

A Milk Product Supplemented with a Herbal Extract for the Prevention of Osteoporosis: Justifications and Clinical Trial

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Abstract: When osteoporosis presents as a disease, effective, quick therapeutic remedy is required. Potent effective pharmaceuticals are available. When osteoporosis is only a threat, prevention and not treatment should be a logical better choice. While the past two decades might have followed a radical treatment direction and adverse effects of potent bisphosphonates have started to appear, it is appropriate to explore effective means of using nutritional supplements specific for the maintenance of bone health when only active prevention is required. Traditional Chinese medicine works on the principle of physiological balance. One classical herb *Fructus Ligustri Lucidi* (FLL) has been studied in the laboratory for its bone protection effects which are found very positive. FLL is added to milk powder for daily consumption in a proper evidence-based clinical trial with a placebo group. The results showed that 39 women with post-menopausal period of 8.5 ± 3.5 years, achieved an average increase of 0.97% in the spine bone mineral density (BMD) and a 1.47% increase in the hip score. No increase in body weight was found. It is therefore suggested that FLL could be a suitable bone health supplement in the prevention of osteoporosis.

Keywords: Milk, Osteoporosis, Herb, Chinese Medicine

1. Introduction

Increasing human longevity is complicated by aging related physiological deteriorations. Osteoporosis, weakening of the skeletal bony units, is one of the major concerns which has developed into a major public health problem [1]. According to the World Health Organization, osteoporosis affects approximately 75 million people in Europe, USA, and Japan. Although data are not available in China, with her large population, a vast number of people would be expected to be affected [2].

The aging individual might not be aware of osteoporosis until fracture complications occur. When the apparently normal aging process abruptly turns into a disastrous mishap with the occurrence of fracture, the orthopaedic surgeon becomes directly involved. The rising incidence of hip fractures is often related to osteoporosis. A large number of patients with low back pain among the elderlies is caused by or related to osteoporotic compression of the vertebral bodies [3, 4].

The last 40 years have demonstrated a show of the strength of

pharmaceutical departments in their successful attempts to search for potent anti-osteoporotic agents. Starting with hormonal replacement therapy in the 1960's, to oestrogen-receptor mediators (SERMS), and osteoclast suppression therapy and promotion of osteoblast activity, more and more potent therapies for the maintenance of bone density have become available [5].

In 1995 the Federal Drug Administration (FDA) recommended alendronate as the first anti-osteoporosis medication for post-menopausal osteoporosis. This member of a group of drugs known as bisphosphonates suppresses the activities of the osteoclasts which initiate bone resorption, thus indirectly protects the bone structure. Since then more potent bisphosphonates have been produced in the laboratory, requiring less frequent administration. Zoledronic acid is the latest product which, when given intravenously, has a prolonged effect of one year [6]. The use of bisphosphonates for the treatment as well as prevention of osteoporosis has been a routine practice in the past decade, irrespective of the severity of the actual decline in bone density, until unexpected

observations, namely, odd fractures in long bones and osteonecrosis of the jaw, started to be reported.

In fact weakening of the bone structure and decline in the bone mineral density is a physiological process related to aging. The severity of deterioration depends on the status of the bony skeleton before aging, individual variations, nutritional and life-style situations. Over energetic treatment has already shown possible ill-effects [7]. A more logical approach could be adopted with reference to risk management, confronting osteoporosis as a genuine risk to fracture which needs to be prevented from occurrence. Nutritional prevention would be the immediate answer

Apart from general nutritional considerations, the importance of calcium for bone health started to be recognized in the 1980's and together with Vitamin D, has been widely advocated to be taken as nutritional supplements for the maintenance of bone health [8]. A most recent systematic review released from the National Institutes of Health in the United States further confirm the need of Vitamin D and Calcium as the basic requirements for bone health [9]. To date, most if not all, commercial milk products available in markets, would contain added calcium and vitamin D. Competitions may turn furious when different brands boast about the efficacy of their additional supplements although it remains unclear whether special chemical forms are generally better absorbed and metabolized. Milk products may give additional attraction by incorporating chemicals that apparently support failing cartilages of weight bearing joints. Glucosamines for instance, have been highly accepted in spite of the controversial study reports about the efficacy.

As a matter of fact people over 60, or women in the perimenopausal era, need not worry about their bone health as long as they are keeping up with their nutritional demands for Vitamin D and Calcium. For those who might feel threatened, due to various reasons, they might consider suitable additional supplements instead of taking potent drugs immediately.

Communities with different cultural backgrounds have divergent health promotion practices with general or specific purposes. In the Chinese communities, herbal supplements are

very popular. In the traditional practice of Chinese medicine, many herbs are noted for their "Kidney tonifying" effects and Kidney function has long been considered to be highly related to bone metabolism. Henceforth in order to supplement the nutritional need for bone health of food products apart from Vitamin D and calcium, a suitable herb with known Kidney supporting effects could be considered.

2. A Milk Product Supplemented with a Herb Extract

Many medicinal herbs have been used clinically by traditional Chinese medicine practitioners for the treatment of symptoms related to bone and joints like joint pain in arthritis, muscle pain and spasm due to neurological irritations or damages and also after skeletal injuries. The general assumption that these herbs might have protective effects on the musculo-skeletal system, though not proven, is logical. For a proper scientific study, we need to select a number of herbs that are likely to be bone strengthening and put them onto proper scientific research platforms.

More than twenty "Kidney tonifying" herbs have been described in traditional literature. Chinese medicine and a suitable one, viz., *Fructus Ligustri Lucidi* (FLL), the fruit of a scrub, grown widely in Southern China was chosen [10]. We need to subject the water extract of *Ligustri* to experimental platforms to study its effects on bone metabolism, followed by clinical trials.

Since we are using a herb as a therapeutic agent, we need to follow the recommended procedures of herbal research which consist of three major components, viz., (i) working up the chemical profiles of the herb; (ii) putting the extract on biological research platforms to identify its effects on bone metabolism, particularly via the osteoblastic (build-up) end and the osteoclastic (break-down) end; and (iii) putting the product extract to a proper clinical trial. The procedures could be represented diagrammatically [Fig 1] as follows.

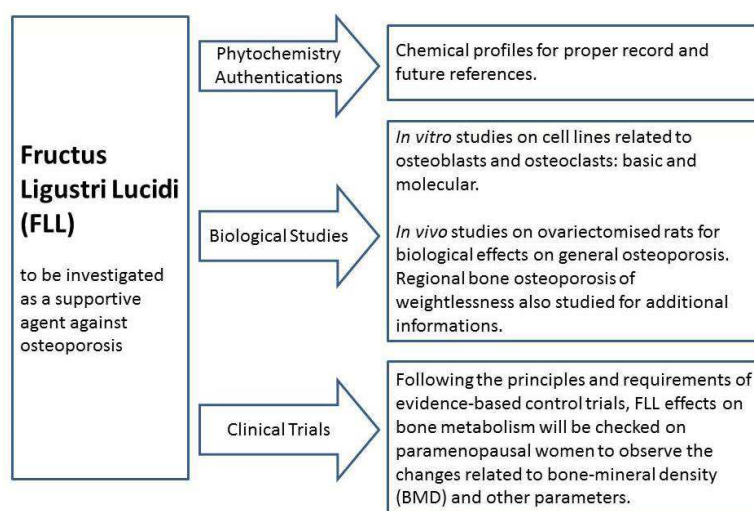


Figure 1. The Research Procedures using *Fructus Ligustri Lucidi* (FLL) as a supplement specific for maintenance of bone density.

2.1. Laboratory Studies on *Fructus Ligustri Lucidi* (FLL)

Preparation of FLL extract: FLL was obtained from the Jiangsu province of China. A voucher specimen was deposited in the school of Chinese medicine, the Chinese University of Hong Kong. The dried and powdered (25 kg) forms of the crude plant were extracted with 70% ethanol twice, the preparation was filtered at a yield of 38.1%, by weight of the starting materials. For *in vivo* studies 15 ml portions of the extract were stored at -20°C for subsequent use when they were diluted tenfold with distilled water. For *in vitro* studies the extract powder was prepared by freeze-drying, stored in the desiccator and reconstituted on the day of use with sterilized water.

Oleanolic acid and ursolic acid are the two main active compounds in FLL and oleanolic acid is a commonly used marker for authentication of FLL according to the Chinese Pharmacopoeia.

FLL has long records of clinical efficacy on improvement of symptoms related to aging, and skeletal pain [9]. The influence of FLL on bone metabolism has been worked out by a number of scientific groups in Hong Kong. They tested FLL on *in-vitro* and *in-vivo* experimental platforms and reported the following observations.

Three *in-vitro* tests platform were used. (1) Using UMR106 cells a FLL containing herbal mixture significantly increased the cell proliferations in dose-dependent manner. (2) Using RAW264.7 cells upon receptor activation of nuclear factor κ B ligand induction, the same mixture and FLL inhibited osteoclast formation [11]. (3) Using a mast cell platform (which studies how mast cells initiate osteoclastosis), FLL has counteracting effects, i.e. protects bone integrity [12].

In *in-vivo* tests, Zhang and Wong found positive effects on the bone turn-over and calcium balance in ovariectomised rats. They also demonstrated positive effects on calcium metabolism and vitamin D dependent gene expressions in the same rats [13-16].

Using a tail-suspension regional osteoporosis resulting from weightlessness model, Ko and Leung demonstrated improvement of osteoporosis in response to FLL in the osteoporotic femurs [17]. Cheng systematically evaluated the therapeutic effects of FLL on ovariectomised rats and found significant prevention of bone loss, increase serum calcium,

decreased bone turnover markers like ALP, BALP, OCN, DPD.

2.2. Clinical Trial Using FLL Supplemented Milk Powder

The milk powder was manufactured in New Zealand and is a popular brand containing supplements of vitamin D, calcium and glucosamine. Vitamin D and calcium are added in the standard proportions. Glucosamine is included more as a popular choice among the general public rather than any assumption that glucosamine contributes towards bone integrity [18].

49 women aged 50-67 years were successfully recruited. All of them experienced menopause for more than 2 years. 39 of this group consumed 1 packet of FLL milk powder (containing 20gm dried milk and 5.6gm FLL) per day, continuing for 3 months. 10 women did not take FLL supplemented milk powder but only normal milk powder and were studied as controls. The primary end point was the bone mineral density (BMD) changes at the end of the study. Secondary end points were body weights and Quality of Life (SF36).

Testing the effects of a biological agent on bone metabolism should require a longer period of continuous consumption rather than three months. However, in view of the limited resources available and the fact that we are not evaluating a drug but rather, a special nutrient, a shorter period of testing might be sufficient to reveal a trend of efficacy.

2.3. Results of Clinical Trial

The FLL milk powder group had mean age of 58.9 \pm 3.6, and they experienced menopause 8.8 \pm 5.6 years. The control group was aged 59.2 \pm 4.3 and with mean menopause 8.5 \pm 3.5 years.

After 3 months of FLL milk consumption the spine BMD increased 0.97% compared with before the consumption. The control group increased only 0.37% which was insignificant. The test group increased 1.47% at the Hip region compared with 0.28% only for the control group (Table 1).

With regard to Quality of life, the changes in both groups were insignificant. Concerning body weight, both groups did not show significant change.

Table 1. Bone Mineral Density (BMD) Scores in Spine and Hip.

	FLL Milk	Control	p-value
Spine			
Baseline (g/cm ²)	0.8344 \pm 0.1014	0.9178 \pm 0.1543	0.044
Percentage change after 3 Months	0.97%	0.37%	0.491
p-value*	0.004	0.238	
Hip			
Baseline (g/cm ²)	0.7675 \pm 0.0832	0.8207 \pm 0.0836	0.078
Percentage change after 3 Months	1.47%	0.28%	0.134
p-value*	0.177	0.622	

*Comparing with baseline.

3. Discussion

Since osteoporosis has become an issue of concern, particularly among the para-menopausal group of women, the pharmaceutical industries have invested extensively on the development of anti-osteoporotic drugs with specific targets. Blocking the bone catabolism has been a convenient direction of new drug production and the bisphosphonates family has enjoyed hundreds of times of increases in potency since its early development. Unfortunately, prolonged administration and high doses revealed the existence of thickening of the cortical component of bone leading to odd fractures and problems in the jaw bone [19].

The occurrence of jaw necrosis among the long-termed consumers of anti-resorptive drugs is a real threat to those suffering from osteoporosis. The American Dental Association has in 2014, studied thoroughly the related problems and concluded that although the risk of developing jaw necrosis was only around 0.1%, it was not possible to predict which subject would be particularly vulnerable to the complication [20]. Hence it would be advisable not to “over-treat” people with osteoporosis. Indeed, experts in osteoporosis have started advising general clients to have alternate years of bisphosphonates.

A review of the situation would support a revised view that bone integrity depends on a balanced metabolism where both osteoblastic (build up) and osteoclastic (breakdown) activities are at a good balance. The maintenance of the balance would depend on adequate nutritional input, exercises and sunlight. The avoidance of fractures would depend on the successful counteracting of all risk factors, apart from unhealthy bones. When a quick correction of bone density is required under special pathological circumstances, specific pharmaceuticals serve well. However, when only maintenance is required, non-aggressive nutritional supplements specific for bone health could be a better choice.

Traditional Chinese medicine is built on a principle of maintenance of physiological balance. A harmonious state of balanced physiological activities would prevent the development of adverse pathologies. The traditional concept of “Kidney tonification” in Traditional Chinese medicine covers the area of bone health. Our choice of FLL as a Champion of bone supplement is based on extensive literature review and laboratory platform studies which are still going on. Indeed Zhang and Wong recently demonstrated the protective effects of FLL against hypercalciuria and trabecular bone deterioration in experimentally induced type I diabetic mice, and the underlying mechanism was attributed to FLL’s regulations on duodenal calcium transporting proteins and renal CaSR [21].

The rich laboratory evidences on the bone protection effects of FLL, together with positive clinical observations, have convinced us to believe that FLL is a perfect choice of nutritional supplement for bone health.

Our clinical study has the limitations of being a small

clinical trial and the duration of supplement intake was only three months. Nevertheless, we followed closely the requirements of drug trials in the design of study, and took reference to the current principles of assessment for osteoporosis. In any osteoporosis study using BMD as an endpoint, only more than 0.5% increases after 3 months’ testing would be considered significant. In our trial of 3 months’ consumption, we observed increases of more than 0.5% in both the hip and spine BMD’s and the results compared positively against the control group. Importantly, no adverse effects were encountered and one other concern among the consumers, viz., body weight increase, was not observed. We therefore conclude that FLL is a safe and effective supplement for the maintenance of bone mineral density.

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