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ORIGINAL ARTICLE

## Role of L-arginine in Treatment of Osteoporosis

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### ABSTRACT

**AIM:** Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue. Today, an increasing number of medications are available in order to treat osteoporosis and reduce fracture risks. However, these agents are expensive and have adverse effects, such as upper gastrointestinal irritation and ulceration, constipation, enhanced arterial and venous thrombosis, etc. The aim of the present study is to study the role of L-arginine in the treatment of osteoporosis.

**METHOD:** A Total of 180 osteoporotic female with DEXA T-score <-2.5 and vitamin D level >20ng/mL were selected and divided in to two study groups, 90 patients in each group. Study group A was given the test drug L-arginine 2 g, along with vitamin D 600 IU and calcium 500 mg as supplements similarly group B was given the comparative drugs Zoledronic acid in the dosage of 5 mg iv stat over 15 min once a year, along with vitamin D 600 IU and calcium 500 mg as supplements. The average BMD in group A before starting the treatment was compared with BMD 2 yrs after treatment, similarly in group B BMD before starting the treatment was compared with

BMD 2 yrs after treatment and percentage increase was calculated. Finally the percentage increased in group A was compared with the respective of the group B and the result was analysed.

**RESULT:** On comparing our test drug combined with L-arginine with the standard drug zoledronic acid IV infusion, we found that there is no difference in increase in BMD in the two groups. The drug combined with L-arginine is as good as inj. zoledronic acid in the treatment of osteoporosis.

**CONCLUSION:** The Zoledronic acid iv infusion and L-arginine both increase the bone mineral density of the LS spine and both are equivalent in efficacy and both can be conveniently be used in the treatment of osteoporosis in the peri and post menopausal osteoporotic females.

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**Key words:** L-arginine; Zoledronic acid; Osteoporosis; DEXA Scan

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### INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue predisposing to an increased risk for fracture. The number of people affected by osteoporosis has become more significant worldwide over the last decade, and is now regarded by the World Health Organisation as one of the 10 most serious global disease<sup>[1,2]</sup>. Today, a number of medications are available to treat osteoporosis and reduce fracture risks. However, these agents are costly and all have adverse effects, such as upper gastrointestinal irritation and ulceration, constipation, and enhanced arterial and venous thrombosis, etc<sup>[3]</sup>. Some agents even have the potential of increasing fracture incidence with prolonged treatment (e.g., fluoride, bisphosphonate). Essential amino acids, such as L-Arginine (Arg) and L-Lysine (Lys) are involved in bone metabolism and growth. Arginine is in fact involved

both in the synthesis of substrates (polyamine and L-proline) implicated in collagen synthesis, and in the production of growth hormone (GH), insulin like growth factor-I (IGF-I) and nitric oxide (NO). Also L-arginine may inhibit osteoclastic bone resorption by stimulating endothelial NO release and may stimulate bone formation by activating the growth hormone-IGF-I axis. Because of this dual effect on physiological regulators of bone remodeling, L-arginine has the potential to increase bone formation above bone resorption, and hence, to increase bone mass. Therefore, the aim of the present study is to study the role of L arginine in treatment of osteoporosis, effectiveness of L-arginine in osteoporosis and to compare the efficacy of L-arginine with bisphosphonates (Zoledronic acid) in the treatment of osteoporosis.

## METHOD

The present study was conducted in the department of orthopaedics, in collaboration with department of Endocrinology and Metabolism, from November 2011 to July 2013. The study was approved by institute ethical committee and Written and informed consent taken from each and every patient

### Selections of the patients

Peri and post menopausal females were selected after the diagnosis of osteoporosis on the basis of clinical symptoms like low back pain and X-ray of LS and DL spine showing multiple level biconcave vertebra.

DEXA scan of LS spine along with preliminary investigations conducted like complete blood count, random blood sugar, liver function test, renal function test, serum calcium, serum phosphate, serum vitamin D for the diagnosis and selections of primary osteoporotic patients.

**Inclusion criteria were:** (1) Perimenopausal and postmenopausal women; (2) Clinical symptoms like low back pain; (3) X-ray of LS and DL spine showing multiple level biconcave vertebra; (4) DEXA T-score <-2.5.

**Exclusion criteria:** (1) Males and premenopausal women; (2) Therapy with steroids, antiepileptic drugs; (3) serum vitamin D<20 ng/mL; (4) Uncontrolled diabetes; (5) Alcohol, tobacco, smoking; (6) Hormone replacement therapy; (7) Thyroid and parathyroid disease; (8) Any other osteoporosis therapy.

It was longitudinal prospective study in which a total of 180 osteoporotic female with symptoms of low back pain and X-ray of LS and DL spine showing osteoporotic changes with DEXA T-score <-2.5 and vitamin D level >20 ng/mL were selected and divided in to two study groups on the basis of standard table of random numbers (90 patients in each group). Study group A was given the test drug combined with L-arginine 2 g, along with vitamin D 600 IU and calcium 500 mg as supplements similarly group B was given the comparative drugs Zoledronic acid in the dosage of 5 mg iv stat over 15 min once a year, along with vitamin D 600 IU and calcium 500 mg as supplements. During our study, both the study groups were closely followed for 2 year and parameters like immediate and late side effect of the drug, improvement in the symptoms of the patients, compliance to the therapy, any fresh complain during the period of study related to the disease and the treatment along with cost of therapy were closely observed.

At the end of study BMD of each and every patient were again taken and the average BMD before treatment in group A was compared with average BMD after 2 yr of treatment and percentage increase in the bone mineral density was calculated. Similarly in

group B average BMD before treatment was compared with average BMD after 2 yr of treatment and the percentage increased was calculated. Finally the percentage increased in group A was compared with the respectives of group B and the result was analysed.

The result was compared in the two study groups on the basis of percentage increased in BMD, and was analysed whether the percentage increased was significant in each group. Also efficacy of test drug (L arginine) with respect to standard drug (Zoledronic acid) which is most potent bisphosphonate and is bench mark in treatment of osteoporosis was analysed.

The statistical analysis was done using SPSS for Windows version 16.0 software. The mean and standard deviation of the parameters studied during observation period were calculated for two treatment groups and compared using Student *t* test. The critical value of '*p*' indicating the probability of significant difference was taken as <0.05 for comparisons.

## RESULT

Only 150 patient turned for follow up may be because of poor literacy in this part of world, with 75 patient of group A and 75 patient from group B.

All the patient were primary osteoporotic female with mean age of 57 in group A and 59 in group B with no known co-morbidities (Table 1). The average BMD before treatment in group A and B was observed to be -3.32 and -3.27 respectively (Table 2).

The average BMD in group A after treatment for 2 yr with daily dose of test drug 2 g L-arginine was found to be -2.97 while in group B average BMD after treatment with zoledronic acid yearly injection for 2 yr was found to be -2.84.

There is significant difference observed in average BMD before and after treatment in group A (Table 3), also significant difference is present in average BMD before and after treatment of group B (Table 4) but there is no significant difference in BMD of two groups after treatment (Table 5 and 6).

**Table 1** Mean Age Of Group A And B.

Age	Mean±SD	<i>p</i> value
Group 1	57.45±8.317	0.182
Group 2	59.75±6.909	

**Table 2** Mean BMD Pre Therapy of group A and B.

BMD_Pre_Therapy	Mean±SD	<i>p</i> value
Group A	-3.36±0.73	0.601
GroupB	-3.25±0.71	

**Table 3** Mean BMD pre and post therapy of group A.

Group A	Mean±SD	<i>p</i> value
BMD Pre Therapy	-3.34±0.73	<0.001
BMD Post Therapy	-2.97±0.69	

**Table 4** Mean BMD pre and post therapy of group B.

Group B	Mean±SD	<i>p</i> value
BMD Pre Therapy	-3.25±0.71	<0.001
BMD Post Therapy	-2.84±0.65	

**Table 5** Percentage change in BMD in group A and B.

GROUPS	%INCREASE
A	11.60%
B	12.61%

**Table 6** Mean BMD post therapy.

BMD Post Therapy	Mean±SD	p value
Group A	-2.97±0.69	0.506
Group B	-2.84±0.65	

On comparing our test drug L-arginine with the standard drug zoledronic acid IV infusion we found that there is no significant difference in result with the increase in BMD in the two groups. The drug L-arginine is as good as inj. zoledronic acid in the treatment of osteoporosis.

All the patients on L-arginine were satisfied to start with the therapy as the drug could be orally administered, palatable with the therapeutic dosage of the drug for the treatment of osteoporosis. 15 patients out 90 patient showed gastric intolerance but that was easily managed by the modifications of dietary habit, and giving proton pump inhibitors at the prophylactic dosage, no other side effect was complained by the patients. There were no fresh complaint in the patient after the start of therapy, the symptoms like low back pain and radiculopathy found to be improved after administration of L-arginine therapy. Cost of therapy also was reasonable. However out of the 90 patient treated with Zoledronic acid 6 patients had side effect like fever, myalgia, generalized weakness, paresthesia and impending doom despite preloading with normal saline prior to therapy, the symptom was probably due to the transient hypocalcemia due the effect of the drug and the symptom persisted for 3 to 5 days, however patients wellbeing gradually improved.

## DISCUSSION

Osteoporosis, a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and fracture risk. Osteoporosis is deficient matrix with normal mineralization and there is loss of bone mass but there is an equivalent loss of matrix and mineral also therefore matrix to mineral ratio remains normal. The number of osteoporotic fractures is increasing worldwide, Osteoporotic female with BMD <-2.5 of LS spine had sustained fragility fracture and were at the increased risk of getting fracture. There are number of pharmacological and non pharmacological agents that have been proven to reduce the incidence of osteoporotic fracture. Treatments option are limited by costs, side effects, and lack of availability. An inexpensive and widely available treatment is necessary to alleviate this increase in fractures.

Oral administration of L arginine in pharmacological dosage induces growth hormone and insulin like growth factor- 1 responses and stimulates nitric oxide synthesis<sup>[4]</sup>. Growth hormone and insulin like growth factor 1 are important mediators of bone turnover and osteoblastic bone formation, while nitric oxide is inhibitor of osteoclastic bone resorption<sup>[5]</sup>. Because of this dual effect on physiological regulator of bone remodeling, L-arginine could potentially increase bone formation over resorption and consequently increase bone mass<sup>[6,7]</sup>. Also L-arginine, a nitric oxide donor could be a novel agent that has the potential to influence both the trabecular and cortical bones<sup>[8]</sup>.

On the other hand Bisphosphonates, which are the current standard of care in the treatment of osteoporosis are potent anti resorptive agent that inhibits osteoclastic activity and Zoledronic acid is the most potent bisphosphonates currently available for clinical use<sup>[9]</sup>. Oral bisphosphonates are associated with complicated dosing regimes along with poor absorption and have the potential for gastrointestinal tract irritation resulting in poor adherence and persistence. Zoledronic acid 5 mg once yearly intravenous bisphosphonate is approved for

the treatment and prevention of postmenopausal osteoporosis and treatment and prevention of glucocorticoid induced osteoporosis. In woman with osteoporosis an annual treatment of Zoledronic acid increased lumbar spine bone mineral density with by 6% compared with baseline. Zoledronic is generally safe and well tolerated with 5 mg and has potential to improve patient compliance with osteoporosis therapy and consequently, to reduce fracture risk in clinical practice. Also Zoledronic acid is a preferable alternative to oral bisphosphonate therapy in patients with polypharmacy, significant gastrointestinal intolerance or suspected medication noncompliance, cognitive dysfunction and inability to sit upright.

Several previous clinical studies confirmed that nitrate use has favorable effects on the skeleton in postmenopausal osteoporosis<sup>[10-14]</sup>. Adequate supplementation in animals or humans with no precursor like L-arginine could also be effective in prevention of bone losses. In addition, the role of combination therapies especially with the combination of no donors with Bisphosphonates needs to be investigated.

In our study not much difference is present in percentage increase of BMD after 2 yr of treatment with test drug (L Arginine ) and comparative drug (zoledronic acid), which is 11.60 percent in group A and 12.61 percent in group B. However, increase in BMD with zoledronic acid was found to be better than the earlier studies<sup>[15]</sup> and L-arginine has increased BMD as good as iv zoledronic acid. However L arginine is safer antiosteoporotic as compared with bisphosphanates.

In most of the prior studies<sup>[16,17]</sup> the test drug in postmenopausal studies that is either bisphosphonates like alendronates, hormone replacement therapy, selective estrogen receptor modulators are all compared with the placebo, in contrast we gave our patient with Larginine and zoledronic acid because it will always be unethical not to treat peri and post menopausal women with osteoporosis, as once the patient is diagnosed as osteoporosis they are always at the high risk of getting fragility fracture, so treating them with placebo is always a crime.

However some side effect of L-arginine like breathing problems, chestpain, swelling in the legs, low blood pressure nausea and bloating can happen at higher doses, however L-arginine at the dosage of 2 g is safe with mild side effect of gastro intestinal intolerance. However Zoledronic acid had severe side effect of jaw osteonecrosis<sup>[18]</sup>. In our study also some patient did suffer from the immediate reactions like fever, myalgia, impending doom, transient hypocalcemia leading to severe distress.

L-arginine a nitric oxide donar has indications in plenty of diseases like congestive heart failure, high blood pressure, coronary heart disease, intermittent claudication, erectile dysfunction and male infertility, improving kidney function in renal transplant, speeds wound healing, increases blood flow to cold hands and feet in people with diabetes, hence L-arginine can be easily administered in all these comorbid osteoporotic patients with synergistic therapeutic effect in these diseased state as well<sup>[19,20]</sup>.

Osteoporosis and fracture go side by side, L-arginine upregulates every metabolic pathway to optimise and augment bone healing, induces strong bone formation by enhancing GH and IGH-1 level, Enhances callus formation by 30%, induces angiogenesis and reduces inflammatory cytokines IL-6<sup>[21]</sup>. Analysing all these facts we can conclude there is role of L-arginine in treatment of osteoporosis and it can be easily administered in all the peri and post menopausal osteoporotic females with greater therapeutic value and minimal side effect profile with satisfactory increase in the bone mineral density and reducing incidence of fragility fractures, promoting healthy

and fracture free life style. However longer follow up with bigger sample size required for further evaluation of efficacy and potency of L-arginine in clinical practice.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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