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Mini Review

Health Benefits of Curcumin and Curcumin Phytosome in Bone Density Disorders

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Abstract

Osteopenia, or low bone density, is a chronic condition characterized by decreased calcification, density, and mass of bones, it represents a major health issue. Nutrition plays a key role in the prevention and management of this condition. Among different nutritional supplementation, curcumin is characterized by a wide spectrum of pharmacological activities, also with potential reference to the management of osteopenia. This review discusses current evidence supporting the use of curcumin supplementation in osteopenia. In multiple experimental studies on osteopenia models, curcumin reduced osteoclasts activity and promoted the action of osteoblasts, thus contributing to restore the physiological balance between these two cell populations which underlies the onset of osteopenia.

However, curcumin in its native form presents poor pharmacokinetic properties which greatly limit the effectiveness of this supplementation in daily practice. To address this limitation, our group has developed Meriva®, a phytosome-based technology which ensures optimal pharmacokinetic and allows curcumin to exert its multiple effects. On these bases, we studied Meriva® also in the management of osteopenia in otherwise healthy subjects, showing improved bone health parameters already after few weeks of administration and without any side effect.

These clinical findings represented the first evidence supporting the use of curcumin in the phytosome-form for the management of bone loss. Although larger studies are needed to further explore the effectiveness of curcumin in this condition, we believe that Meriva®, in combination with an appropriate lifestyle, may play a key role in the prevention and management of osteopenia in otherwise healthy subjects.

INTRODUCTION

Osteopenia, or low bone density, is a chronic condition characterized by decreased calcification, density, and mass of bones [1]. Eventually, this progressive loss of bone tissue may lead to osteoporosis and, consequently, increased risk of fractures. In most cases, osteopenia is found in elderly individuals, in particular – but not only - postmenopausal women [2]. Indeed, the reduction of sexual hormone levels with aging leads to loss of bone mass [3]. Osteopenia is usually diagnosed by Dual Energy X-ray Absorptiometry (DXA), which assesses bone mineral density (BMD) [4,5]. According to the World Health Organization (WHO), patients are considered osteopenic when their BMD t-score of the spine or hip ranges between -1 and -2.5, whereas osteoporosis is diagnosed when the subjects presents a t-score of -2.5 or lower [5].

Noteworthy, the majority of fractures is reported in patients with BMD scores within the osteopenic, and not osteoporotic, range, likely due to the Gaussian distribution of BMD values in the general population [6-8]. Current estimates show a lifetime risk of hip fracture – i.e., the most disabling one – of up to 17% in women and 6% in men [8,9], and the prevalence of osteopenia is likely to increase in the next decades [10].

On these bases, osteopenia appears to be a major health issue. However, osteopenic patients are frequently poorly managed, particularly over the long-term [11,12]. Current pharmacological therapy for bone loss includes estrogen- or androgen-based therapies and bisphosphonates; however, these treatments are not without side effects and should be considered mainly for patients with diagnosed osteoporosis or those with osteopenia and the high risk of fractures [7]. Noteworthy, osteopenic patients or subjects at risk of osteopenia should be advised to

adopt a "bone friendly" lifestyle which includes regular physical exercise, limited alcohol consumption, and smoking cessation in order to prevent further progression [7]. Also nutrition plays a key role in the prevention and management of osteopenia [7]. The importance of proper intake of calcium and vitamin D is well-established [13-15]. Moreover, other mineral elements (magnesium, phosphorus, copper, zinc, fluoride, sodium, potassium) and vitamins (vitamin K, vitamin C, vitamins B) as well as carotenoids, may improve bone health [16-19].

However, other nutritional supplements can be of benefit in the prevention and treatment of osteopenia. Curcumin is a bis-α, β-unsaturated diketone, commonly called diferuloylmethane, which along with demethoxycurcumin and bisdemethoxycurcumin, constitutes the group of curcuminoids of the rhizome extract of *Curcuma longa* [20,21]. Curcumin is characterized by a wide spectrum of pharmacological activities [22-27], also with potential reference to the management of osteopenia. We review here current evidence supporting the use of curcumin supplementation in this condition.

MOLECULAR MECHANISMS OF CURCUMIN: RELEVANCE FOR OSTEOPENIA

Several *in vitro* and *in vivo* studies have associated curcumin with bone health [28,29]. For instance, curcumin potently inhibits the transcriptional factors activator protein-1 and nuclear factor-kappaB (NFkB), which play a functional role in the survival of osteoclasts, and was shown to stimulate apoptosis in this cell line, in a dose- and time-dependent fashion [30]. In addition, curcumin suppressed RANKL-induced NFkB activation, which is a key determinant of osteoclastogenesis [31].

An *in vivo* study on 32 female rats assessed the potential effect of curcumin in prevention of bone loss following ovariectomy [32]. The animals were divided into four groups: sham, ovariectomised control, ovariectomised treated with curcumin 110 mg/kg and ovariectomised treated with premarin (conjugated estrogens tablets) 100 μg/kg. After 60 days, bone volume, trabecular number, trabecular thickness and trabecular separation were deteriorated in ovariectomised rats compared with sham group. Moreover, reduced osteoblast count, increased osteoclast count increased eroded surface were found in all ovariectomised groups, but with a lesser extent in the curcumin-treated group. Of note, bone volume and eroded surface were significantly better with curcumin than with premarin. On these bases, the Authors of that study concluded that curcumin may represent an alternative to estrogens in prevention of postmenopausal osteoporosis [32].

In an experimental model of bone loss, curcumin alleviated reduction of bone mineral density in tibiae and preserved bone structure in tibiae and mechanical strength in femurs of rats [33]. Moreover, curcumin reduced the formation of reactive-oxygen species and attenuated osteoclastogenesis. The beneficial effects of curcumin on bone tissues were also confirmed in a recent study by Chen et al, who showed that curcumin administration (100 mg/kg) for 60 days increased BMD and bone-alkaline phosphatase, decreased carboxy-terminal collagen cross links, enhanced bone mechanical strength, and improved trabecular microstructure in a rat model of osteoporosis [34]. In the same study, curcumin reversed osteoblast apoptosis by down-regulating the ratio of Bax/Bcl-2 as well as the levels of cleaved caspase-3 and cleaved poly ADP-ribose polymerase (PARP). These findings were mirrored in another study by the same group, which also demonstrated an upregulation of the expression levels of transcription factors that favor osteoblast differentiation [35]. Last, a recent *in vivo* study – which also employed advanced bioinformatics techniques – showed that curcumin improves bone microarchitecture in secondary osteoporosis mice by regulating the expression of MMP9 [36].

CURCUMIN AND OSTEOPENIA: CLINICAL EVIDENCE

Overall, experimental evidence supporting the role of curcumin in improving bone parameters appears sound and well-grounded. However, clinical studies in humans investigating curcumin effects on bone health are scant. This is due, at least in part, to some well-known issues on the pharmacokinetic properties of curcumin. They include chemical instability at intestinal pH, poor water solubility, modest oral bioavailability and high rate of urine elimination [20,21,37]. Collectively, these issues greatly limit the effectiveness of curcumin in clinical practice.

However, over the last decade our group has developed a food-grade formulation of curcumin, in form of phytosome (Meriva®, Indena SpA, Milan, Italy) [38-40]. In the pharmacokinetic study in rats, peak plasma levels and area under the plasma concentration (AUC) values for parent curcumin after administration of Meriva® were fivefold higher than the with unformulated curcumin. Similarly, liver levels of curcumin were higher after administration of Meriva® [38]. In the human pharmacokinetic study, total curcuminoid absorption was about 29-fold higher for Meriva® [39] than for unformulated curcuminoid mixture; remarkably, the major plasma curcuminoid after administration of Meriva® was demethoxycurcumin, a more potent analogue of curcumin [39]. On these bases, we recently studied Meriva® in subjects suffering from low bone density. To our knowledge, this was the first study investigating the effects of curcumin on bone health in humans.

In more details, this was a registry, supplement study conducted in 57 otherwise healthy subjects with low bone density (DXA t-score -1 - -2.5). Participants freely decided to follow either a standard management (SM) aimed at controlling low bone density (control group, n=28) or SM associated with oral daily supplementation with one tablet of Meriva® (1 g) (supplement group, n=29), for 24 weeks. SM included a complete nutritional evaluation, a diet with adequate content of vitamins D, C and calcium, regular exercise program at least 4 times/week. The supplemented group and the control group were comparable in term of age and gender distribution [41].

All subjects were reasonably fit, with a body mass index <25 and all routine blood tests, erythrocyte sedimentation rate and C-reactive protein were within the normal values. No drugs or other products were used during the follow-up period. We evaluated bone density at the heel, small finger and upper jaw at inclusion and at 4, 12 and 24 weeks using validated instruments. The bone density of the heel 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. Moreover, bone densities of small finger and upper jaw significantly increased during the study in supplemented subjects, reaching +7.1% and +4.8%, respectively, at week 24, with respect to inclusion. On the other hand, no changes of heel, small finger and upper jaw densities were observed in subjects not receiving Meriva®. Notably, no tolerability issues were reported with the curcumin supplementation.

CONCLUSIONS AND IMPLICATION FOR CLINICAL PRACTICE

Osteopenia and osteoporosis remain major health issues in Western countries. In order to prevent and manage these conditions, nutritional supplementations can be suggested. Such interventions should address the main molecular and cellular mechanisms underlying the onset of bone loss. Bone homeostasis and health is maintained by a proper balance between bone resorption by osteoclasts and bone formation by osteoblasts. In multiple experimental studies on models of osteopenia and osteoporosis, curcumin was shown to reduce osteoclasts activity and promote the action of osteoblasts, thus contributing to restore the physiological balance between these two cell populations.

However, this strong mechanistic rationale did not immediately translate into potential clinical use. Indeed, curcumin in its native form presents poor pharmacokinetic properties which greatly limit the effectiveness of this supplementation in daily practice. Our group has developed Meriva®, a phytosome-based technology which ensures optimal pharmacokinetic and allows curcumin to exert its multiple effects. On these bases, we studied Meriva® also in the management of osteopenia in otherwise healthy subjects, showing improved bone health parameters already after few weeks of administration and without any side effect.

These clinical findings represent the first evidence supporting the use of curcumin in the phytosome form for the management of bone loss. Although larger studies are needed to further explore the effectiveness of curcumin in selected population of patients, we believe that Meriva®, in combination with an appropriate lifestyle, may play a key role in the prevention and management of osteopenia in otherwise healthy subjects. In line of principle, it may be possible to recommend this supplementation – under proper medical control - also from an early age (e.g., 40 years), in order to benefit also of its documented effects on muscle and strength [25], in the context of the so-called “healthy aging”.

CONFLICT OF INTEREST

AR, FF and ST are employees of Indena S.p.A. LG is a consultant of Indena S.p.A.

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