

Effects of a curcumin-based supplementation in asymptomatic subjects with low bone density: a preliminary 24-week supplement study

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Abstract. – **OBJECTIVE:** Osteopenia is a chronic bone condition characterized by decreased calcification, density, or bone mass that, if untreated, can lead to osteoporosis and bone fractures. Although its increasing prevalence, nowadays osteopenia is not adequately prevented and managed. In this study, we evaluated the efficacy, in term of changes in bone density, and safety of an oral formulation based on turmeric phytosome (Meriva®), in subjects suffering from low bone density.

PATIENTS AND METHODS: 57 otherwise healthy subjects with low bone density were enrolled in this pilot, supplement study. Informed participants freely decided to follow either a standard management (SM) to control low bone density (control group=28) or SM associated with a curcumin-based oral supplementation (supplement group=29). The bone densities of heel, small finger and upper jaw were evaluated at inclusion and at different time points during the observational period (4, 12 and 24 weeks), in all subjects.

RESULTS: The bone density of the heel measured by the Sahara densitometer remarkably improved in the Meriva®-supplemented group, with a significant decrease of ultrasounds transmission values at week 12 (-18.4%) and at week 24 (-21.0%), compared with baseline values. The bone densities of small finger and upper jaw also significantly increased during the study in supplemented subjects, reaching +7.1% and +4.8%, respectively, at week 24, with respect to values at inclusion. Noteworthy, no significant changes of heel, small finger and upper jaw densities were observed in the control group. Last, no safety and tolerability issues were reported during the observational period.

CONCLUSIONS: This preliminary study suggests that a curcumin-based supplementation in

combination with an appropriate lifestyle could be beneficial in the prevention and management of osteopenia.

Key Words

Osteopenia, Bone density, Curcumin, Supplementation.

Introduction

Osteopenia (low bone density) is a chronic bone condition characterized by decreased calcification, density, or bone mass¹; the progressive loss of bone can eventually lead to osteoporosis and fractures if unrecognized and untreated. Most cases of low bone density occur in aged subjects, particularly postmenopausal women²; indeed, a decline of estrogen levels in females at menopause or estrogens and androgens in males later in life leads to loss of bone mass and strength and contributes to the development of bone diseases such as osteopenia and osteoporosis³. Nowadays, the increased risk of fracture is being diagnosed by Dual Energy X-ray Absorptiometry (DXA), which assesses the amount of mineralized bone in the skeleton (bone mineral density, BMD)⁴. According to the World Health Organization (WHO) criteria based on DXA measurements, patients are considered having low bone mass (osteopenic), when their BMD t-score of the spine or hip ranges between -1 and -2.5, whereas osteoporosis subjects have a t-score of -2.5 or lower⁵. Noteworthy, the majority of fractures occur in women whose BMD

scores are within the osteopenic, and not osteoporotic, range. From an analysis of the National Osteoporosis Risk Assessment (NORA) study database including 200,160 postmenopausal women who had no prior diagnosis of osteoporosis⁶, emerged that the number of subjects at risk of fractures is much higher in the osteopenic range due to the Gaussian distribution of BMD values in the population⁷. The lifetime risk of hip fracture, the most disabling one, is around 17.5% in white women and 6.0% in men in the US⁸, whereas is estimated at 11.4%, and 3.1% for women and men, aged 50 years, in the UK, respectively⁹. Furthermore, osteopenia among 50-year adults in the US is predicted to increase from 43.4 million in 2010 to 52.0 million in 2020 and 57.2 million in 2030¹⁰. Despite the increasing prevalence and the advances in pharmacotherapy, the majority of patients with osteopenia and osteoporosis are not adequately treated, and follow-up scans at 2 years as well as adherence to therapy remain poor¹¹. Taking into account the side effects associated with a long-term use, drug treatment such as estrogen- or androgen-based therapies and bisphosphonates should be considered only for patients with osteoporosis and for patients with osteopenia at high risk of fractures⁷. On the other hand, osteopenic patients without such risk factors should be advised to adopt a “bone friendly” lifestyle including regular physical exercise, moderation in alcohol use, smoking cessation and nutritional modifications⁷. Actually, proper nutrition is one of the most important preventive methods for osteopenia; in addition to calcium and vitamin D¹²⁻¹⁴, adequate intake of other mineral elements (magnesium, phosphorus, copper, zinc, fluoride, sodium, potassium) and vitamins (vitamin K, vitamin C, vitamins B) as well as carotenoids, have been associated with bone health¹⁵⁻¹⁸. Among nutritional supplements, curcumin is one of the most investigated because of its low toxicity and the broad range of molecular targets, leading to multiple pharmaceutical activities such as hepatoprotective, anti-inflammatory and antioxidant properties¹⁹⁻²⁵. Interestingly, *in vitro* and *in vivo* studies have associated curcumin with bone health, particularly with improved BMD and mechanical properties, suggesting potential applications of curcumin to treat bone disorders^{26,27}. However clinical studies in human investigating curcumin's effects on bone health are scant. To this end, we evaluated the efficacy, in term of changes in bone density, and safety

of an oral formulation based on turmeric phytosome (Meriva[®], Indena SpA, Milan, Italy), in subjects suffering from low bone density.

Patients and Methods

This was a registry, supplement study conducted in 57 otherwise healthy subjects with low bone density (DXA t-score between -1 and -2.5). Supplement studies define the field of activity of pharma-standard supplements and their possible preventive, pre-therapeutic applications. “Supplement human studies” produce supplementary data to be compared with those from the best available management plans. These types of researches are performed with products with high level of safety and pharmaceutical standards²⁸⁻³⁰. Informed participants (n=57) freely decided to follow either a standard management (SM) to control low bone density (control group=28) or SM associated with oral daily supplementation (supplement group=29). Daily supplementation dosage consisted of 1 tablet of Meriva[®] (Indena SpA, Milan, Italy), containing 1000 mg of the oral curcumin delivery form, for 6 months. Standard management included a complete nutritional evaluation, supplying a diet with adequate content of vitamins D, C and calcium; regular exercise program of 20 min at least 4 times/week including light weight lifting and walking or running according to patients' preferences. All subjects were reasonably fit, with a body mass index <25.

By inclusion criteria, all routine blood tests, *erythrocyte sedimentation rate* and C-reactive protein were within the normal values. Hypertensive and hypercholesterolemic subjects were excluded. No drugs or other products were used during the observational registry period. In all subjects bone densities (measured considering the passage of an ultrasound beam through the bone and its possible attenuation) at the heel, small finger and upper jaw were evaluated at inclusion and at different time points during the observational period (4, 12 and 24 weeks). The quantitative ultrasound measurement of the calcaneus (heel bone) was performed by using Sahara clinical bone sonometer (Hologic Inc., Marlborough, MA, USA). The small finger and upper jaw density were evaluated by using a specific, high-resolution ultrasound scanner (Preirus, Hitachi, Tokyo, Japan) with a defined elastosonography setting measuring in a semi-quantitative way the grey scale median (GSM) of the images³¹ (Figure 1). Treatment tolerability and adverse events were also evaluated.

Table I. Details of subjects enrolled in the study.

	Standard Management	Standard Management + Meriva®
Subjects (males)	28 (14)	29 (13)
Age, years (mean ± SD)	70.8±2.1	71.0±2.1

SD: standard deviation.

Statistical Analysis

Intragroup comparisons were performed by using ANOVA test with post-hoc Bonferroni correction. *p*-value <0.05 was considered significant.

Results

Demographics details of the study population are shown in Table I. The supplemented group and the control group were comparable in term of age and gender distribution. Given that the attenuation of the ultrasound passage is related to absolute bone density, the bone density of the heel measured by the Sahara densitometer remarkably improved in the Meriva®-supplemented group (Table II). In particular, differently from the control group, the quantitative ultrasounds transmission of the calcaneus significantly decreased at week 12 (-18.4%) and at week 24 (-21.0%), compared to baseline values, in subjects taking curcumin-based oral supplementation (Figure 2). The GSM measurement in ultrasound images of small finger and upper jaw significantly increased during the study in supplemented patients, reaching +7.1% and +4.8%, at week 24, respectively (Table II and Figure 3). In the control group no significant changes of GSM were observed. No safety and tolerability issues were observed during the observational period.

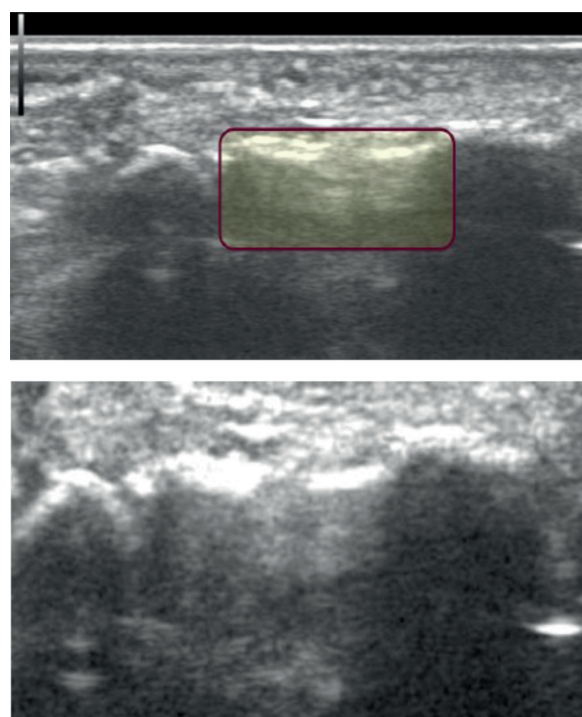


Figure 1. Small finger ultrasound evaluation, distal phalanx. **A**, In the box, the area where the grey scale median (GSM) value was evaluated. **B**, Example of loss of bone density.

Discussion

Bone homeostasis is maintained by a balance between bone resorption by osteoclasts and bone formation by osteoblasts. In subjects with osteopenia, an excessive bone resorption or an inadequate bone formation during remodeling affect this balance, resulting in low bone density³². In particular, the underlying pathogenic mechanisms of low bone density and osteoporosis also involve the ligand for the receptor

Table II. Assessment of the bone density in the heel bone, small finger and upper jaw.

	Standard Management				Standard Management + Meriva®			
	Inclusion	4 weeks	12 weeks	24 weeks	Inclusion	4 weeks	12 weeks	24 weeks
Heel bone density, %	100	-4	-5.4	-6	100	-12.3	-18.4*	-21.0*
Small finger bone density, GSM (range)	30.3 (13.0-36.0)	+1.2% (0.0-3.4)%	+1.3% (0.0-3.0)%	+1.3% (0.0-2.2)%	31.2 (11.0-39.0)	+5.3% (0.0-8.4)%	+6.9%* (3.0-9.0)%	+7.1%* (4.1-9.0)%
Upper jaw bone density, GSM (range)	32.7 (10.0-43.0)	+0.2% (0-2)%	+0.3% (0.0-2.4)%	+0.3% (0.0-1.9)%	33 (12.0-38.0)	+2.3% (1.0-7.7) %	+3.8 %* (2.0-7.6)%	+4.8%* (2.2-6.9)%

Data are expressed as mean (range). **p*<0.05 vs. inclusion.

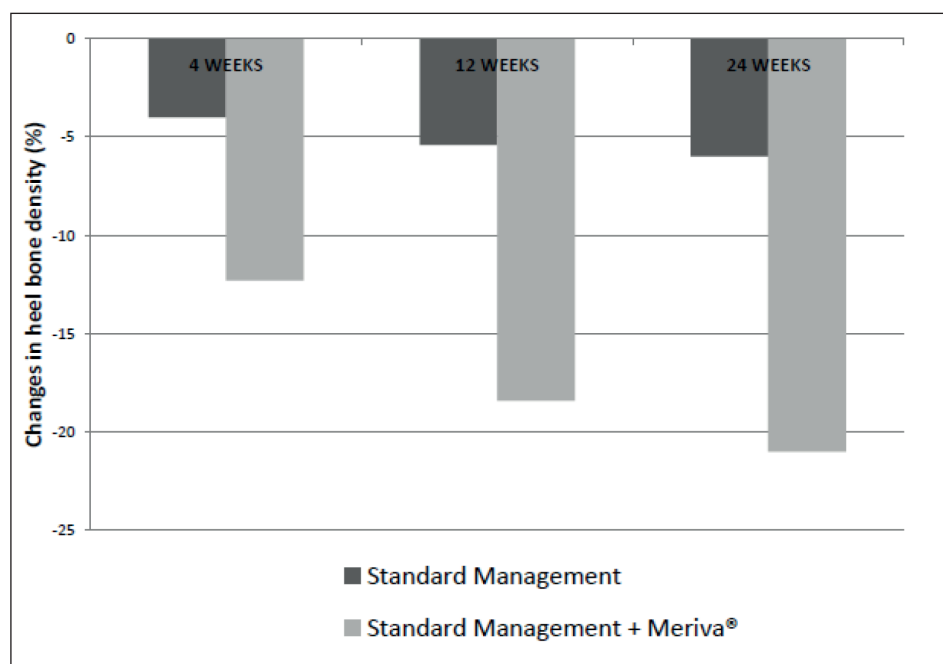


Figure 2. Changes (in percentage from initial values) in heel bone density.

activator of NF- κ B (RANK) namely RANKL, which is expressed by osteoblasts and interacts with RANK to activate differentiation of progenitors into osteoclasts and maintain osteoclast function³³. Recent *in vitro* and *in vivo* studies revealed that curcumin, the polyphenolic com-

pound derived from the Indian spice, turmeric (*Curcuma longa*), can target several molecular mechanisms related to bone homeostasis, including the activation and differentiation of osteoclasts. Experiments performed on cell culture derived from long bone of rabbit demonstrated

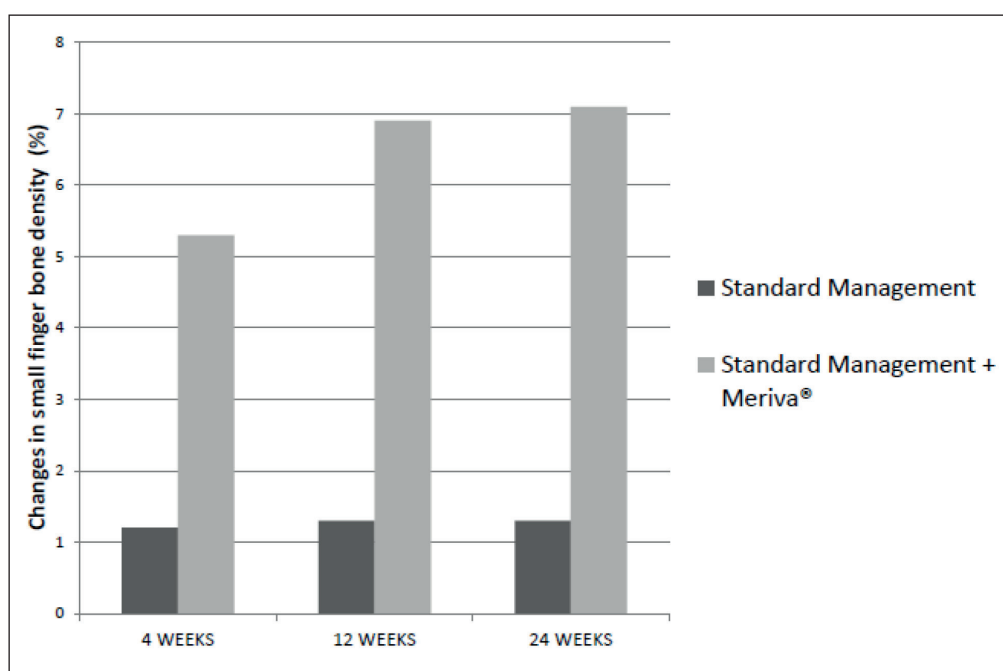


Figure 3. Changes (in percentage from initial values) in small finger bone density.

that curcumin inhibited osteoclastic bone resorption in a dose-dependent manner³⁴. Also, Bharti et al³⁵ demonstrated that curcumin suppresses RANKL pathways and osteoclastogenesis by interfering with the NF- κ B signaling. Translational research studies on postmenopausal osteoporosis models, the ovariectomizing (OVX) female rats, evaluating several bone parameters, gave mixed results^{36,37}. However, although Folwarczna et al³⁷ did not observe any significant improvement of bone mineralization or mechanical properties in curcumin-treated OVX rats, they reported beneficial effects in some bone histomorphometric parameters impaired by estrogen deficiency. Taken together, these observations suggest that curcumin administration could improve several aspects of bone health and may be helpful to alleviate bone disorders such as low bone density. In this registry study, a curcumin-based oral supplementation quickly improved (improvements were observed after few weeks of treatment) bone health parameters such as bone density, in asymptomatic subjects with osteopenia. The beneficial effects observed in Meriva[®]-supplemented subjects were associated with curcumin properties; standard management only produced minimal changes. To the best of our knowledge, this represents the first study investigating the effects of curcumin on bone health, in humans. Further researches in larger and selected populations are needed. We suggest that in osteopenic, otherwise healthy subjects with BMI >25, supplementation with Meriva[®] could lead to even greater changes in bone density.

Conclusions

This preliminary study offers a new indication for the use of curcumin in combination with an appropriate lifestyle in the prevention and management of osteopenia in otherwise healthy subjects.

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Conflict of Interest

AR, ST, FF are employees of Indena S.p.A. Milan, Italy. LG is a consultant for Indena S.p.A. Milan, Italy. The other Authors declare no conflict of interests.

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