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RESEARCH ARTICLE

Effects of Ziyin Jianghuo Ningxin decoction plus dehydroepiandrosterone and femoston in treatment of patients with menopausal symptoms

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Abstract

OBJECTIVE: To determine the therapeutic effect of Ziyin Jianghuo Ningxin Decoction (ZYJHNXD) plus dehydroepiandrosterone (DHEA) and menopausal hormone therapy (MHT) in patients suffering from menopausal symptoms identified as, in terms of Traditional Chinese Medicine, symptom pattern of *Yin* deficiency with hyperactive fire.

METHODS: Totally 180 postmenopausal women aged 40 to 60 years were assigned into four groups and accepted femoston, femoston with ZYJHNXD, femoston with DHEA, femoston with ZYJHNXD and DHEA therapies, respectively, for three months. Common questionnaire-based measure instruments included modified Kupperman index (MKI), Hamilton Rating Scale for Anxiety (HAMA), and Hamilton Rating Scale for Depression (HAMD). Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), 5-hydroxyindole-3-acetic acid (5-HIAA), norepinephrine (NE), dopamine (DA), bone mineral density (BMD), and sleep quality were evaluated before and three months after the treatments.

RESULTS: In all four groups, the scores of MKI, HAMA, HAMD and the levels of FSH, LH decreased significantly ($P < 0.05$) after the treatment, while the levels of E2, 5-HIAA, NE, and DA showed obvious elevation ($P < 0.05$). The group receiving ZYJHNXD and DHEA combined with femoston had superiority in the preservation of bone mineral density and improvement of total sleep time and nighttime sleep time over the other three groups.

CONCLUSION: ZYJHNXD and DHEA combined with MHT therapy have a favorable outcome in managing menopausal symptoms, restoring hormone levels, preventing skeletal rarefaction or osteoporosis,

and improving sleep quality for postmenopausal women.

Keywords: Menopausal symptoms; Menopausal hormone therapy; Femoston, Ziyin Jianghuo Ningxin Decoction; Dehydroepiandrosterone

INTRODUCTION

Menopause, a physiologic aging transition for women, is marked by menstrual variability and hormonal instability. The major changes of menopause are rapid depletion of ovarian follicles, reduction of inhibin B, elevation of follicle-stimulating hormone (FSH), along with low production of estradiol and dehydroepiandrosterone (DHEA). A large-scale 10-year follow-up study pointed out that the risk of menopausal symptom onset reached its peak during the two years surrounding natural menopause.[1] Typical symptoms, signs, or medical problems pertaining to menopause include vasomotor symptoms, cardiovascular disease, osteoporosis, urogenital atrophy, sexual dysfunction, sleep disorders, mood and cognitive dysfunction, which negatively affect quality of life.[2]

Currently, menopausal hormone therapy (MHT) remains to be an effective approach for management of menopause-related symptoms, which introduces exogenous estrogen with or without progestin to restore the endogenous estrogen level. For those experiencing premature or early menopause and having increased risk of overall mortality, MHT provides protective effect against some of the adverse health outcomes. However, the supplementary hormone is strongly related to increased risk of breast cancer, endometrial cancer, coronary heart disease, colorectal cancer, stroke, and so on.[3] MHT initiated before 60 years of age or within 10 years of menopause is considered to be most beneficial for patients.[4] The side effects of MHT, lack of individualized hormone therapy counseling, and misunderstanding about this medication, give rise to other complementary therapies. Based on our clinical practice, femoston alone could not solve all the menopause-related problems or handle all the complaints of some patients.

Serum DHEA, decreased with age, is considered as an important precursor steroid secreted by adrenal gland and ovary and converted to estrogen and androgens in peripheral tissues. The clinical efficacy of DHEA as supplementary therapy for menopausal symptoms is still controversial. Some studies demonstrated that DHEA can effectively reduce vasomotor symptoms, promote vaginal maturation, and increase bone density in postmenopausal women without potential risk of breast and uterine cancer due to predominantly local conversion into androgens.[5] Both *in vivo* and *in vitro* studies revealed that DHEA possessed effective anti-osteoporotic, immuno-regulatory, and anti-inflammatory properties.[6] DHEA promoted proliferation and inhibited apoptosis of osteoblasts through mitogen-activated protein kinase (MAPK) signaling pathway independent of either androgen receptor or estrogen receptor.[7] DHEA was also found to inhibit the bone resorption of osteoclasts in the presence of osteoblasts which might be mediated *via* osteoprotegerin (OPG)/receptor activator of NF-κB ligand (RANKL) of osteoblasts.[8]

Chinese herbal medicine is an alternative to the treatment of menopausal symptoms. Single herbs like Hongsanye (*Trifolium Pretense*), Danggui (*Radix Angelicae Sinensis*), and ginseng have been traditionally used to regulate menstrual cycle and improve blood circulation. Proven by modern pharmacology, some of these herbs are rich in phytoestrogens and other estrogen-like substances.[9] Ziyin Jianghuo Ningxin Decoction (ZYJHNXD), a traditional herbal formula made up of 15 herbs, is formulated according to the symptom pattern identified in terms of Chinese traditional medicine (TCM) and has long been used to nourish vital essence, remove the extra internal heat etc.

In this study, we aimed to evaluate therapeutic effect of ZYJHNXD plus DHEA and femoston in patients suffering from menopausal symptoms identified as, in terms of Traditional Chinese Medicine (TCM), symptom pattern of *Yin* deficiency with hyperactive fire.

MATERIALS AND METHODS

Study design and subjects

This study is a prospective observational one conducted in the Wenling People's Hospital of Wenzhou Medical University in collaboration with Hospital & Institute of Obstetrics & Gynecology of Fudan University with the approval of the institutional review board and the ethics committee of Wenling People's Hospital. Presented below is the flowchart of study (Figure 1). A total of 256 postmenopausal women were recruited at the Outpatient Department of both hospitals from January 2011 to January 2017.

The inclusion criteria were: (a) aged 40-60 years, (b) spontaneous menopause, (c) suffering hot flashes, sweating, emotional instability, dizziness, tinnitus, palpitations, disturbed sleep, back pain and other symptoms related to menopause, (d) total modified Kupperman Index score ≥ 15, (e) "*Yin* deficiency Pattern" with symptom profiles such as dry mouth, thirst, heat flushes, night sweats, dark and scanty urination, reddish tongue with little coating, fast and floating pulse, etc., which can be further stratified as kidney *Yin* deficiency Pattern, liver *Yin* deficiency Pattern, *Yin* deficiency and hyperactive *Yang* Pattern, *Yin-Yang* deficiency Pattern, and so on, (f) endometrium ≤ 5 mm by ultrasound, and (g) written consent for the study. Exclu-

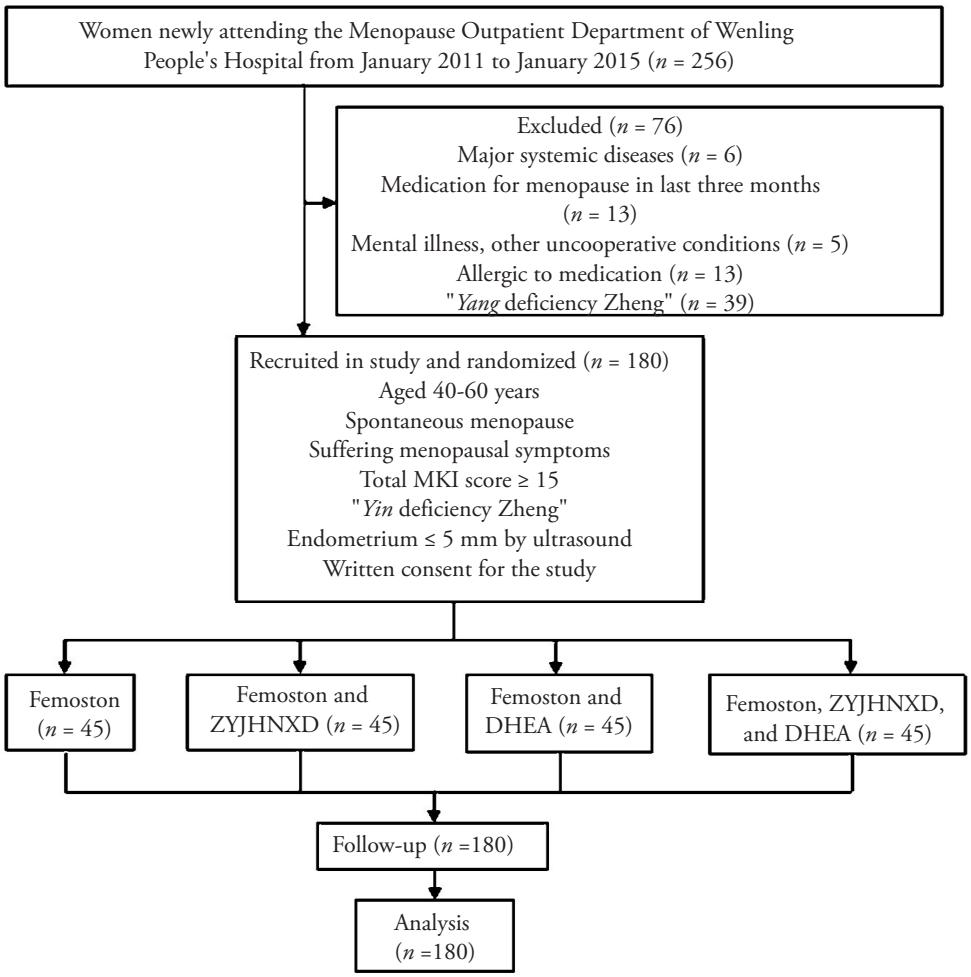

Figure 1 Flowchart of the study design

Postmenopausal women were recruited according to certain inclusion and exclusion criteria. They were divided into four groups receiving femoston, femoston with ZYJHNXD, femoston with DHEA, femoston with ZYJHNXD and DHEA therapies, respectively. The therapeutic effects were analyzed after three-month follow-up.

sion criteria consisted of: (a) major diseases, such as uncontrolled hypertension, ischemic heart disease, stroke, dementia, diabetes, thyrotoxicosis and malignancy, (b) use of medication for postmenopausal symptoms in last three months, (c) mental illness, mental retardation, and other uncooperative conditions, (d) allergic to medication, and (e) "*Yang* deficiency pattern" with main symptoms such as cold limbs, water retention, copious and pale urine, loose stools, pale and swollen tongue, weak and slow pulse, etc.

In total 180 eligible postmenopausal women were divided into four groups receiving hormone replacement therapy of femoston, femoston with Chinese herbal prescriptions ZYJHNXD, femoston with DHEA, femoston with ZYJHNXD and DHEA therapies, respectively. Choice of treatment was based on clinical indication and personal wish of the patient. Written consents to the study were obtained from all participants. The observational period was three months, and the therapeutic effects were followed every month.

Treatments

Hormone replacement therapy of femoston (estradiol/dydrogesterone 2/10 mg) tablets was purchased from Abbott Laboratories, obtained from the pharmacy of both hospitals, and was carried out following the established standard protocol in routine clinical care. In the first 14 d, one red tablet (containing 2 mg estradiol) was taken orally daily, and one yellow tablet (containing 2 mg estradiol and 10 mg dydrogesterone) was taken daily for the following 14 d. DHEA capsules were purchased from Hercules Laboratory Group Ltd., Wilmington, DE 19805 U.S.A, and one capsule (25 mg) was taken each time, twice per day. The herbal formula Ziyin Jianghuo Ningxin Decoction (ZYJHNXD) is composed of 15 crude herbs as shown in Table 1, following the rule of compositions in traditional Chinese medicinal theory. The formula ingredients were purchased in the form of single herbal granules from Jiangyin Tianjiang Pharmaceutical Co., Ltd. (Jiangsu, China). Each different sachet of herb granules was added to 250 mL boiling water and stirred until all solids dissolved. The liquid was then divided into two equal portions to be taken mornings and evenings. Some hot water could be added to the liquid when it was taken at night.

Outcome measures

For clinical evaluation, measure instruments were ap-

Table 1 Crude composition of Ziyin Jianghuo Ningxin decoction

Chinese term	English term	Latin term	Daily dose (g)	Main constituents	Biological activity
Shengdihuang	Chinese foxglove	*Radix Rehmanniae*	12	Monoterpenoids, phenethyl alcohol glycosides, triterpenes	Protect against diabetes, senile osteoporosis, hematological, and gynecological diseases.[26]
Baishao	White Paeony Root	*Radix Paeoniae Alba*	12	Monoterpenes, monoterpene glycosides	Anti-depressant effects.[27]
Nuzhenzi	Glossy Privet Fruit	*Fructus Ligustri Lucidi*	12	Triterpenoids, iridoids, flavones, phenylethanoid glycosides	Anti-tumor, anti-oxidative, anti-aging, anti-inflammation, immune-regulating, hepatoprotective, anti-osteoporosis effects.28
Gouqizi	Barbary Wolfberry Fruit	*Fructus Lycii*	12	Carotenoids, flavonoids, polysaccharides	Immuno-regulating, anti-oxidant, anti-stress, neuroprotective, anti-tumor effects.[29]
Guiban	Tortoise Shell	*Plastrum Testudinis*	12	Esters, carboxylic acids, steroids	Anti-osteoporosis effects.[30]
Zhimu	Anemarrhena Asphodeloides	*Rhizoma Anemarrhenae*	12	Steroidal saponins, flavonoids, phenylpropanoids, alkaloids, steroids, organicacids, anthraquinones	Anti-tumor, anti-oxidation, anti-microbial, anti-virus, anti-inflammation, anti-osteoporosis, anti-skin aging and damage.[31]
Huangbai	Amur Corktree Bark	*Cortex Phellodendri*	12	Berberine, jatrorrhizine, magnoflorine, phellodendrine	Anti-diabetic, anti-heat stress, anti-inflammatory, anti-microbial, neuroprotective, maturation-inhibiting effects.[33]
Yuzhu	Fragrant Solomonseal Rhizome	*Polygonatum Odoratum Druce*	12	Flavonoid, saponin, polysaccharide	Protect against diabetes, hyperlipidemia, atherosclerosis, cancers.[34]
Gegen	Kudzuvine Root	*Radix Puerariae*	12	Puerarin, daidzin, daidzein, genistin, genistein	Cardioprotective, anti-hypertensive, anti-oxidant, anti-fatigue effects.[35]
Danpi	Cortex Moutan	*Paeonia suffruticosa andr.*	12	Gallicacid, oxypaeoniflora, catechin, caffeicacid, paeoniflorin, benzoylpaeoniflorin, paeonol	Analgesic, sedative, anti-microbial, anti-inflammatory, anti-oxidative, anti-apoptotic, cardioprotective effects.[36-37]
Tusizi	Field Dodder	*Semen Cuscutae*	12	Flavonoids, lignans, steroidal compounds	Benefit reproductive, cardiovascular, immune system and protect liver, eyesight.[39]
Xianlingpi	Barrenwort	*Epimedium grandiflorum Morr.*	12	Flavonoids, lignins, ionones, phenol glycosides, phenylethanoid glycosides, sesquiterpenes	Immune-regulating, cardioprotective, anti-tumor, anti-aging, anti-oxidation, anti-hypoxia, anti-fatigue, anti-inflammatory, anti-virus, anti-bacterial, hepatoprotective effects.[45]
Xianmao	Common Curculigo Rhizome	*Rhizoma Curculiginis*	12	Curculigoside	Hepatoprotective, anti-oxidant, neuroprotective, estrogenic, antiosteoporotic effects.[41]
Changpu	Sweet flag Rhizome	*Rhizoma Acori Calami*	12	Alcohol, aldehyde, ester, furan, hydrocarbon, ketone, N-containing miscellaneous	Sedative, anti-convulsant, anti-cancer, cardiovascular, hypolipidemic, immune-regulating, anti-oxidant, anti-inflammatory, cryoprotective, anti-diarrheal, anti-microbial, anti-diabetic effects.[42]
Fuling	Indian Bread	*Poria*	12	Triterpenes, polysaccharides, steroids, amino acids, choline, histidine	Anti-cancer, anti-inflammatory, anti-oxidant, anti-viral effects.[43]

plied including modified Kupperman index (MKI), Hamilton Rating Scale for Anxiety (HAMA), and Hamilton Rating Scale for Depression (HAMD). All parameters were assessed using questionnaires at four time points: before the treatments, one month, two months, and three months after the treatments.

Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E-2), 5-hydroxyindole-3-acetic acid (5-HIAA), norepinephrine (NE), and dopamine (DA) in serum samples of all the patients were determined before the treatments and three months after treatments.

Bone mineral density (BMD) of femoral neck and lumbar vertebrae L2-4 was measured using dual X-ray absorptiometry before and three months after the treatments.

Sleep quality was assessed using self-report instruments such as total sleep time, nighttime sleep time, duration of wake after sleep-onset, frequency of WASO, longest sleep time, and sleep-onset time for LST.

Statistic evaluation

All valuables were

expressed as the mean ± standard deviation. Data were analyzed using SPSS 20.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). *T*-test was conducted to test the differences between groups, and $P < 0.05$ was considered significant.

RESULTS

Demographics of each group showed no significant differences

A total of 180 patients were recruited and completed the entire study, aged (48.2 ± 6.4) years and disease course being (4.7 ± 1.3) years. There were no significant differences of both age and disease course among the four groups ($P > 0.05$).

Menopause is determined retrospectively from the date of final menstrual period. According to the 2011 STRAW criteria, the early postmenopause includes the 12 months of unexplained amenorrhea following the last menstrual period and the next 4-7 years, a period of many physiologic changes and prevalence of symptoms. The late postmenopausal years extend throughout the rest of a woman's lifespan. This time phase is clinically relevant to age-related health problems. In our study, the recruited 180 patients were aged (48.2 ± 6.4) years, disease course being (4.7 ± 1.3) years. With the menstrual history and endocrine examination taken into consideration, they were defined as postmenopause.

The four treatments improved menopausal symptoms

We evaluated the scores of MKI, HAMA, HAMD before and after the treatment in all the four groups. All the groups showed significant decrease in the scores of MKI, HAMA, HAMD ($P < 0.05$) after the treatment (Figure 2 A), suggesting symptom improvement in menopause, anxiety, and depression.

The four treatments restored hormone levels

In all the four groups, the levels of FSH and LH decreased significantly ($P < 0.05$) after the treatment, while the level of E2 showed obvious elevation ($P < 0.05$) (Figure 2 B). Levels of 5-HIAA, NE, and DA increased significantly ($P < 0.05$) after the treatment in all the groups (Figure 2 C).

In women with menopause approaching, follicle recruitment falls so sharply that at STRAW Stages 0 to +2, FSH and LH remain elevated as the follicular pool becomes exhausted subsequently followed by reduction of inhibin B. In contrast, estrogens decline very late after exhaustion of follicular reserve.[11] Our result showed that each group had decreased levels of FSH and LH and elevated levels of E2, 5-HIAA, NE, and DA after the treatment, which suggested the clinical value of these four therapies in restoration of endocrine balance.

ZYJHNXD and DHEA combined with femoston therapy improved BMD in femoral neck and vertebrae L2-4

There were no significant differences before and after the treatment in femoston, femoston with ZYJHNXD, and femoston with DHEA groups (Figure 3A). In vertebrae L2-4, no significant differences were found in femoston and femoston with ZYJHNXD groups (Figure 3B). However, femoston with DHEA therapy improved BMD of vertebrae L2-4 ($P < 0.05$) after the treatment. And ZYJHNXD and DHEA combined with femoston group had notable improvement in BMD of both femoral neck and lumbar vertebrae L2-4 ($P < 0.05$).

ZYJHNXD and DHEA combined with femoston therapy improved sleep quality

We then observed the effect of each therapy on sleep quality and discovered that ZYJHNXD and DHEA combined with femoston group obviously had longer total sleep and longer nighttime sleep time ($P < 0.05$) after the treatment (Figure 4 A and B). The other groups showed no significant differences in total sleep time, nighttime sleep time, duration of wake after sleep-onset, frequency of WASO, longest sleep time, and sleep-onset time for LST (Figure 4 C-F).

DISCUSSION

Our study revealed that all the four therapies had positive effect on improvement of self-reported symptoms and restoration of endocrine balance in postmenopausal women. In symptom assessment, we evaluated the scores of MKI, HAMA, HAMD before and after the treatment in all the four groups. The notably decreased scores after the treatment in all the groups indicated the four therapies were effective in menopausal symptom improvement and mood regulation. For endocrine evaluation, levels of serum FSH, LH, E2, 5-HIAA, NE, and DA were examined. The decreased levels of FSH, LH and elevated levels of E2, 5-HIAA, NE, and DA after the treatment testified the role of all four therapies in endocrine rebalancement. However, these hormone levels are difficult to interpret because they vary widely within and among individuals in the transitional years and could fluctuate between cycles.[12] Moreover, ovulation is still possible even after menopause, adding to the complexity of the hypothalamo-pituitary-ovarian (HPO) axis.[12]

Menopause is accompanied by dramatic bone loss, particularly in lumbar spine, with the greatest BMD reduction occurring in STARW Stage -1 to +1b.[13] As we observed, ZYJHNXD and DHEA combined with femoston therapy notably improved BMD of femoral neck and lumbar vertebrae L2-4. DHEA with femoston therapy was also effective in improving BMD of vertebrae L2-4. It is noteworthy that any intervention

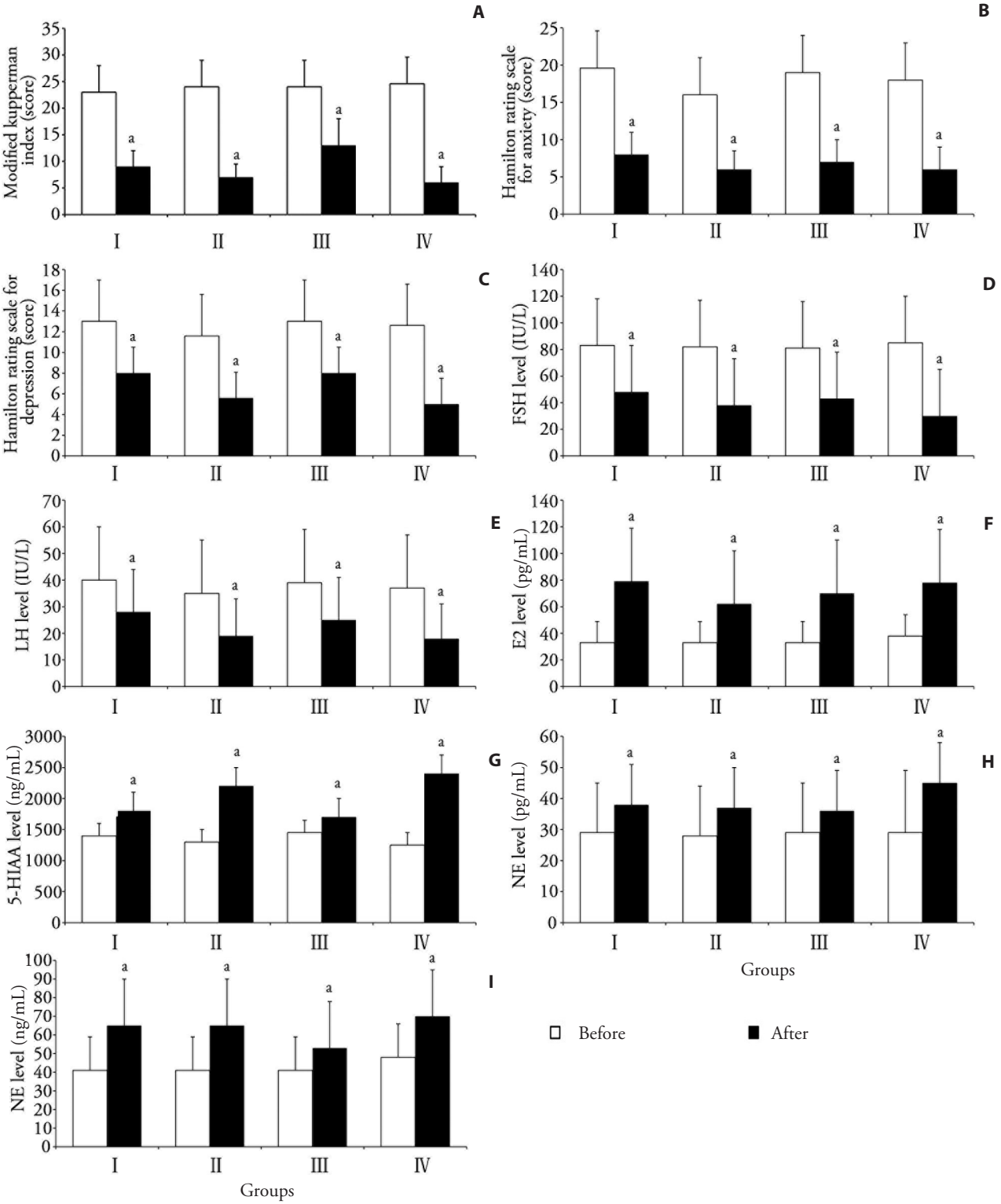

Figure 2 Menopausal symptoms and hormone levels were improved in all the groups

A, B, C: in all the four groups, the scores of MKI, HAMA, and HAMD decreased significantly after the treatment. D, E, F: the levels of FSH and LH decreased significantly after the treatment, while the level of E2 showed obvious elevation after the treatment. G, H, I: in all the four groups, the levels of 5-HIAA, NE, and DA increased significantly after the treatment. ZYJHNXD: Ziyin Jianghuo Ningxin Decoction; DHEA: dehydroepiandrosterone; MKI: modified Kupperman index; HAMA: Hamilton Rating Scale for Anxiety; HAMD: Hamilton Rating Scale for Depression; FSH: follicle-stimulating hormon; LH: luteinizing hormone; E2: estradiol; 5-HIAA: 5-hydroxyindole-3-acetic acid; NE: norepinephrine; DA: dopamine. Ⅰ: Femoston; Ⅱ: Femoston and ZYJHNXD; Ⅲ: Femoston and DHEA; Ⅳ: Femoston, ZYJHNXD, and DHEA. [a]Significant difference at $P < 0.05$ levels compared with pre-treated controls.

should focus on the prevention of fracture rather than the improvement of a single risk factor. In addition, BMD cannot be used as clinical intervention threshold value because it's based on one single risk factor.[14] Re-

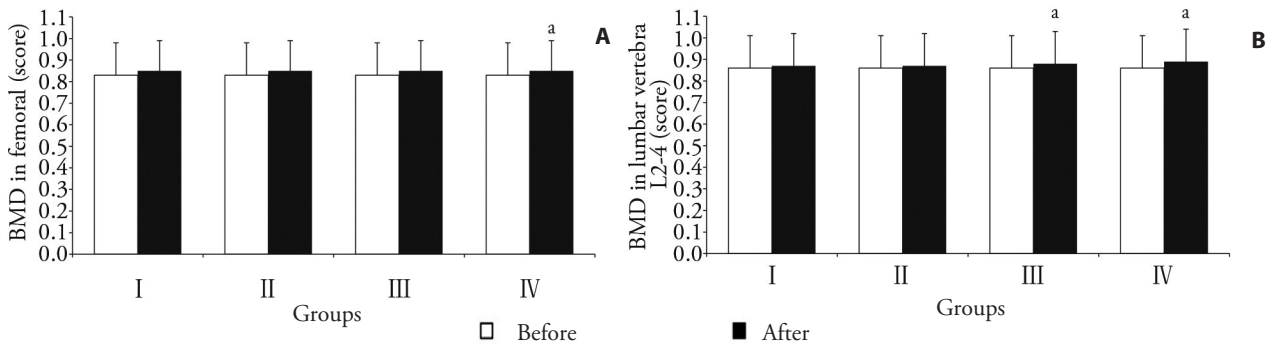

Figure 3 ZYJHNXD, DHEA combined with femoston therapy improved BMD in femoral neck and vertebrae L2-4
A: ZYJHNXD and DHEA combined with femoston group had significant improvement in BMD of femoral neck. B: femoston with DHEA therapy and the combined therapy of ZYJHNXD, DHEA, and femoston notably improved BMD in vertebrae L2-4. ZYJHNXD: Ziyin Jianghuo Ningxin Decoction; DHEA: dehydroepiandrosterone; BMD: bone mineral density. Ⅰ: Femoston; Ⅱ: Femoston and ZYJHNXD; Ⅲ: Femoston and DHEA; Ⅳ:Femoston, ZYJHNXD, and DHEA.[a]Significant difference at $P < 0.05$ levels compared with pre-treated controls.

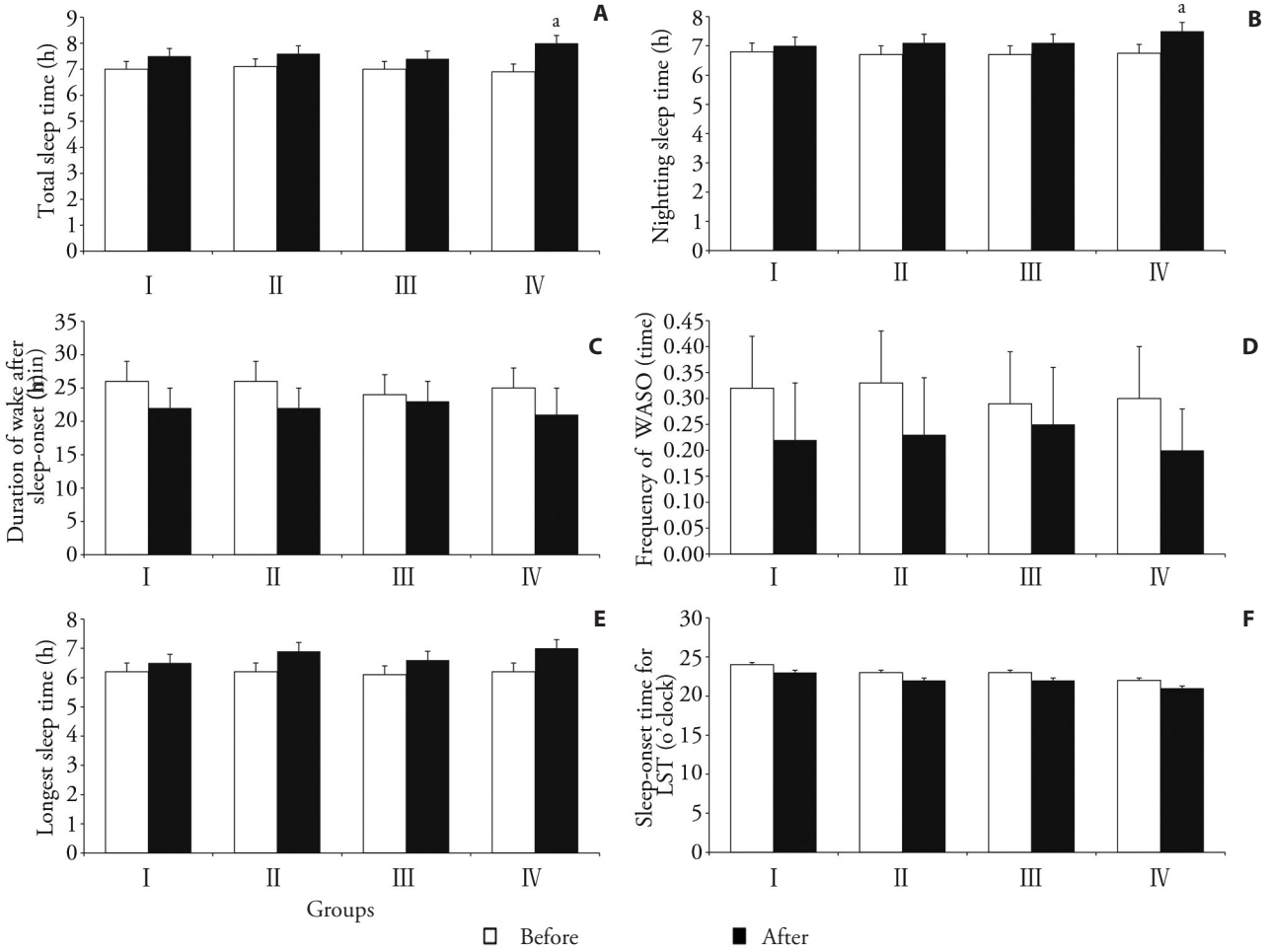

Figure 4 ZYJHNXD and DHEA combined with femoston therapy improved sleep quality
A, B: the ZYJHNXD and DHEA combined with femoston group obviously had longer total sleep time and longer nighttime sleep time after the treatment. C, D, E, F: there were no significant differences in duration of wake after sleep-onset, frequency of WASO, longest sleep time, and sleep-onset time for LST among the four groups. [a]Significant difference at $P < 0.05$ levels compared with pre-treated controls. ZYJHNXD: Ziyin Jianghuo Ningxin Decoction; DHEA: dehydroepiandrosterone; WASO: wake after sleep-onset; LST: long sleep time. Ⅰ: Femoston; Ⅱ: Femoston and ZYJHNXD; Ⅲ: Femoston and DHEA; Ⅳ: Femoston, ZYJHNXD, and DHEA.

cent study revealed that high levels of FSH rather than low levels of E2 seemed to have direct effect on bone metabolism, partially through stimulating receptor activator of NF-κB ligand (RANKL) induced osteoclastogenesis and bone resorptive activity.[15] This exploration added weight on the cross-talk between endocrine system and skeletal metabolism, giving rise to new explanations for the pharmacological mechanism of the ZYJHNXD and DHEA combined with femoston therapy.

Sleep behavior is affected by endogenous, environmental, HPO hormones interface with neurochemicals and

sleep timing components.[16] 25% of women aged 50-64 years reported sleep problems, and 15% of them had severe sleep disorders. In fact there are many potential contributors to sleep disorders in postmenopausal women, including menopausal symptoms, primary insomnia, co-existence of medical illness, medications, and environmental factors. It remains to be a question whether menopause per se specifically contributes to sleep problems. Some researchers found that age and menopause status alone were not predictors of sleep quality, but night sweats and hot flashes, stress and depression were.[17] These studies discovered that postmenopausal women had poorer general sleep quality by Basic Nordic Sleep Questionnaire most evidently because of vasomotor symptoms.[18] Sleep quality was strongly related to hot flashes and night sweats in subjective perception, but was not necessarily translatable from objective physical detections.[12] Meanwhile, correlation between the subjective and objective measures is not high.[19] Our result exhibited that the combined use of ZYJHNXD and DHEA with femoston therapy had notably longer total sleep time and longer nighttime sleep. However, sleep is relatively variable across individuals and is probably influenced by aging itself and the emotional overlay on menopausal symptoms. Whether the indexes we adopted better describe sleep quality needs further investigation.

As shown in a randomized controlled trial of 290 postmenopausal women, the combined application of 17-oestradiol and dydrogesterone achieved excellent endometrial safety and offered acceptable bleeding profile.[20] As treatment for postmenopausal women in improvement of well-being and vasomotor symptoms, DHEA is proposed to have mainly androgenic effects and possibly very little estrogenic effects. Studies found that DHEA, providing protective effects on bone, could not only increase local concentration of E2 and induce transcription of estrogen receptors (ERα/ERβ) in bone using ovariectomized mice, but also increase ERα, ERβ, and androgen receptor (AR) in osteoblasts.[21] The safety of exogenous DHEA has been well recognized because it follows the same physiological laws of menopause and "intracrinology" like endogenous DHEA and provides sex steroids locally and specifically to the peripheral tissues.[22] A recent double blind, placebo-controlled randomized clinical trial, however, failed to confirm that DHEA of 50 mg per day for 52 weeks offered beneficial effects in menopausal symptoms, mood, sexual function or well-being in menopausal women.[23] The oral administration of DHEA as a sole treatment for menopause is not recommended based on existing literature.[24] Compared with DHEA alone, oestrogen-progestogen plus DHEA therapy exhibited better effects in improving ovarian function.[25] As our study indicated, femoston plus DHEA therapy also had better improvement of BMD in vertebrae L2-4 than femoston alone.

ZYJHNXD is a traditional herbal formula whose compositions have been proven to possess multiple biological activities and therapeutic effects by modern pharmacology studies and clinical trials. *Radix Rehmanniae* has been widely accepted in the treatment of postmenopausal, senile, and secondary osteoporosis.[26] *Radix Paeoniae Alba* is found to had antidepressant-like effect in mouse model of depression when combined with *Radix Bupleuri*.[27] *Fructus Ligustri Lucidi* is believed to be capable of nourishing liver and kidneys as well as benefiting bone and eyes according to the theory of Traditional Chinese Medicine. Modern studies have revealed its osteoprotective, hepatoprotective, anti-cancer, anti-viral, and immuno-modulatory activities.[28] Fructus Lycii has been found to regulate HPO axis hormones and apoptotic pathway in rats of ovulation failure.[29] Plastrum Testudinis extracts are able to promote proliferation of rat bone-marrow-derived mesenchymal stem cells.[30] *Rhizoma Anemarrhenae*, traditionally used in clearance of evil-heat and purge of body-fire, has demonstrated pharmacological effects in nervous system and hematological system.[31] Its effective properties are including but not limited to anti-depression, anti-diabetes, anti-oxidation, and anti-osteoporosis.[32] Cortex Phellodendri is a *Yin*-nourishing and Fire-removing herb in traditional medicine practice, which is able to inhibit gonadotropin-releasing hormone (GnRH) synthesis while promote growth hormone (GH) synthesis in GT1-7 and GH3 cells.[33] Polygonatum Odoratum Druce, rich in saponin and flavonoid, exerts hypoglycemic and anti-oxidant effects in HepG2 cells, high-fat diet induced obese mice and streptozotocin-induced diabetic rats.[34] *Radix Puerariae* is clinically utilized for cardio-cerebrovascular related health problems, whose bioactivities include cardiovascular protection, neuroprotection, osteonecrosis prevention, anti-oxidation, and anti-fatigue.[35] Paeonia suffruticosa and r. is found to protect against inflammation on diabetic nephropathy using mesangial cells and streptozotocin-induced rats.[36] It also exerts cardioprotective effect in rat model of acute myocardial ischemia/reperfusion injury, and anti-allergic, anti-inflammatory activities in human basophils.[37,38] *Semen Cuscutae* regulates the expression of sex hormone receptors in rats of psychological stress.[39] Epimedium is considered to be effective in strengthening sexual function, anti-osteoporosis, immuno-regulation, anti-tumor, anti-aging, and anti-fatigue.[40] Recent research testified the anti-osteoporotic activity of the metabolites of *Rhizoma Curculiginis*.[41] *Rhizoma Acori Calami* possesses immuno-modulatory, anti-microbial, anti-convulsant, anti-diabetic, and analgesic effects.[42] Poria has great health benefits such as anti-cancer, anti-inflammation, and anti-oxidation.[43] Even though the independent pharmacological effects of each herb have been well discovered, the potential interactions among the mixtures remain to be explored. The combination might lead to excellent beneficial effects on health or

unexpected compromise of the therapeutic efficacy. For instance, the combination of *Fructus Ligustri Lucidi* and *Radix Puerariae* was found to offset the independent actions of each herb on skeletal metabolism in ovariectomized rats.[44] However, studies pertaining to herb-herb interactions and the efficacy of such combination are still needed.

Our study demonstrated the efficacy of the ZYJHNXD and DHEA combined with femoston therapy. We discovered that it had a more promising outcome in improving bone mineral density of femoral neck, total sleep time, and longer nighttime sleep time than the therapies of ZYJHNXD with femoston or DHEA with femoston or femoston alone. In addition to its role in symptom management, mood regulation, and hormone restoration, the integral therapy was superior in preventing skeletal rarefaction and improving sleep quality for postmenopausal women. However, the interpretation of our study was limited by inadequate sample size, short treatment duration, and inconsistent results with other available studies. Thus, well-designed, prospective, randomized clinical trials are in great need before therapeutic application of ZYJHNXD and DHEA for postmenopausal women receiving MHT. Moreover, the potential interactions between the herbal formula and the drugs when they are taken at the same time require further study.

In conclusion, ZYJHNXD and DHEA combined with MHT therapy have a favorable outcome in treating menopausal symptoms, restoring hormone levels, preventing skeletal rarefaction or osteoporosis, and improving sleep quality for postmenopausal women.

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