency can be distinguished in theory and clinic, but their research findings are a bit vague on the significance of gonadal axis connotation which is described as changing the structure and/or its function. However, is there any difference in the degree or link of gonadal axis changes? What is the difference? These questions have not been addressed yet. Presumably the main reason is that the other syndromes disturbed the syndromes investigated. It may draw a positive conclusion that the characteristics of syndrome are selected to establish the multi-syndrome comparative study.

In order to conduct an in-depth study of syndrome, animal experiments must be conducted and comply with the theory and clinical practice of TCM. The experiment would be meaningless if an appropriate animal model fails. As syndrome is a summarization of the pathological changes of a disease at a certain stage in its course of development, it can be affected by variations of the season, geographical conditions, weather, and other operation practices. Batch-to-batch inconsistency is also a common problem. In different periods, different syndromes can transform and reinforce each other in the same individual, which are relative clinical concepts. The TCM theory puts a great emphasis on the dialectical relationship between yin and yang, especially as the concept of holism. For example, no matter the kidney or spleen deficiency, qi or blood deficiency, they are ultimately interrelated and reinforced with each other as a holism. In this regard, a standard principles outline of animal experiments should be formulated by following scientific test and good collection practice for starting materials of clinical syndrome origin.

However, traditional Chinese medicine and modern medicine are two different academic disciplines, and have different ways of thinking. Modern medicine lays emphasis on the structure and part and usually uses unilateral antagonist therapy. However TCM focuses on function and the whole, and generally gives multifaceted regulation therapy. In fact, TCM is complementary with modern medicine by commensurate treatment and (or) proportional amelioration of disease. Meanwhile, as the costs and time involved with drug discovery show no immediate sign of decreasing, despite the advent of many new technologies, most savings will be made by parallelizing processes. For example, instead of waiting for a protease and (or) gene to be validated as an osteoporosis-relevant target, Chinese herbal medicines whose effectiveness have been substantiated by human experience are applied. A vast amount of information, including clinic experience, substrate specificity, assay development and initial screening for the interacting compounds, can be gathered beforehand and potentially extrapolated to other, related osteoporosis-relevant material basis based on the fusion of traditional Chinese medicine with western medicine. Going forward, application of these different treatment theories to the issue of the modern medicine disease has great promise.

Syndrome (Zheng) and disease are intrinsically interrelated on one hand, but are also different from each other. Disease includes the whole pathological course, while syndrome is just the summarization of certain stage in the course of the disease. For this reason one disease may display different syndromes, while different diseases may demonstrate the same syndrome in their course of development. TCM places emphasis on analyzing the common nature and difference of syndrome in the course of disease development.

In conclusion, kidney deficiency and osteoporosis have a joint pathological basis. Based on the existing evidence, we further deduce that TCM syndrome possibly has a joint pathological basis with modern disease. If TCM theory is to be accepted and further fused with the western medicine theory, the micro pathological basis of TCM syndrome must be investigated extensively, thus bridging these two theoretical systems. The fusion of TCM with modern medicine will pay more attention to analyzing the common nature and differences of the disease and syndrome.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No.81173462) and the Open Research Fund of State Key Laboratory Breeding Base of Systematic Research, Development and Utilization of Chinese Medicine Resources (ME2015006).

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Figure 1 TCM syndrome (Zheng) and modern disease probably has a joint pathological basis

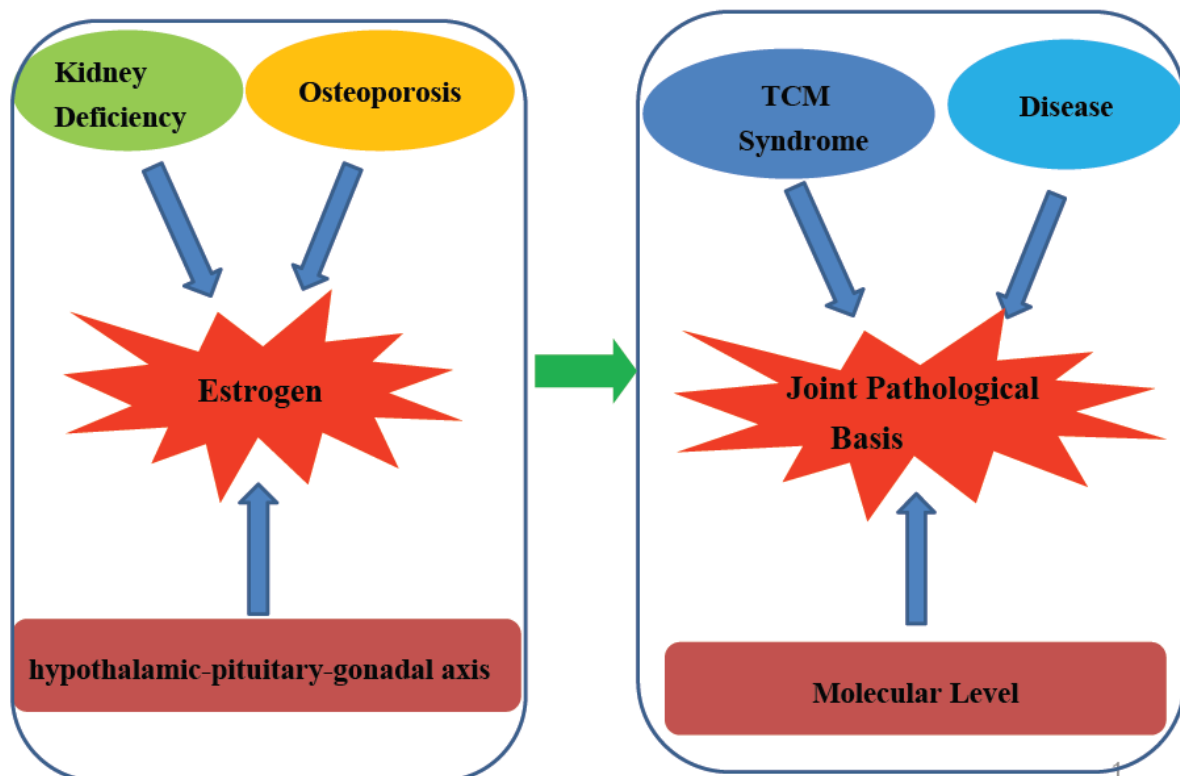


Table 1 Traditional medicines for the treatment of osteoporosis induced by estrogen deficiency

Botanical name	Family	Medicinal part	Pharmacological effect	Model	Reference
<i>Achyranthes bidentata</i> Blume	Amaranthaceae	Root	Decrease of bone loss in ovariectomized rats by inhibiting osteoclast formation	Ovariectomized rats	[28]
<i>Cuminum cyminum</i> L.	Apiaceae	Fruit	Prevention of bone loss caused by ovariectomy	Ovariectomized rats	[29]
<i>Ferula hermonis</i> Boiss	Apiaceae	Root	Prevention of bone loss caused by severe estrogen deficiency	Ovariectomized rats	[30]
<i>Acantho panax senticosus</i> Harms	Araliaceae	Stem	Decrease of bone loss in postmenopausal women	Postmenopausal women	[31]
<i>Lepidium meyenii</i> Maca	Brassicaceae	Root	Improvement of the bone mass in ovariectomized rats	Ovariectomized rats	[32]
<i>Sambucus williamsii</i> Hance	Caprifoliaceae	Stem and ramulus	Suppression of the ovariectomy induced increase in bone turnover, inhibition of bone resorption, and stimulation of bone formation	Ovariectomized rats	[33]
<i>Silybum marianun</i> (L.) Gaertn	Compositae	Seed	Prevention of bone loss caused by ovariectomy with mild proliferative effects in uterus	Ovariectomized rats	[34]
<i>Cibotium barometz</i> (L.) J.Sm.	Dicksoniaceae	Rhizome	Prevention of bone loss induced by ovariectomy	Ovariectomized rats	[35]
<i>Dipsacus asperoides</i> C. Y. Cheng et T. M. Ai	Dipsacaceae	Root	Inhibition of bone loss induced by ovariectomy	Ovariectomized rats	[36,37]
<i>Vaccinium angustifolium</i> Ait. and V.	Ericaceae	Fruit	Prevention of bone loss in ovarian hormone deficiency	Ovariectomized rats	[38]

<i>myrtilloides</i> Michx.					
<i>Eucom miaulmoides</i> Oliv	Eucommiaceae	Bark	Prevention of bone loss induced by estrogen deficiency	Rat pituitary cells/ five ovariectomy (OVX) subgroups	[39,40,41]
<i>Butea monosperma</i> (Lamk.) Kuntze	Fabaceae	Stem bark	Prevention of bone loss induced by ovariectomy through stimulating bone formation	Ovariectomized rats	[42]
<i>Phaseolus vulgaris</i> L.	Fabaceae	Seed	Prevention of osteopenia induced by estrogen deficiency without affecting the uterine mass	Ovariectomized rats	[43]
<i>Allium cepa</i> L.	Liliaceae	Bulb	Decrease of the ovariectomy-induced bone resorption	Ovariectomized rats	[44]
<i>Allium sativum</i> L.	Liliaceae	Bulb	Prevention of bone loss, reverse of the low BMD and decrease of tensile strength caused by ovariectomy	Ovariectomized rats	[45]
<i>Anemarrhena asphodeloides</i> Bunge	Liliaceae	Rhizome	Prevention of bone loss induced by ovariectomy through promotion of bone formation but not inhibition of bone resorption	Ovariectomized rats	[46]
<i>Abelmoschus manihot</i> (L.) Medicus	Malvaceae	Leaf	Reduction of bone loss in conditions of estrogen deficiency		[47]
<i>Tinospora cordifolia</i> Vanda	Menispermaceae	Stem	Prevention of bone loss induced by ovariectomy	ovariectomized rats	[48]
<i>Anoectochilus formosanus</i> Hayata	Orchidaceae	Whole plant	Suppression of the bone loss caused by estrogen deficiency		[49]

<i>Cistanche salsa</i> (C.A.Mey) G. Beck	Orobanchaceae	Stem	Prevention of bone loss induced by ovariectomy	ovariectomized mice	[50]
<i>Rubus coreanus</i> Miq.	Rosaceae	Fruit	Prevention of bone loss caused by estrogen deficiency by dual regulation of the enhancement of osteoblast function and induction		[51,52]
<i>Rehmannia glutinosa</i> Libosch	Scrophulariaceae	Root	Increase of the cortical bone thickness in ovariectomy-induced osteoporotic rats	ovariectomized rats	[53]
<i>Withania somnifera</i> (L.)Dunal	Solanaceae	Root	Inhibition of bone loss in ovariectomized rats	ovariectomized rats	[54]
<i>Taxus yunnanensis</i> Cheng	Taxaceae	Seed, bark	Increase of bone mineral content and bone mineral density in ovariectomized rats	ovariectomized rats	[55]
<i>Ulmus wallichiana</i> Planch.	Ulmaceae	Bark	Mitigation of ovariectomy-induced osteoporosis in rats, stimulation of osteoblast function and inhibition of osteoclast differentiation	ovariectomized rats	[56,57]
<i>Cissus quadrangularis</i> L.	Vitaceae	Aerial parts, root	Prevention of bone loss in ovariectomized rats.	ovariectomized rats	[58]
<i>Curcuma comosa</i> Roxb.	Zingiberaceae	Rhizome	Prevention of bone loss induced by estrogen deficiency		[59]

Table 2 Traditional formulations for the treatment of kidney deficiency and osteoporosis

Formulation	Syndrome	Model	Composition	Pharmacological effect	Reference
Er-Zhi Wan	Deficiency of kidney-yin	10% Monosodium glutamate (MSG), 2, 4, 6, 8, 10 d, 4 g/kg·d ⁻¹ , neonatal rat, Male	<i>Eclipta prostrate</i> , <i>Ligustrum lucidum</i>	Prevention of osteoporosis induced by the deficiency of kidney-yin through inhibition of the hypothalamic nerve cells apoptosis and up-regulation of serum estradiol.	[60]
Jiawei Yanghe decoction	Deficiency of kidney-yang	Postmenopausal women	<i>Colla Plastris Testudinis</i> , <i>Colla Cornus Cervi</i> , <i>Rhizoma Rehmannina Praeparatae</i> , <i>Cortex Cinnamomi</i> , <i>Herba Ephedrae</i> , <i>Rhizoma Zingiberis</i> , <i>Glycyrrhiza uralensis</i> Fisch, <i>Salvia miltiorrhiza</i> Bunge	Prevention and treatment of osteoporosis through inhibition of osteoclasts formation and resorption, promotion of bone formation, and improvement of bone mineral density.	[61]
Qiangji Jianli Yin	Deficiency of kidney-yang	Hydrocortisone, 25 mg·kg ⁻¹ ·d ⁻¹ , Sprague–Dawley rat, Male	<i>Astragalus membranaceus</i> , <i>Codonopsis pilosula</i> , <i>Atractylodes macrocephala</i> , <i>Angelica sinensis</i> , <i>Cimicifuga heracleifolia</i> , <i>Glycyrrhiza uralensis</i>	Prevention and treatment of Deficiency of kidney-yang in rats is related with the regulation of the hypothalamic-pituitary-gonad Axis.	[23]
You-Gui Wan	Deficiency of kidney-yang	Hydrocortisone, 25 mg/kg, Wistar rat, Male	<i>Dioscorea opposita</i> , <i>Cuscuta australis</i> , <i>Eucommia ulmoides</i> , <i>Rehmannia glutinosa</i> , <i>Lycium barbarum</i> ,	Improvement of the deficiency of kidney-yang through up-regulation of testosterone content.	[24]

Jiawei Zuogui Wan	Deficiency of kidney-yin	Clinical treatment	<i>Rehmannia glutinosa</i> , <i>Lycium barbarum</i> , <i>Dioscorea opposita</i> , <i>Cornus officinalis</i> , <i>Cyathula officinalis</i> , <i>Cuscuta australis</i> , <i>Colla cornus cervi</i> , <i>Poria cocos</i> , <i>Astragalus membranaceus</i> , <i>Atractylodes macrocephala</i> , <i>Epimedium brevicornu</i>	Improvement of osteoporosis symptoms and increase the bone BMD. [62]
Liuwei Dihuang decoction	Kidney deficiency	Clinical treatment	<i>Rehmannia glutinosa</i> , <i>Dioscorea opposita</i> , <i>Cornus officinalis</i> , <i>Poria cocos</i> , <i>Alisma orientalis</i> , <i>Paeonia suffruticosa</i>	Prevention and treatment of osteoporosis is related with stimulate bone formation. [63]
Rongjin Tablets	Kidney deficiency and blood stasis type	Clinical treatment	<i>Glycyrrhiza uralensis</i> , <i>Achyranthes bidentata</i> , <i>Tribulus terrestris</i> , <i>Poria cocos</i>	Significant improvement of the kidney deficiency and blood stasis type of primary osteoporosis. [64]
Invigorating kidney pill		Oestrus stage mice, female	<i>Rehmannia glutinosa</i> , <i>Dioscorea opposita</i> , <i>Cornus officinalis</i> , <i>Lycium barbarum</i> , <i>Rubus chingii</i> , <i>Morinda officinalis</i> , <i>Cuscuta australis</i> , <i>Eucommia ulmoides</i> , <i>Achyranthes bidentata</i> , <i>Astragalus membranaceus</i> , <i>Poria cocos</i>	Increase of FSH, LH and E2, esp., wet weight of ovary. Integration of the reproduction and endocrine system with different levels of hypothalamus, pituitary and sexual gland. [65]