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The Connotation of Kidney Stores Essence Theory and Kidney Endocrine Substance

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Abstract

Traditional Chinese medicine (TCM) is a traditional healing system with unique theoretical system. The Zang-Fu theory is the closest mapping to body's physiological and pathological changes. Kidney is the most vital Zang organ in TCM system. However, the material basis of kidney essence is still undefined. In this chapter, we propose the idea that kidney endocrine substances, such as renin, kallikrein, erythropoietin (EPO), calcitriol, bone morphogenetic protein (BMP)-7, and klotho, are potential candidates of the material basis of kidney essence. In addition, kidney-nourishing therapy and related Chinese medicinal herbs are also introduced.

Keywords: TCM, kidney stores essence theory, renal endocrine, material basis, kidney nourishing therapy

1. Introduction

Traditional Chinese medicine (TCM) is one of the oldest medical treatments in the world. Limited by the times, it is characterized by the Yin-Yang, Five-Element, and Zang-Fu theory. The Zang-Fu theory explains the physiological function and pathological changes of human body, and the most vital organ would be the kidney. In western medicine, the kidneys are excretory organs with endocrine function. In TCM, it is not only related with anatomical concept but beyond of that. The material basis of kidney essence has long puzzled Chinese scientists. Dysfunction of hypothalamic-pituitary-adrenal (HPA) axis [1], hypothalamic-pituitary-gonadal (HPG) axis [2], and hypothalamic-pituitary-thyroid (HPT) axis [3] have been putting forward proposals. Nowadays, the stem cells self-control system depending on neuro-endocrine-immune (NEI) system regulated microenvironment [4] is the dominant

academic view. Moreover, chromosome [5], vitamin D (calcitriol) [6], and erythropoietin (EPO) [7] were also considered to be the material basis of kidney essence. In modern medicine, the kidneys are endocrine organs that secrete a variety of hormones, such as renin [8], kallikreins [9], EPO [10], calcitriol [11], BMP-7 [12], and klotho [13]. This chapter aims to compare the similarities of the essence of kidney in TCM and the active substance secreting by the kidneys, and to propose the idea that renal endocrine function has the potential to be one of the kidney essence.

2. Kidney stores essence theory

2.1. Kidney stores essence (Jing)

Essence (Jing) is the basic substance both constituting the body and supporting its functional activities. The functions of essence are controlling reproduction, growth, and development, promoting the transformation of blood. For example, the forward movement of sperm in infertile men with kidney deficiency was much lower than that in fertile men, and the expression of c-kit mRNA, a marker of sperm damage, was increased [14]. For female, more than half of premature ovarian failure (POF) patients were differentially diagnosed by TCM as deficiency of kidney in 122 cases [15]. Destruction of the gonad was usually used to induce kidney deficiency animal model. Kidney-essence deficiency mice showed lower sperm density and motility, and lesser number of baby mice. The same is true for their descendants [16].

According to Suwen (Plain Questions), a classical work of the TCM theory, kidney essence controls the natural human processes from birth to death. There is an abundance of kidney essence in childhood, which provides the power to grow teeth, hair, and bones. During puberty, the kidney essence is even more plentiful resulting in the ability of fertility. Then female fertility begins to decline after 35 years old and male's after 40, as the kidney essence starts to decline. In old age, the kidney essence depletes as time passes, accompanying with infertility, osteoporosis, anemia, baldness, tinnitus, and even hearing loss. Therefore, aging is considered to be physiological kidney deficiency [17].

2.2. Kidney rules water

As urinary organs, TCM kidney and anatomical kidneys both bear consistency of functional. In the rat model of kidney-yang deficiency, classical kidney-nourishing formulas strongly regulated the RAA system hormone disorder [18].

2.3. Kidney governs reception of qi

According to the TCM theory, kidney controls deep and normal breathing in spite of the difficult-to-understand relationship between the kidneys and the lungs. It has been proved that kidney deficiency related closely with stable phase of chronic obstructive pulmonary disease (COPD) [19]. Geng et al. [20] found that the number of asthma attacks of children treated

with tonifying qi and kidney TCM significantly decreased, and the effect remained after withdrawal of TCM for 9 months.

2.4. Kidney controls the bones

Stored in the kidneys, essence can transform into the marrow that fills up the bone cavities, where the blood is produced. The brain is even named as the “sea of marrow.” For this reason, kidney essence is so important for bone development, healthy teeth, blood formation, and normal cognitive function. For example, the risk of fracture is significantly higher in chronic kidney disease (CKD) patients than in the general population [21]. The expenditures of oral problems also increased steadily along with the severity of CKD stages [22]. Homeostasis of calcium and phosphate maintain the development of bones. Many renal endocrines take part in the courses of bone metabolism, such as $1, 25(\text{OH})_2\text{D}_3$, Klotho, BMP-7, and EPO. Aging may increase the risk of kidney dysfunction, and finally results in cardiovascular events, metabolic bone diseases, and even death [23].

When people are getting old, cognitive problems become more and more evident, such as amnesia, retard response, apathy, agnosia, and depression. The disorder of memory and cognitive deficit are usually related to Alzheimer's disease (AD) and vascular dementia (VD). TCM considered that the elderly person initially with kidney deficiency tends to have dementia. Promoting the transformation of blood is another function of kidney essence. Therapy of nourishing kidney [24] could promote the proliferation and differentiation of bone marrow hematopoietic progenitor cells *in vitro*.

2.5. The kidney influences the hair luster

Hair is nourished by the blood, which is generated from essence. Hairs collected from kidney deficiency patients [25] showed the shortest hair diameter and the relatively wide intervals between cuticles. Meanwhile, the levels of trace elements [26] and amino acids [27] in hair of patients with renal diseases decreased.

2.6. Ears as window of kidney

Presbycusis is regarded as a model of “kidney deficiency” deafness in TCM. The GC/MS analysis showed that hearing loss in the elderly people were positively correlated with kidney deficiency score in TCM [28]. It may be related to glutathione metabolism, amino acid metabolism, glucose metabolism, NMDA receptors, and GABA receptors. In addition, the ear length declined with the diminished kidney function after kidney donation [29].

In summary, the Five-Element theory serves to categorize all things in nature with the characteristics of five elements (**Figure 1**). Meridian tropism is used to explain the selectivity of drug action on a part of the body. For example, TCM considered that “salty flavor entering the kidney,” “black food nourishing the kidney,” and “correspondence of kidney with winter.” Modern research has shown that salt is associated with the secretion of renin and the occurrence of high blood pressure. Black rice rich in several anthocyanins are effective in the prevention of hypertension [30].

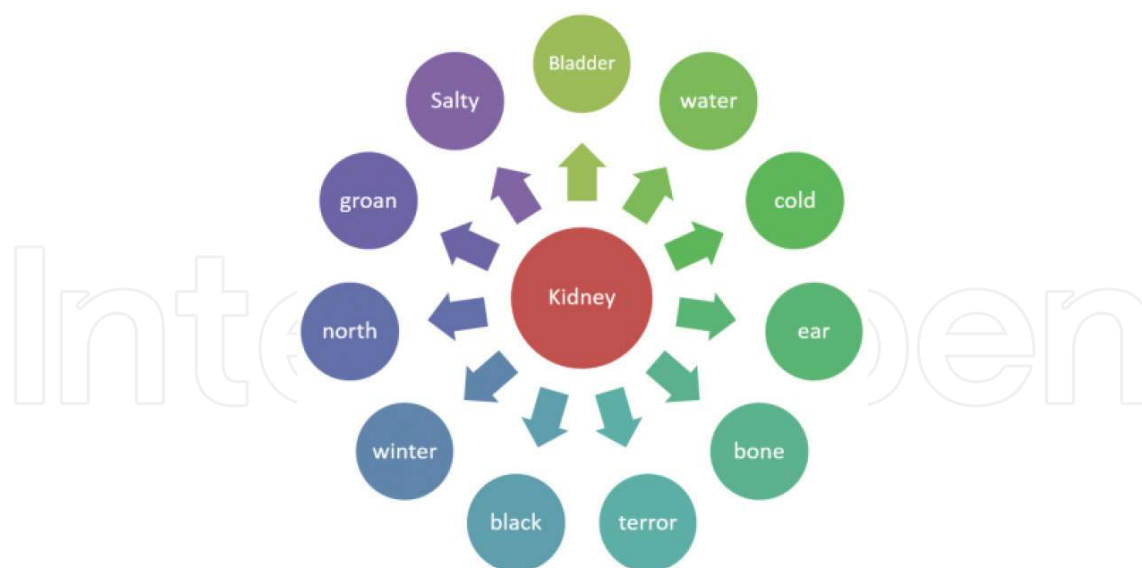


Figure 1. Categorization of kidney manifestation.

3. Renal endocrine and the “kidney stores essence” theory

According to the similarities of the kidney endocrine substances and the kidney essence in the sources and functions (**Figure 2**), we summarize several hormones secreted by the kidneys.

Renin is produced by renal juxtaglomerular epithelioid cells [8], and its secretion is with salt sensitivity [31]. Renin is believed as the regulators of kidney-yang, due to its participation in the blood pressure control system. In contrast, kallikrein-kinin system (KKS), mainly expressed in the distal tubules and collecting ducts of kidney [9], can lower blood pressure and promote the differentiation of stem cells, as the regulator of kidney-yin. Unlike the two above, EPO is exclusively secreted by renal interstitial fibroblast cells [10], which can regulate differentiation of red blood cells, stem cells, and progenitor cells. It is a veritable substance of nourishing blood. Calcitriol and BMP-7 are the presentations of the “kidney controls the bones” theory. The former is produced via 25-hydroxyvitamin D₃ 1 alpha-hydroxylase (CYP27B1) in renal proximal tubular cells [11], while the latter is expressed in the renal outer medulla and in glomeruli, and in several glomerular cell types, such as mesangial, epithelial, and endothelial cells [12]. Knocking out BMP-7 in mice resulted in death shortly after delivery, with kidney failure, skeleton deformity, and eye loss [32].

As one of the material basis of the “kidney stores essence” theory, we will highlight α -klotho in this chapter. Klotho is mainly expressed in the distal tubule and the collecting duct [13]. As a longevity gene klotho has been widely known, as its reduction directly affects life expectancy [33]. Compared with the wild-type littermates, serum klotho level is reduced by approximately 80% in mice with renal-specific deletion of klotho, and exhibited severe growth retardation, kyphosis, and premature death. Serum α -klotho levels in healthy people rise with age to young adults and then gradually decline while age increased, showing a parabola [34]. The change of α -klotho level (**Figure 3**) is consistent with the description of kidney essence in Suwen.

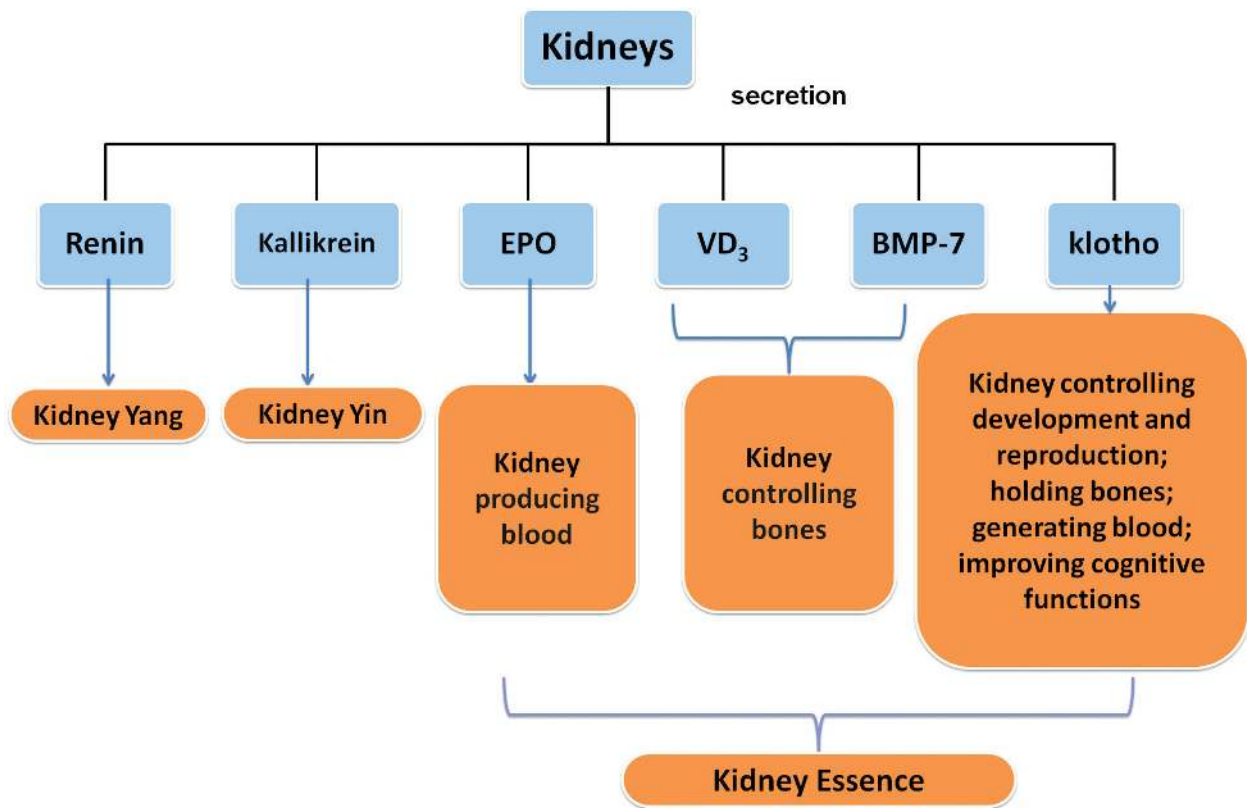


Figure 2. Similarity of kidney endocrine substances and kidney essence.

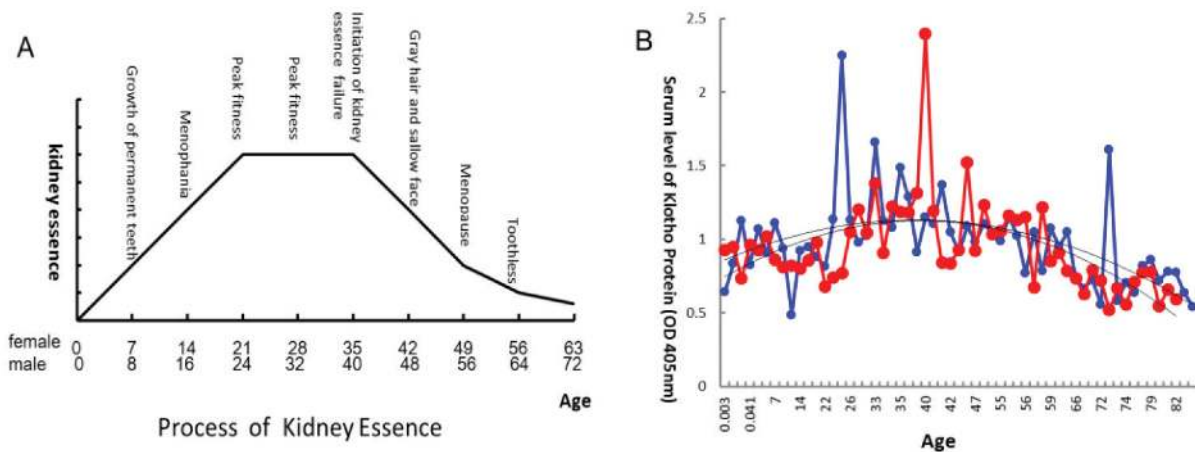


Figure 3. (A) Changes of kidney essence with age according to description of “Suwen.” (B) Serum level of klotho protein changes with the human age [34].

Many studies have shown that α -klotho deficiency affects bone marrow stem cells and blood cell growth, development, and differentiation [35–37]. α -Klotho and EPO can be regulated by each other [38, 39]. Obviously, the role of α -klotho is very similar to the TCM theory of “kidneys essence generating marrow and producing blood.”

Modern medical research has elucidated that α -klotho deficiency causes bone matrix protein distribution changes and calcification defect [40]; and participates in calcium and phosphorus metabolism [41]. α -Klotho also regulates the expression of vitamin D receptor [42]. It is clear that the lack of 1,25-dihydroxyvitamin D₃ can lead to osteoporosis [43]. Studies have shown that the introduction of variant KL-VS of the human KLOTHO gene in mice enhances cognitive function and increases serum α -klotho levels [44].

It has also been observed that there is a relationship between klotho and reproductive function [39]. The Nabeshima group also found that klotho-deficient mice have abnormal regulation of gonadotropins [45]. Recent studies have shown that maternal serum α -klotho exhibits positive association with fetal birth weight [46]. Our research shows that klotho expression in testis in 30-week-old SHR is significantly lower than that of normal controls Wistar-Kyoto (WKY) rats [47]. At present, although there is no direct evidence to prove the relationship between angiotensin II and klotho in testes, a lot of circumstantial evidence appears that klotho protect the organs and antagonistic effects of angiotensin II [48, 49]. Overall, we find that klotho function and the “kidney stores essence” theory have many overlapping and covering, reflecting the similarities between the two.

4. Reinforcing kidney drugs and diseases

There are many successful medical records of diseases treatment through kidney-nourishing therapy. For a good illustration of the fundamental role of tonifying kidney, as shown in **Table 1**, we summarize 10 common Chinese medical herbs for tonifying kidney and sum up their pharmacological activities.

2,3,5,4'-Tetrahydroxystilbene-2-O- β -D-glucoside (THSG) is the main composition of Polygonum Multiflorum (Thunb.) Harald., a traditional kidney-yin reinforcing herb. Our research has showed that THSG inhibited vascular aging [50] and regulated the expression of klotho, especially in the brain, testis, and kidney [47]. It also has the therapeutic benefits in bone diseases. For instance, THSG enhances the bone strength *in vivo* [47]. It has been reported that kidney-nourishing herbs improve the metabolism of calcium and phosphorus [51], regulate the levels of estrogen and 1,25-dihydroxyvitamin D₃ [52], and increase the activity of 1- α hydroxylase in renal disorder diseases [53]. Another kidney-yang nourishing herb, Epimedium brevicornu Maxim., and its active ingredient icariin can increase the klotho expression *in vitro* and *in vivo* [54]. The extract of polysaccharides of Cornus officinalis Sieb. et Zucc. [55] has a similar effect.

Bavachalcone, one of the effective components of Psoralea corylifolia L., is also a kidney-yang reinforcing herb. Our results demonstrated that bavachalcone not only prevents endothelial cells senescence [56, 57], but also promotes differentiation of bone marrow stem cells and endothelial progenitor cell via EPO/AMPK pathway (our unpublished data). Effects of kidney-nourishing herbs on differentiation of bone marrow mesenchymal stem cells also have been reported recently. For example, Epimedium brevicornu Maxim. enhances proliferation and osteogenic differentiation [58]; Davallia mariesii Moore ex Bak. stimulates differentiation into chondrocytes [59]; icariin facilitates differentiation into cardiomyocytes [60]; Rehmannia glutinosa polysaccharides

Chinese name	Latin name	Medicinal parts	Therapeutic efficacy
Yin-yang-huo (淫羊藿)	<i>Epimedium brevicornu Maxim.</i>	Whole-herb	To treat impotence and seminal emission, weak and cold and sterile, frequent urination and urinary incontinence, asthma, soreness and weakness of waist and knees, rheumatic arthralgia, hemiplegia, insensitivity of the limbs.
Bu-gu-zhi (补骨脂)	<i>Psoralea corylifolia Linn</i>	Dried fruit	To treat kidney-deficiency, backache, frequent urination, enuresis in children, leakage of protein or red blood cells in the urine, warming spleen and stopping diarrhea, asthma.
He-shou-wu (何首乌)	<i>Polygonum multiflora (Thunb.) Harald.</i>	Root	To treat light-headedness hemopenia, palpitation, insomnia, soreness and weakness of waist and knees, premature graying hair, tinnitus, spermatorrhea, constipation due to intestinal dryness, weakness by chronic malaria, rubella itching, carbuncle, scrofulous, hemorrhoids, hyperlipemia.
Tu-si-zi (菟丝子)	<i>Cuscuta chinensis Lam.</i>	Dried seed	To treat impotence and seminal emission, urine dripping after urination, frequent urination and urinary incontinence, soreness and weakness of waist and knees, eyes faint and tinnitus, threatened abortion, embryonic instability, diarrhea caused by deficiency of spleen and kidney, leukoderma.
Du-zhong (杜仲)	<i>Eucommia ulmoides Oliver</i>	Dried bark	To treat soreness and weakness of waist and knees, atrophy and weakness of foot and knee, dribble after voiding, genital damp itch, embryonic instability, threatened abortion, hypertension.
Shu-di-huang (熟地黄)	<i>Rehmannia glutinosa</i>	Prepared root	To treat liver and kidney Yin deficiency, soreness and weakness of waist and knees, osteopyrexia and fever, night sweat and spermatorrhea, blood-deficiency and pale complexion, palpitation, irregular menstruation, uterine bleeding and morbid leukorrhea, vertigo and tinnitus, premature graying hair, intrinsic heat and diabetes.
Gu-sui-bu (骨碎补)	<i>Davallia mariesii Moore ex Bak.</i>	Root and stem	To treat soreness and pain of waist and knees, vertigo and tinnitus, toothache and tooth mobility, injury and broken bones, alopecia areata, leukoderma.
Xian-mao (仙茅)	<i>Curculigo orchioides Gaertn</i>	Root	To treat impotence and cold semen caused by kidney-yang deficiency and yin-cold excess, urinary incontinence, abdominal cold-pain, soreness and pain of waist and knees, weak bones and lower limb spasm, menopausal syndrome.

Chinese name	Latin name	Medicinal parts	Therapeutic efficacy
Suo-yang (锁阳)	Cynomorium songaricum Rupr.	Succulent stem	To treat soreness and weakness of waist and knees, impotence and spermatorrhoea, constipation due to intestinal dryness.
Shan-zhu-yu (山茱萸)	Cornus officinalis Sieb. et Zucc.	Dried fruit	To treat soreness and pain of waist and knees, vertigo and tinnitus, impotence and spermatorrhoea, frequent urination and urinary incontinence, uterine bleeding and morbid leukorrhoea, incessant sweating due to debility, intrinsic heat and diabetes.

Table 1. Ten kinds of kidney-nourishing herbs used in clinical treatments.

induces the formation of neuron-like cells or endothelial-like cells [61]; *Curculigo orchioides* Gaertn promotes differentiation into neurons [62]; and polysaccharides from *Morinda officinalis* How. and THSG promotes the proliferation and differentiation of bone marrow stem cells, and increases the number of peripheral blood cells in cancer chemotherapy [63].

Kidney-nourishing herbs also display effects of promoting cognitive function in type 1 diabetes and vascular cognitive impairment [64, 65]. Moreover, they successfully support the luteal insufficiency infertility [66]. Animal experiments further confirmed that the nourishing kidney treatment can promote ovulation and ovarian luteinizing hormone receptor expression in infertile rats [67].

5. Conclusion

Kidney essence declines with aging and leads to a variety of diseases, such as infertility, osteoporosis, senile dementia, aplastic anemia, and senility. Given the importance of kidney essence to life, researchers seek to understand the connotation of the “kidney stores essence” theory. Although “stem cells are congenital essence” is prevailing now, the plausible models and nonspecific indexes still need improvement. The kidney endocrine substances are similar with the kidney essence in their source and functions. It may have some help for the comprehension of the Zang-Fu theory and point to new targets for antiaging drugs. However, whether the kidney-nourishing medicine has implications on the kidney endocrine substance, still need further researching and discussing.

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