Chin J Integr Med 2011 Oct;17(10):744-749

ORIGINAL ARTICLE

An Innovative Herbal Product for the Prevention of Osteoporosis

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ABSTRACT **Objective**: To prevent the deterioration of osteopenia, a triple herb product Bo-gu Ling (补骨灵, ELP) was created for a clinical trial on post-menopausal women suffering from osteopenia. **Methods**: The design of the clinical trial was of randomized, double-blind, placebo-controlled nature. A total of 150 women aged 40–60 years, who were after menopause for at least 1 year and their lumbar spine bone mineral density (BMD) must be lower than 0.891 g/cm^2, were recruited and randomly divided into the ELP group treated with ELP and the placebo group, with 75 in each group. The primary endpoint was the BMD of the lumbar spine that was assessed at baseline, 6 and 12 months after treatment. Secondary endpoints included peripheral quantitative computed tomography (pQCT) measurements of distal tibia and the changes in the quality of life (QOL). **Results**: The spine BMD of the ELP group was increased by 0.69% in the subjects who were more than 10 years after menopause. In contrast, the placebo group of the same stratum decreased by 0.61% (P=0.067). In the subjects with more than 10 years duration of menopause, the hip BMD increased by 0.21% in the ELP group, compared with a decrease of 0.52% in the placebo group (P=0.159). The tibia strength-strain index was increased by 1.94% in the ELP group compared with 0.33% in the placebo group (P=0.047). Physical function of SF-36 QOL questionnaire was remarkably improved compared with the baseline, but did not show dominance over the placebo group. **Conclusion**: ELP showed potential benefit in improving BMD on the women who experienced over 10 years of menopause.

KEYWORDS prevention of osteoporosis, herbal product, bone mineral density

As the aging population is becoming more and more aware about osteoporosis and the awareness has sometimes developed into a crucial factor about osteoporotic fractures, the need for the prevention of a continuation of bone loss is real. The fundamental requirements to maintain bone health, like balanced nutrition, exercises and sunlight, although widely known, appear theoretical and unrealistic because the practice might be considered either too late or not substantial.[1,2]

In the last decade, pharmaceutical companies developed a rich collection of new drugs that offer specific and clearly targeted therapeutic effects on the improvement of bone quality. The new drugs have been developed based on the understanding of the metabolism of the bone tissue so that building it up could work through the stimulation of the anabolic side or suppression of the catabolic side. Teriparatide and strontium products represent the former and the bisphosphonates the latter.[3,4] While therapeutic drugs created for the treatment of a well-developed pathology could be used for prevention, in the case of osteoporosis, uncertainties exist. Firstly, because the therapeutic agents offer an unbalanced effect through a specific artificial influence on either end of the metabolic cycle of bone physiology, whether long-term treatment could be bad to the structural changes of bones remains unknown. Secondly, adverse reactions of the therapeutic agents may yet appear minor; uncertainty exists with longer uses.[5,6] Indeed odd fractures were already reported with prolonged treatment, and large doses of bisphosphonates could induce osteonecrosis of the jaw bone.[7]

It seems, therefore, that more prudent use of the therapeutic agents against osteoporosis becomes mandatory. Their use to counteract severe osteoporosis already developed should continue. However, for borderline situations, when only prevention is indicated, the administration of the popular agents would need

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DOI: 10.1007/s11655-011-0876-y

careful planning and should not be considered a routine or a "food supplement".

Medical scientists in China have studied many medicinal herbs and found that they have anti-osteoporotic effects in the laboratory and subsequently in clinical trials.[8] This discovery is based on the traditional use of these herbs in bones and joints related clinical problems.[9] Like all medicinal herbal products, the bioactive components are yet unknown; neither is the mode of action known about their pharmacological targets of influence. The laboratory evidences of some of these herbs when used singly or in combination to strengthen bone structure are quite strong.[10,11] However, the clinical reports do not match the laboratory findings. In the first place, clinical trials done in China are very often crude and poorly conducted.[12] In the second, basically the medicinal herbal products do not have specific targets of pharmacological action, and they are known as agents to support an overall balance of physiological activities, which is achieved very slowly. It is therefore expected that positive therapeutic effects might fail to reach biostatistical significance and would be apparently inferior to therapeutic agents.[13]

In this study, we chose 3 medicinal herbs well known to have bone supporting effects to form a combined cocktail in a proportion expected to give synergistic effects, for the prevention of deterioration of early osteopenia in the post-menopausal women. This group of women did not have an urgent need to bring their osteopenia up, and they were aware of the availability of potent therapeutic agents for the treatment of osteoporosis which they did not prefer.

METHODS

Study Design

Since the chemical components of the herbs and their extract pharmacological actions were not known, the clinical trial needed to follow a strict evidence-based design. A protocol designed as a phase Ⅱ clinical trial for a new drug was adopted. Since the 3 selected herbs all were botanical and clinical records of safety, and they had been used clinically for hundreds of years, the phase Ⅰ study could be skipped.[14]

The design of the clinical trial was of randomized, double-blind, placebo-controlled nature. Randomization was done with a stratified block method and programmed in a designated computer for the research technician at the time of preparing the herbal capsule treatment. Proper ethical approval was obtained before starting the clinical trial and proper consent was given by the clients.

Subjects

The date of the first subject screened was December 29, 2003; the date of last subject visit was October 18, 2005. The inclusion criteria were women who experienced menopause for at least 1 year and their lumbar spine bone mineral density (BMD) must be lower than 0.891 g/cm^2 which indicated osteopenia. Those suffering from serious concomitant diseases and were maintained on complicated medications and those suffering from psychiatric or addiction disorders were excluded.

Two hundred and twenty-eight patients from volunteer in community centre in Hong Kong, China, were screened and 78 were found unsuitable. A total of 150 subjects were considered adequate for this study basing on at least 1% difference in BMD between the treatment with herbal formula and placebo could be detected with 90% power if the standard deviation of BMD measurements was 3.6% that was obtained from our previous study.[15]

The subjects enrolled were randomized to either ELP (75 cases) or placebo group (75 cases). In the ELP group, the mean age of subjects was 58.4±3.6 years old, the mean time since last menses was 8.1±4.4 years and mean age of menopause onset was 50.4±3.8 years; while in the control group, they were 58.4±3.8 years old, 8.4±4.7 years and 50.0±4.2 years, respectively. There were no significant differences between the ELP and placebo groups. The demographic and baseline characteristics of the intention-to-treat (ITT) population are insignificant between two groups, and their BMD also showed no statistically significant differences.

Treatment

The ELP was created from 3 herbs (provided by the Institute of Modern Chinese Medicine of the Hong Kong Polytechnic University in Shenzhen, China) that had been found to be positively supportive to bone metabolism in the laboratory in recent years.[16] They were selected from a list of herbs traditionally used for

bone and joint pain which were considered in Chinese medicine as symptoms of Kidney (Shen) deficiency". The 3 herbs, *Herba Epimedii, Frutus Ligustri Lucidi* and *Fructus Psoraleae*, were authenticated properly and then boiled together to give an aqueous extract which was subsequently lyophilized into a powder for the manufacture of standard capsules which were labeled as ELP (Bo-gu Ling, 补骨灵) capsules for the clinical trial. Use of a number of herbs for special treatment purposes is a well-recognized practice in Chinese medicine. The placebo is composed of ponceau 4R, tartrazine, caramel colorings and starch; all of them are inert materials. Eligible subject orally took 6 capsules (380 mg/capsule) once daily for 12 months.

Endpoint Measurement

The primary outcome was the BMD of the lumbar spine which would be assessed at baseline, 6 and 12 months after treatment by using a Hologic type 4500 DEXA machine.

Secondary endpoints included peripheral quantitative computed tomography (pQCT) measurements of distal tibia and an analysis of the physical components of the quality of life (SF-36 questionnaire). The SF-36 quality of life (QOL) questionnaire which contained 8 domains, viz., physical function (PF), physical role (PR), bodily pain (BP), general health (GH), vitality, social function, emotional role and mental health, was used. Only the 4 physical domains more relevant to bone and joint problems were evaluated. Among the 150 subjects, there were 79 subjects (41 in the ELP group and 38 in the placebo group) who performed pQCT examination.

Adverse events (AEs) were carefully monitored clinically and biochemical checking for the liver and renal functions further rules out liver and renal toxicity.

Statistical Analysis

The resulting data was analyzed according to the ITT principle. Statistical comparison between the two groups was done with the Chi-square test, or two samples *t* test or Mann-Whitney test. The percentage changes from baseline for each variable were assessed with paired *t* test. Repeated measurement analysis and multivariate analysis of variance (MANOVA) were used for repeated comparisons at 6 and 12 months intervals. Analysis of covariance (ANCOVA) was used to adjust for possible covariates whenever appropriate. All statistical analyses were performed with SPSS 16.0 version.

RESULTS

General Condition

In the ELP group, 75 subjects completed the 12-month clinical study; 74 subjects in the placebo group completed the 12-month study; one subject in the placebo group lost follow-up at visit 4 (month 9, Figure 1). The mean drug compliance rates were 73.7% and 81.2% in the ELP and placebo groups, respectively. There were no statistical differences between the two groups in the overall drug compliance (*P*=0.093, Table 1).

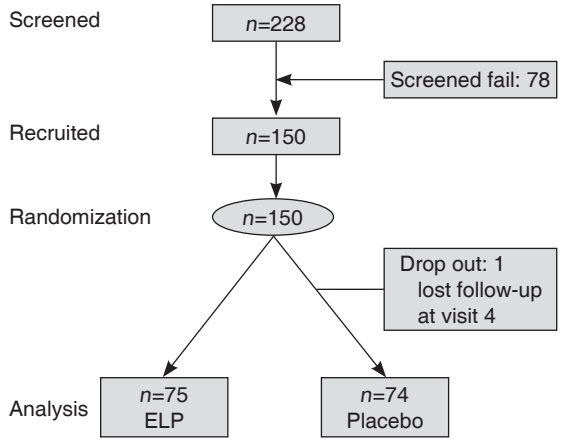

Figure 1. Flowchart for Inclusion of Patients

Table 1. Drug Compliance (75 Cases in Each Group, %)

Group	Drug compliance				Total
	Month 3	Month 6	Month 9	Month 12	
ELP	89.9	77.3	74.9	75.8	73.7
Placebo	90.6	86.1	86.3	84.1	81.2
P value	0.495	0.061	0.080	0.105	0.093

Comparison of BMD Changes

Both ELP and placebo groups showed a decrease in spine BMD over the 12-month treatment (–0.31% in the ELP group and –0.39% in the placebo group). However, the spine BMD of the ELP group was increased by 0.69% in subjects who were more than 10 years after menopause. In contrast, the placebo group of the same stratum decreased by 0.61% (*P*=0.067).

The hip BMD of the ELP group remained unchanged over 12-month treatment, whereas the placebo group decreased by 0.22%. In the subjects with more than 10 years duration of menopause,

the hip BMD increased by 0.21% compared with a decrease of 0.52% in the placebo group (*P*=0.159, Table 2).

Table 2. Comparison of BMD Changes

Item	ELP (75 cases)	Placebo (74 cases)	*P* value
Spine			
Baseline (g/cm^2)	0.7994 ± 0.1089	0.7949 ± 0.1011	0.794
Change from baseline (%)			
Month 6	–0.01	0.35	
Month 12	–0.31	–0.39	
Menopausal duration >10 years			
Month 6	0.13	0.18	
Month 12	0.69	–0.61	0.067
Hip			
Baseline (g/cm^2)	0.7573 ± 0.0736	0.7592 ± 0.0904	0.885
Change from baseline (%)			
Month 6	0.19	0.44	
Month 12	0.03	–0.22	
Menopausal duration >10 years			
Month 6	0.63	0.30	
Month 12	0.21	–0.52	0.159

In this study, after 12-month treatment with the herbal preparation, the distal tibia pQCT decreased by 2.43% in the ELP group compared with 3.67% in the placebo group (*P*=0.052). The tibia (T33%) strength-strain index (SSI) was increased by 1.94% in the ELP group compared with 0.33% in the placebo group (*P*=0.047, Table 3).

Comparison of QOL

PF was remarkably improved in the ELP group compared with the baseline, but did not show dominance over the placebo group. Likewise the PR showed similar improvement (Figure 2).

Adverse Events

The overall incidences of AEs were 80 with ELP and 62 with placebo (*P*=0.688). The most common AEs included common cold, back pain, and gastrointestinal upset in both groups. With regard to liver and renal functions, there were no significant changes in the serological tests of both the ELP and placebo groups.

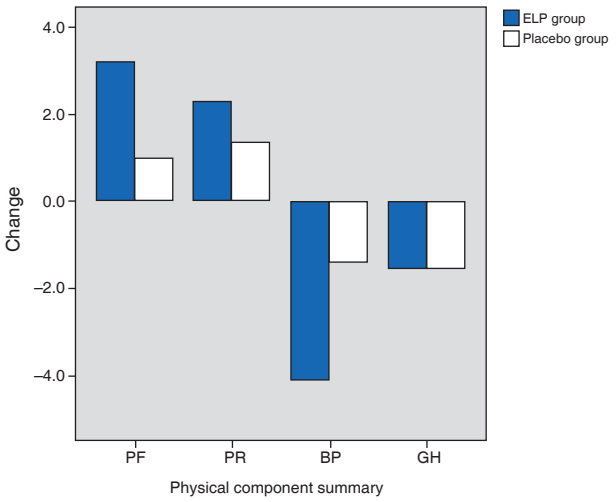

Figure 2. Changes in the Four Subscales of the SF-36 after 12-Month Treatment

DISCUSSION

We have chosen the most commonly adopted parameters to assess objectively the efficacy of our 3 herbs formula in the prevention of deterioration of osteopenia. The best results were shown among the group of clients who had experienced menopause for over 10 years. Statistically this group of patients when treated with ELP for 12 months showed better results than the placebo group. Other women with shorter periods of menopause also showed a better trend of bone preservation which, however, was statistically insignificant. If BMD represents the standard changes in the bone density, pQCT which looks at the distal tibia is more sensitive to early influences and mild reactions. Changes in pQCT are known to respond faster to stimulations. Indeed the positive influence of ELP on the distal tibia was well shown with statistical significance.

Although there are many reports in China, endorsing the therapeutic value of various herbs originally used as "Kidney tonics" against "Kidney

Table 3. Annual Changes of BMD at Different Anatomic Sites Measured by pQCT (%)

Group	Case	BMD of distal radius		BMD of distal tibia		Tibia (T33%) SSI
		Total	Cortical	Total	Trabecular	
ELP	41	6.65	3.57	–2.43	6.15	1.94
Placebo	38	2.03	–0.28	–3.67	12.17	0.33
P value		0.724	0.322	0.052	0.525	0.047

deficiencies", the claims have not been based on reliable clinical trials.[12] For therapeutic requirements, significant superiority over the placebo needs to be demonstrated. However, for preventive purposes using herbal preparations, since there is no specific target of pharmacological action, the efficacy would be inferior to target orientated pharmaceuticals. A longer period of observation and a large sample size might be mandatory for a more scientific revelation of the result of treatment. Herbal supplements might be considered to provide additional support on top of the essential needs against osteoporosis like vitamin D and calcium. Herbal treatments in Chinese medicine are well known to be working slowly and non-specifically. The mechanism of action of the 3 herbs formula EPL has been shown in our laboratory to be both pro-osteogenic and anti-resorptive. In further planning of research, more explorations on the mode of action of the herbs need to be done. We also need to know whether the support on the BMD is working through a cellular level, or indirectly via an increased absorption or decreased excretion of calcium, and whether vitamin D is involved.[17]

We believe that an evidence-based methodology could be followed in the development of an effective agent for the prevention of osteoporosis, which is not meant for active treatment. Long-termed effects and absence of adverse reactions are of more importance than immediate responses and rapid substantial improvements in preventive therapy. In prevention, general improvement could be more desirable than specific responses, and multiple foci of attention could be good alternatives to specific, single targets therapy.

Exercises-related improvements of BMD without the influence of drugs have been reported among people with osteopenia. Many reports on the practices of aerobic and non-aerobic exercises showed that the BMD improved slowly and not as significantly as in therapeutic treatments, using either hormonal agents or bisphosphonates.[18]

Some chemicals contained in the ELP formula are already known.[19] Chemists and pharmacologists could further fractionate its extracts to workout the groups of chemicals that are mainly responsible for the bioactivities and are responsible for the anti-osteoporotic effects. There is also a possibility of identifying some individual chemical molecules that are solitarily responsible for the bioactivities. In the latter situation, it would be a successful drug discovery.[20,21] However, before any success, the extracts could be used as safe preventive agents for those already showing osteopenia.

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(Received December 15, 2010)
Edited by WANG Wei-xia