Evaluation of efficacy and safety of Reosto in senile osteoporosis: A randomized, double-blind placebo-controlled clinical trial

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INTRODUCTION

Osteoporosis is a commonly encountered entity in an orthopedic clinical practice. Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration leading to enhanced fragility and an increased risk of fractures. Osteoporosis may be either primary or secondary. Primary osteoporosis is subdivided into type I (postmenopausal) and II (senile), and secondary OP is also referred as type III OP. Senile OP (Type II OP) occurs as a result of calcium deficiency and occurs in individuals over the age of 70 years, in a 2:1 ratio of women to men. Both trabecular and cortical bone are affected and a causal association with hip fractures has been observed.

The World Health Organization has recommended diagnosing OP based on BMD measurements of the hip and spine. Patients with BMD 1 to 2.5 SD below peak bone mass measurements are classified as osteopenic and patients with BMD >2.5 SD below peak bone mass measurements, are classified as osteoporotic. For BMD measurements DEXA is the gold standard, due to its distinct advantages (low radiation dose, short scanning time and feasibility of scanning of both axial as well as appendicular sites).

The goal of OP treatment is the prevention of consequent complications. Balanced diet, weight-bearing exercises and vitamin D intake are important components of renormalizing peak bone mass.

Reosto is a herbomineral formulation indicated for OP and it contains the powders of Terminalia arjuna, Withania somnifera, Commiphora wightii, Sida cordifolia and Vanda roxburghii alongwith organic calcium (Godanti bhasma and Kukkutandatvak bhasma). Various experimental studies and clinical trials conducted with Reosto have reported the beneficial effect of Reosto in OP, as evidenced by improvements in bone density and remineralization alongwith symptomatic relief. This study was planned to evaluate the efficacy and safety of Reosto in senile OP.

ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual-energy x-ray absorpiometry</td>
</tr>
<tr>
<td>DPPH</td>
<td>1,1-diphenyl-2-picrylhydrazyl</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>OP</td>
<td>osteoporosis</td>
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<tr>
<td>TNF-α</td>
<td>tumor necrosis factor-alpha</td>
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Aim of the study
The present study was aimed to evaluate the clinical efficacy and safety (short- and long-term) of Reosto in senile OP.

Study design
This study was a randomized, placebo-controlled, double-blind clinical trial, conducted at the Department of Orthopedics, Medical College and S.S.G. Hospital, Baroda, India as per the ethical guidelines of Declaration of Helsinki, from April 2002 to March 2003, among 100 patients of either sex. The study protocol, case report forms, regulatory clearance documents, product related information and informed consent forms (in English) were submitted to the Institutional Ethics Committee and were approved by the same.

Inclusion criteria
All patients who were diagnosed as either osteoporotic by DEXA scanning for BMD and who were willing to give informed consent in writing were included in the study.

Exclusion criteria
Pregnant and lactating women, patients with congenital disorders (dysosteogenesis and Marfan’s syndrome) or endocrine disorders (hyperthyroidism, hypogonadism or Cushing’s syndrome), patients with evidence of malignancy or any major systemic illness necessitating long-term drug treatment (diabetes mellitus and rheumatoid arthritis) and patients with cardiac, hepatic or renal failure were excluded from the study.

Study procedure
All patients were examined for BMD of the right heel by DEXA (Machine make: LUNAR PIX # 50295) and randomization of patients was done by using computer generated random allocation program, with 50 patients in each (drug and placebo) group. Double-blinding of the patients ensured that both the placebo and drug groups received the study drugs without the knowledge about the type of drug. The decoding of drugs was done only after the end of the study to ensure that the participating patients and investigators were unaware of the identity of the study drugs.

A detailed personal, family and medical history was obtained from all patients and they were subjected to a thorough clinical examination. Complete hematological (hemoglobin, total leucocyte count, differential leucocyte count and erythrocyte sedimentation rate) and bone-specific biochemical investigations (serum calcium, serum phosphorus and serum alkaline phosphatase) were done for all patients.

The patient groups (placebo and drug) were advised to consume 2 tablets of either placebo or Reosto respectively, orally, twice-daily for a period of 12 months.

Monitoring and follow-up
All the patients were monitored at monthly intervals for a period of 12 months for any reported or observed adverse effects. At each follow-up visit, the investigator recorded any information about intercurrent illness, therapeutic interventions and concomitant medication. Medications considered necessary for the patient’s welfare and which will not interfere with the study medication (nonsteroidal anti-inflammatory drugs [NSAIDs]) were allowed at the discretion of the investigators. A detailed evaluation with BMD, hematological and bone-specific biochemical investigations were repeated at the end of 12 months.
Adverse events
All adverse events reported by the patients or observed were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as Unrelated (A reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), Possible (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient) and Probable (follows a known response pattern to the suspected drug; that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Any patient getting nontraumatic osteoporotic fragile fracture, from third month onwards was taken as treatment failure. Non-compliance (defined as failure to take ≥ 80% of the medication) was not regarded as treatment failure and reasons for non-compliance were noted.

Primary and secondary end points
The predefined primary efficacy end points were improvement in BMD score and bone-specific biochemical parameters. The predefined secondary safety end points were incidence of short- and long-term adverse events and overall patient compliance to the drug treatment.

Statistical analysis
The statistical analysis was performed on the basis of an intention-to-treat analysis. Changes in various parameters from baseline values and values after 12 months were analyzed by “Two-tailed paired ‘t’ test”. The minimum level of significance was fixed at 95% confidence limit and a 2-sided ‘p’ value of <0.05 was considered as significant.

RESULTS
Out of 143 initially screened patients, 100 patients who fulfilled the inclusion criteria were enrolled in the study. Ten patients were lost to follow-up and 90 patients completed the study.

There was a female preponderance in the study population (57 females and 33 males) and a total of 52 (57.78%) patients were above 60 years of age. Of the 52 patients who were above 60 years, 24 were males and 28 were females. There were a total of 47 (52.22%) patients in the Reosto group and 43 (47.78%) patients in the placebo group.

| Table 1: BMD score – before and after treatment in placebo and Reosto group |
|---|---|---|---|---|
| Parameter | Placebo Before treatment | Placebo After treatment | Reosto Before treatment | Reosto After treatment |
| Mean | 0.8633 | 0.8564 | 0.882 | 0.9029 |
| Std. Deviation | 0.1281 | 0.1346 | 0.1377 | 0.1391 |
| Std. Error | 0.0185 | 0.01942 | 0.01928 | 0.01948 |
| Lower 95% CI of mean | 0.826 | 0.8041 | 0.8432 | 0.8638 |
| Upper 95% CI of mean | 0.9005 | 0.9086 | 0.9207 | 0.942 |
| Mean of differences | -11.73 | -0.02092 | | |
| t value | 0.9994 | 3.794 | | |
| 95% confidence interval | -35.37 to 11.91 | -0.03201 to -0.009835 | | |
| R squared | 0.02081 | 0.2235 | | |
| p value | 0.3227 | p=0.0004 | | |
| p value summary | NS | *** (Highly significant) | | |
The minimum age, maximum age, mean, standard deviation, standard error mean, lower 95% CI of mean and upper 95% CI of mean (in years) of patients in the Reosto and placebo group was 51.00 and 49.00, 81.00 and 83.00, 62.51 and 63.08, 6.909 and 7.613, 0.9675 and 1.088, 60.57 and 60.90 and 64.45 and 65.27 respectively and there was no significant difference between the Reosto and placebo group at the time of the enrolment in the study (Mean ± SEM of drug group=62.51 ± 0.9675, Mean ± SEM of placebo group=63.08 ± 1.088, Difference between means=-0.5718 ± 1.453, 95% confidence interval=-3.459 to 2.315, R squared=0.001579, t=0.3936, p=0.6947, NS).

There was a highly significant increase in the BMD (Table 1 and Figure 1), 'T Score' (Table 2 and Figure 2) and 'Z Score' (Table 3 and Figure 3), in the patients from the Reosto group as compared to the patients from the placebo group, at the end of the study.

There was a highly significant increase in the serum calcium levels (Table 4 and Figure 4) with a simultaneous highly significant decrease in serum phosphorous (Table 5 and Figure 5) and alkaline phosphatase (Table 6 and Figure 6) levels in the Reosto group patients, as compared to the patients from the placebo group at the end of the study.

There were no clinically significant adverse events; either reported or observed during the entire study period and the overall compliance to the study drug was excellent.
DISCUSSION

The skeleton has cortical and trabecular bone tissues. Cortical bone (compact or lamellar bone) forms the thin outer shell of the long bones and it is the major portion of the cortex of other bones (75% of the weight of the skeleton is cortical bone). Trabecular bone (spongy or cancellous bone) is made of a network of intersecting trabeculae within the cortex, which serves as the supportive infrastructure of the bone and trabecular bone is the most metabolically active type of bone. Although trabecular bone accounts for only 25% of the skeleton by weight, it accounts for 75% of bone remodelling surface area. The vertebrae and the ends of the long bones of the arms and legs contain a higher percentage of trabecular bone than other areas of the skeleton.

Osteoporosis results from a combination of genetic and environmental factors that affect both peak bone mass and the rate of bone loss. Osteoporosis is thought to be due to the cumulative loss of bone through an imbalance in bone remodelling. Bone is actively remodelled throughout the life of an individual. During normal remodelling, osteoclasts (bone-resorbing cells) excavate small cavities in the bone, which are subsequently refilled by osteoblasts (bone-forming cells). Peak bone mass is achieved in the mid to late twenties. However, at about 35 years of age, an imbalance in bone turnover leads to the beginning of a gradual loss of bone (0.5 to 1% per year) in both men and women.

Table 3: Z score - before and after treatment in placebo and Reosto group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Before treatment</th>
<th>Placebo After treatment</th>
<th>Reosto Before treatment</th>
<th>Reosto After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.2404</td>
<td>-0.3705</td>
<td>-0.2725</td>
<td>-0.1136</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.8789</td>
<td>0.8844</td>
<td>0.9239</td>
<td>0.9591</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.1282</td>
<td>0.1333</td>
<td>0.1294</td>
<td>0.1446</td>
</tr>
<tr>
<td>Lower 95% CI of mean</td>
<td>-0.4985</td>
<td>-0.6393</td>
<td>-0.5324</td>
<td>-0.4052</td>
</tr>
<tr>
<td>Upper 95% CI of mean</td>
<td>0.01763</td>
<td>-0.1016</td>
<td>-0.01269</td>
<td>0.1779</td>
</tr>
<tr>
<td>Mean of differences</td>
<td>0.07273</td>
<td>-0.2614</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t) value</td>
<td>1.389</td>
<td>4.679</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-0.03293 to 0.1784</td>
<td>-0.3741 to -0.1486</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.04294</td>
<td>0.3373</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p) value</td>
<td>0.172</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p) value summary</td>
<td>NS</td>
<td>***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Serum calcium (mg/dL) - before and after treatment in placebo and Reosto group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Before treatment</th>
<th>Placebo After treatment</th>
<th>Reosto Before treatment</th>
<th>Reosto After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. Deviation</td>
<td>1.385</td>
<td>1.398</td>
<td>0.9625</td>
<td>0.9832</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.1978</td>
<td>0.1998</td>
<td>0.1348</td>
<td>0.1419</td>
</tr>
<tr>
<td>Lower 95% CI of mean</td>
<td>8.67</td>
<td>8.655</td>
<td>8.886</td>
<td>9.102</td>
</tr>
<tr>
<td>Mean of differences</td>
<td>0.0102</td>
<td>-0.2313</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(t) value</td>
<td>0.6069</td>
<td>7.238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.02363 to 0.04404</td>
<td>-0.2956 to -0.1669</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R^2)</td>
<td>0.007615</td>
<td>0.5271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p) value</td>
<td>0.5468</td>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p) value summary</td>
<td>NS</td>
<td>*** (Highly significant)</td>
<td></td>
<td></td>
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DISCUSSION

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The various risk factors for osteoporotic fractures are classified as modifiable and nonmodifiable risk factors. Nonmodifiable risk factors include personal history of fracture, history of fracture in first-degree relatives, advanced age, female sex and dementia. Potentially modifiable factors include smoking, low body-weight, estrogen deficiency, early...
menopause, bilateral ovariectomy, poor health and fraility. Several
diseases (and conditions), and drugs are associated with development of
secondary OP. Diseases associated with an increased risk of generalized
OP in adults include acromegaly, adrenal atrophy, Addison’s disease,
amyloidosis, ankylosing spondylitis, chronic obstructive pulmonary
disease (COPD), congenital porphyria, Cushing’s syndrome, endometriosis, gastrectomy, gonadal
deficiency, hemochromatosis, hemophilia, hyperparathyroidism,
hypophosphatasia, lymphoma, leukaemia, malabsorption syndrome, insulin dependant
diabetes mellitus (IDDM), multiple myeloma, multiple sclerosis,
pernicious anemia, rheumatoid arthritis, sarcoidosis, severe liver
disease, thalassemia and thyrotoxicosis. Drugs which induce
OP include anticonvulsants, cytotoxic drugs, thyroxine,
corticosteroids, heparin, lithium and premenopausal use of tamoxifen
(the long-term effects of inhaled corticosteroids on fracture risk is
currently unknown)\textsuperscript{10}.

Nutritional factors, which have an
influence on OP include dietary intake of calcium, protein and calories, and vitamin D status. Other nutrients and trace minerals (phosphorus, vitamins C and K, copper, zinc, and manganese) have also been implicated but are less certainly associated with development of OP. Calcium intake is positively correlated with bone mineral mass at all ages, and supplementation is shown to reduce the rate of bone loss and decrease fracture incidence in calcium-deficient elderly. Vitamin D is essential for bone mineral metabolism through its role in calcium absorption and osteoclastic resorption and supplementation with vitamin D reduces the rate of all fractures in the elderly who are deficient in vitamin D. Protein and caloric malnutrition predisposes to falls and diminishes the soft tissue cover (fat and muscle) over bony prominences. Protein intake is a major determinant of outcome after hip fracture and serum albumin level is the single best predictor of survival in these patients.

Behavioral factors important in the pathogenesis of OP include physical activity, smoking and alcohol consumption. Bone mass is higher in athletes than in non-athletes. Mechanical loading is shown to increase bone mass and the relationship between load and bone density is curvilinear and much more pronounced at low levels of loads, best seen as a bone loss during immobilization (in completely immobilized patients, bone mass loss may be up to 40% in a year).
The mechanisms of bone loss in OP are numerous, but, ultimately, there is an increased recruitment and responsiveness of osteoclast precursors and an increase in bone resorption, which outpaces bone formation. The end result is a decrease in trabecular bone and increased risk of Colles and vertebral fractures. Osteoclasts are under the influence of gonadal hormone status, calcium intake and bioavailability, vitamin D status, physical activity and hormones (parathyroid hormone, corticosteroids, thyroid hormone, growth hormone and calcitonin) and cytokines (TNF-α, IL-1 and IL-6, whose production by mononuclear cells may be increased).

This study observed highly significant improvement in the BMD, ‘T’ score and ‘Z’ score, alongside highly significant increase in the serum calcium levels with a simultaneous highly significant decrease in serum phosphorous and alkaline phosphatase levels in the patients from Reosto group. These results indicate that Reosto might be a useful therapy in patients who have either osteopenia or OP and it might prevent age-related bone loss. This finding may be linked with increased rate and extent of calcium absorption with Reosto, which provides 1449.6 mg of calcium per day, matching the recommended quantity for osteoporotic patients. This study also observed that Reosto alleviated common symptoms such as backache, joint swelling, joint pain and joint stiffness. Reosto also appeared to be safe for long-term usage, as there were no clinically significant adverse events recorded and this finding is important, as OP management demands drug therapy for longer periods of time. The beneficial effects of Reosto can be attributed to the potent anti-inflammatory, antioxidant, analgesic and bone remineralization activities of the ingredients along with the high bioavailability of natural organic calcium.

*Terminalia arjuna* has been documented for its therapeutic efficacy in metabolic bone disorders. The active ingredients of *Terminalia arjuna* are arjunetoside, terminoside A arjunaphthanoloside (triterpene glycosides), oleanolic acid and arjunic acid. The anti-inflammatory effect of *Terminalia arjuna* can be attributed to its potent antioxidant action. Munasinghe et al. reported the potent antioxidant activity of *Terminalia arjuna* both in vitro (by DPPH radical scavenging and deoxyribose damage protection assays) and in vivo (by effects on lipid peroxidation). Ali et al. demonstrated that *Terminalia arjuna* is a potent antioxidant and it inhibits NO production in LPS-stimulated peritoneal macrophage. Gupta et al. reported significant antioxidant action of *Terminalia arjuna* comparable to that of vitamin E. In another study, Sumitra et al. observed the potent antioxidant activity of *Terminalia arjuna*.

*Commiphora wightii* contributes in the critical process of bone remineralization. Singh et al. investigated *Commiphora wightii* for reduction of pain, stiffness and joint mobility in older patients with OA of the knee and reported significant improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score with symptomatic improvement. The active ingredients of *Commiphora wightii* are flavanones (muscaneone and naringenin). Zhu et al. observed the scavenging effect of *Commiphora wightii* against DPPH radicals.

*Withania somnifera* is an analgesic, which helps relieve pain associated with osteodystrophic disorders. The active ingredients of *Withania somnifera* are withanolides lactones, coumarins, scopoletin, aesculetin, beta-amyrin and phytosterols (stigmasterol and sitosterol). Russo et al. reported the anti-inflammatory effects of *Withania somnifera*. Gupta et al. and Singh et al. observed the therapeutic potential of *Withania somnifera* in chronic degenerative conditions. Al-Hindawi et al. assessed *Withania somnifera* for anti-inflammatory activity by measuring the suppression of carrageenan-induced paw oedema and
the results showed that *Withania somnifera* possessed potent anti-inflammatory activity\(^28\). Davis et al. reported that administration of *Withania somnifera* extract enhanced the levels of interferon-alpha, IL-2, granulocyte macrophage colony-stimulating factor (GM-CSF) and decreased TNF-\(\alpha\) production\(^29\). The clinical efficacy (evaluated on the basis of severity of pain, morning stiffness, Ritchie articular index, joint score, disability score and grip strength) of *Withania somnifera* was evaluated in a randomized, double-blind, placebo-controlled, crossover clinical trial in patients with OA and a significant reduction in the severity of pain and disability score was observed\(^30\). Iuovne et al. documented that *Withania somnifera* is a potent antioxidant and causes a significant inhibition of NO synthetase, protein synthesis and nuclear factor-kappaB (NF-kappaB) activation\(^31\). Agarwal et al. studied *Withania somnifera* for anti-inflammatory activity in immune mediated inflammation (active paw anaphylaxis, delayed type hypersensitivity and ovalbumin-induced paw oedema) and significant increase in white blood cell and platelet counts were observed with *Withania somnifera* pre-treatment\(^32\). Gautam et al. documented the immunopotentiating properties of *Withania somnifera*\(^33\).

*Vanda roxburghii* is being used as a topical analgesic in rheumatic joint pains\(^34\). Karandikar et al. reported remarkable anti-inflammatory effects of *Vanda roxburghii*\(^35\). Chawla et al. and Prasad et al. reported significant anti-inflammatory activity of *Vanda roxburghii* against acute inflammation induced by carrageenan\(^36\), serotonin and formaldehyde\(^37\).

Franzotti et al. observed potent anti-inflammatory and analgesic effects of *Sida cordifolia*\(^38\). Kanth et al. also reported potent analgesic and anti-inflammatory activities of *Sida cordifolia*, which was comparable to indomethacin\(^39\). Auddy et al. reported the free radical scavenging activity of *Sida cordifolia* in 2,2'-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid radical cation decolorization assay (both *in vitro* and *in vivo*) and there were no toxic effects on the viability of PC-12 cell lines\(^40\).

Godanti bhasma and Kukkutandatvak bhasma are rich organic sources of calcium, which increase the absorption and bioavailability of calcium\(^41\).

**CONCLUSION**

Osteoporosis is a commonly encountered entity in orthopedic practice and is responsible for enhanced bone fragility and a consequent increased risk of fractures. Senile osteoporosis (type II osteoporosis) is a result of calcium deficiency and occurs in individuals over the age of 70 years, in a 2:1 ratio of women to men. World Health Organization had recommended diagnosing OP based on BMD measurements of the hip and spine. For BMD measurements, DEXA is the gold standard. The goal of OP treatment is prevention of consequences and complications. This study was planned to evaluate the efficacy and safety of Reosto in senile OP.

This study observed a highly significant improvement in the BMD, ‘T’ score and ‘Z’ score, along with highly significant increase in the serum calcium levels with a simultaneous highly significant decrease in serum phosphorous and alkaline phosphatase levels in the Reosto group patients. These results indicate that Reosto might be a useful therapy in patients who have either osteopenia or OP, as it might prevent age-related bone loss. Reosto also alleviated common symptoms such as backache, joint swelling, pain and stiffness. Reosto also appeared to be safe for long-term usage, as there were no clinically significant adverse reactions recorded. Therefore, it can be concluded that Reosto is clinically effective and safe in the management of senile OP.
REFERENCES


