Identification of a New Clinical-Diagnostic Threshold for the Therapeutic Prevention of Vertebral Fractures: The Vertebral Pre-Fracture

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Citation

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Abstract

Purpose: To evaluate the effectiveness of intervention at a praecox stage of vertebral fracture, using a sensitive diagnostic method (using the sensitive MorphoXpress® software) and therapeutic treatment (risedronate).

Materials and Methods: 96 patients of postmenopausal age with lumbar pain symptomatology, osteoporosis with bone mineral density score > -2.5 and a 5-10% reduction of the height of at least one vertebral body of the lumbar region were treated for 10 months with risedronate 5 mg/day in association with non-steroidal anti-inflammatory drugs (Group 1, n=49) or with non-steroidal anti-inflammatory drugs alone (Group 2: n=47) and studied with densitometry and morphometry.

Results: Statistically significant differences were found in favor of Group 1 for the risk reduction of vertebral fracture (80%) and for the reduction of kyphoplasty interventions (81%) (each $p<0.001$).

Conclusions: Vertebral pre-fracture is a new clinical-diagnostic threshold that should be treated to prevent the progression to frank vertebral fracture.

INTRODUCTION

Osteoporosis is a disease with relevant social impact: its incidence increases with age and the majority of people in their 80s are affected by osteoporosis. In Italy, there are about 3.5 million women and one million men with osteoporosis [1, 2]. The quick aging process of the population (Italy is the "oldest" country in the world: the percentage of people >65 years is >18%, 4% being >80 years) makes, in our country, osteoporosis and, as a consequence, osteoporotic fractures a sanitary and a social priority, with severe economical implications [2,3,4]. The postmenopausal osteoporotic and senile forms are considered "primary", while "secondary" forms are those due to diseases and drugs [2].

The most common types of fractures observed in patients with osteoporosis are i) wrist fractures, ii) femoral fractures, and iii) vertebral fractures. Although femoral and non-vertebral fractures represent 87% of total fractures [5, 6], vertebral fractures need special attention for the following reasons:

- Some surveys report that 50-65% of vertebral fractures are not clinically diagnosed due to their poor symptomatology [7,8,9]
- In postmenopausal women, the risk of vertebral fracture is around 16% [7]
- Mortality within five years after a vertebral fracture statistically significantly increases in respect to the non-fractured population [10,11,12]
- The presence of a vertebral fracture increases the risk of a new fracture within a year by at least five times and the risk further increases in case of recurrent fractures (domino effect) [13]
- Among patients with vertebral impairments, 1/4 will undergo a new osteoporotic (not necessarily

vertebral) fracture within one year [14].

From the above, it is imperative that a correct and systematic diagnosis of vertebral fracture could block the vicious circle represented by vertebral fracture other vertebral and non-vertebral fractures femoral fracture high morbidity and mortality.

The available data suggest that only 56% of orthopedic specialists prescribe a densitometry in patients with suspected osteoporotic fractures; moreover, only one of five women with osteoporotic fractures receives adequate treatment [7,8,9]. Therefore, it is important that the specialist considers early and precise diagnosis as a priority. According to recent guidelines [2], densitometry is a relatively accurate and precise way to measure bone mass and specifically bone mineral density (BMD) [15], however, evaluation of bone quality (microarchitecture, geometry, collagen and crystallinity properties, others) is gaining higher importance as an indicator of tendency to fracture [16]. Vertebral morphometry allows diagnosing and evaluating in a semi- or quantitative way – thus, identifying objectively and reproducibly – a vertebral fracture due to fragility, or a tendency of the vertebral body to undergo a fracture [17]. Vertebral morphometry applies a threshold value of 4 mm or a 15% reduction of one vertebral body's height (cuneal fracture, mono-biconcave, due to compression) and can be measured either manually or by computer. MorphoXpress® is an innovative semiautomatic software (developed by ImageMetrics plc, UK and Procter&Gamble, Italy) that allows the execution of vertebral morphometry on traditional radiograms, thus shortening diagnostic time, increasing the accuracy and reproducibility and reducing the intra- and inter-observer variability [18,19,20].

The objectives of the current study were to evaluate:

- The evolution of a lumbar pain symptomatology accompanied by an instrumental sign of a 5-10% reduction of the height of at least one vertebral body of the lumbar region (L1-L5) studied by MorphoXpress®
- The possibility to counteract the evolution of above lesion vs. the osteoporotic fracture by the prophylactic therapeutic intervention with risedronate (RIS).

MATERIALS AND METHODS

STUDY POPULATION

We selected patients according to the following inclusion criteria:

- Women of postmenopausal age
- Presence of lumbar pain symptomatology arbitrarily defined as “bone pain”
- Osteoporosis with BMD T-score > -2.5 measured by bone densitometry of the lumbar region.

The main exclusion criteria were presence of vertebral fractures and/or lumbar pain with radicular involvement and ascribed to other causes than osteoporosis (lower back pain, cancer, others).

The study was conducted in accordance with the principles of the Helsinki declaration, Good Clinical Practices, and the current National rules for conducting clinical studies. The Institutional Ethical Committee of the Casa di Cura S. Zita di Lucca approved the Protocol, the Patient Information Sheet, and the Informed Consent. All patients gave their written informed consent to participate.

TYPES AND TIMES OF EVALUATION

At baseline (T0), all patients were submitted to the following evaluations:

- Clinical examination
- Bone densitometry of the lumbar region to measure BMD T-score
- Vertebral morphometry analyzed by MorphoXpress®.

At regular times during the study, the patients were submitted to clinical check-ups to evaluate their general health status and the possible need to change their therapeutic regimen. At the end of the treatment period of about 10 months (T10), we repeated the clinical examination and the vertebral morphometry. Vertebral morphometry was performed also during the study period, in case there was the clinical suspect of a vertebral fracture.

The incidence of kyphoplasty interventions and side effects was also evaluated during the treatment period.

STUDY DESIGN AND TREATMENT

The study followed an open design and the patients who showed at least a 5-10% reduction of the height of at least one vertebral body of the lumbar region (L1-L5) at vertebral morphometry analyzed by MorphoXpress® were randomized into two groups:

- Group 1: RIS 5 mg/day in association with non-steroidal anti-inflammatory drugs (NSAIDs)
- Group 2: NSAIDs alone

Treatment was for 10 months, a time interval considered sufficient, according our experience, to evaluate progression vs. frank vertebral fracture.

Patients included in the study were already on treatment with NSAIDs. The type and dosage of NSAIDs taken by the patients were similar between the two groups at baseline and were maintained as such during the study.

METHODOLOGICAL LIMITATIONS

For technical reasons, we could not follow a double-blind experimental design and so far we treated a relatively small study population.

STATISTICAL ANALYSIS

Baseline characteristics of the two groups (age, height, body weight, and BMD T-score) were statistically summarized as mean, SD, and range. The number of patients showing a vertebral body height reduction of ≥15% and/or and the number of patients undergoing kyphoplasty surgery were summarized using descriptive statistics for each of the two groups.

The treatment effect (RIS 5 mg/day with NSAIDs vs. NSAIDs alone) on the progression of the vertebral pre-fracture and the incidence of kyphoplasty surgery was investigated by calculating the relative risk and 95% confidence interval, applying the Cochran-Mantel-Haenszel to evaluate the statistical significance.

RESULTS

Between January 2004 and December 2005, we enrolled 96 patients (49 randomized to Group 1 and 47 to Group 2).

The baseline (T0) characteristics of the population enrolled are reported in Table 1.

Figure 1

Table 1: Baseline (T0) Characteristics of the Population Enrolled

	RIS 5 mg + NSAIDs N=49	NSAIDs alone N=47	Total N=96
Age (years)			
mean (SD)	*76 (9.7)*	*77 (6.9)*	*77 (8.4)*
range	*54 - 95*	*63 - 91*	*54 - 95*
Height (cm)			
mean (SD)	*161 (4.3)*	*161 (4.0)*	*161 (4.1)*
range	*155 - 170*	*150 - 168*	*150 - 170*
Weight (Kg)			
mean (SD)	*65 (6.3)*	*67 (5.8)*	*66 (6.1)*
range	*55 - 79*	*52 - 80*	*52 - 80*
BMD T-score			
mean (SD)	*-2.02 (0.233)*	*-2.09 (0.272)*	*-2.06 (0.254)*
range	*-2.5 to -1,4*	*-2.5 to -1.5*	*-2.5 to -1.4*

At baseline (T0) the two groups are homogeneous

As shown in Table 1, the two groups are homogeneous with respect to the parameters evaluated at T0.

Table 2 shows the results relevant to the end of the treatment period (T10).

Figure 2

Table 2: Results at the End of the Treatment Period (T10)

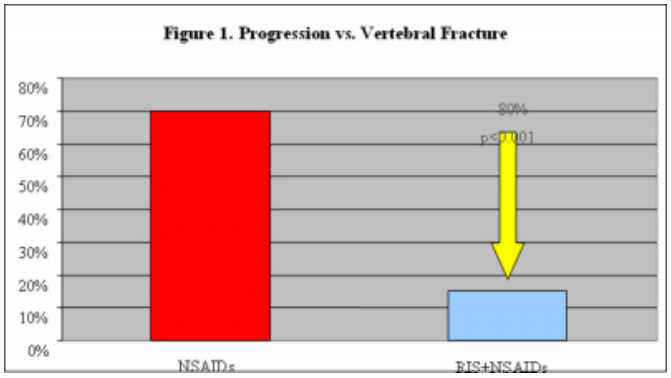
	RIS 5 mg + NSAIDs N=49	FANS alone N=47
≥15% Reduction of Vertebral Body's Height		
n/N (%)	*7/49 (14%)*	*33/47 (70%)*
RR (95 % CI)	*0.20 (0.10- 0.41)*	*--*
p	*<0.001*	*--*
Incidence of Kyphoplasty Intervention		
n/N (%)	*5/49 (10%)*	*25/47 (53%)*
RR (95 % CI)	*0.19 (0.08-0.46)*	*--*
p	*<0.001*	*--*

At T10 significant differences in favor of Group 1 for lower incidence of vertebral fractures and kyphoplasty intervention

As shown in Table 2 and Figure 1, the difference in progression of vertebral fracture is statistically significant between the two groups, with a risk reduction of vertebral fracture by 80% in Group 1 ($p<0.001$). Seven of 49 patients (14%) treated with RIS in combination with NSAIDs (Group 1) had a ≥15% reduction of the vertebral body's height compared with 70% of patients (33 out of 47) treated with NSAIDs alone (Group 2).

Figure 3

Figure 1: Progression vs. Vertebral Fracture – Differences between Group 1 (RIS+NSAIDs – blue bar) and Group 2 (NSAIDs – red bar)

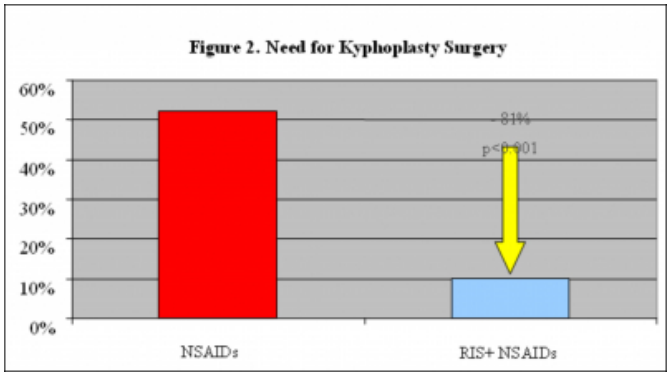


RIS indicates risedronate; NSAIDs, non-steroidal anti-inflammatory drugs

The need for kyphoplasty surgery was also highly reduced (RR=0.19) by RIS in combination with NSAIDs: only five patients (10%) had such intervention compared with 25 patients (53%) of Group 2. The difference between the two groups was statistically significant ($p<0.001$) with an 81% reduction in Group 1 (Table 2 – Figure 2).

Figure 4

Figure 2: Need for Kyphoplasty Intervention – Differences between Group 1 (RIS+NSAIDs – blue bar) and Group 2 (NSAIDs – red bar)



RIS indicates risedronate; NSAIDs, non-steroidal anti-inflammatory drugs

We did not observe significant differences between the two treatment groups a far as the incidence of side effects was concerned. Nor did we observe side effects not previously reported in studies with RIS and/or NSAIDs, alone or in association.

DISCUSSION

Osteoporosis and consequent fractures are, among elderly, one of the most common causes of mortality, with an incidence more or less overlapping that for stroke and breast cancer [21].

Also the economical implication of fracture is rather important. In particular, if we exclude wrist fractures whose epidemiological data available are probably underestimated, the consequences due to femoral fractures are very severe both in terms of morbidity and mortality (15-25% in the first year), accompanied by a major reduction in self-sufficiency (60%) with need of long term hospitalization [2, 3]. Also costs are quite high: the costs relevant to hospitalization alone and to the needed surgical interventions in 2001-2002 in Italy sum up to about half billion euros/year. This amount is similar to the one estimated by the International Osteoporosis Foundation [22] and higher by 20% than the costs for myocardial infarction [23].

As with wrist fractures, the epidemiological data on the incidence and prevalence of the vertebral fracture are also not really clear [7, 8], since this type of fracture is often accompanied by a silent symptomatology and there is no standardized morphometric definition. Although typically asymptomatic, the presence of vertebral fracture, especially if multiple, is associated with a reduction in quality of life due to the worsening of the physical and functional capacities that negatively affect normal daily life activities. Effects may include sleeping alterations, lack of appetite, and psychological disturbances such as anxiety, depression, reduced self-esteem, alteration of the social role [24,25,26]. With a different profile than femoral fractures, the mortality in the first year after a vertebral fracture overlaps that of the general population, while it statistically significantly increases in respect to non-fractured subjects after five years [10,11,12]. The annual cost of vertebral fractures is estimated around 4132,00 euros [14].

The above data clearly suggest that the objectives of the specialist are:

Early diagnosis both of osteoporosis and fractures: According to recent guidelines approved by the principal medical-scientific organizations [2], densitometry allows to measure, in a relatively accurate and precise way BMD. However, the therapeutic decision should be based also on other signs as bone quality (deterioration) and impaired remodeling. These factors have a negative influence on the

structural properties (microarchitecture) and on the properties of the bone materials (degree of mineralization, crystallinity, collagen).

In our study, we used vertebral morphometry that allows diagnosing and evaluating in an objective and reproducible way a vertebral fracture due to fragility. Moreover, the use of the semiautomatic software MorphoXpress® gave us the ability to perform the vertebral morphometry on a traditional radiogram with optimization of all the parameters needed for a correct diagnosis. The semiautomatic software MorphoXpress® was developed on more than 3000 available radiograms, examples of normal or altered vertebrae, analogical and digital, lumbar or thoracic drawn from the databases of the FEDRO and GIOVE studies [19, 20] and subsequently validated on a sample of 92 radiograms in lateral projection of the vertebral column, lumbar or thoracic randomly chosen between normal and fractured. This study showed an high accuracy of the system (2.1%) with a cumulative distribution of the error (cut-off ~2.5% on the vertebral width) without manual correction of the reference points by the radiologist.

Treating all patients with osteoporosis to prevent further fractures [27]: For people older than their 50s, the absolute risk of undergoing a new fracture within two years is about 11%. Of the total, 60% of new fractures occur in the first year and only 40% are observed in the second year [4]. Bisulfonates have a key role in the treatment of osteoporosis and are considered nowadays the first treatment choice. RIS and alendronate have shown anti-fracture efficacy in all types of fractures—vertebral, non-vertebral, and femoral—and have obtained the relevant indications in the in summary of product characteristics; while the clinical studies on ibandronate gave positive results only in vertebral fractures. In particular, RIS is so far the only bifosfonate that showed specific efficacy in the reduction of the femoral fractures in an ad hoc study in more than 9000 patients of only 6-month treatment duration [29]. For these reasons, RIS seems to be the bifosfonate with the most complete efficacy profile (data available from six months to seven years).

CONCLUSIONS

The results of our study gave us the possibility to identify a new clinical-diagnostic threshold, the vertebral pre-fracture [lumbar pain with the instrumental finding of 5-10% reduction of the height of at least one vertebral body of the lumbar region (L1-L5)] can be considered as a new marker of the evolution fracture potential in the patient with osteoporosis. In fact, in a 10-month period, we have demonstrated that the stage of fracture is observed in 70% of the patients treated with drugs that have no action on bone quality (NSAIDs). On the contrary, the early treatment with RIS (a bifosfonate of last generation with a complete anti-fracture efficacy profile) in association with NSAIDs in patients with a vertebral pre-fracture result in a reduction of the vertebral fracture risk by 80% in respect to patients treated with NSAIDs alone.

In view of the results obtained, we believe it is important to:

1. Intervene with drugs at a first-approach level at the stage of vertebral pre-fracture; these lesions are very often underestimated and not accurately considered. The careful evaluation of symptoms and the accuracy of the software MorphoXpress® are crucial to define this stage;

2. Use as prevention treatment a drug such as RIS that has shown an anti-fracture efficacy for all sites where osteoporotic fractures occur (vertebrae, femoral bone, other non-vertebral sites)

3. Start an adequate surgical approach (kyphoplasty) for the vertebral pre-fracture lesions, followed by an accurate monitoring.

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References

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser 1994;843:1-129.
2. Adami S, Nuti R. Linee Guida per la Diagnosi, Prevenzione e Terapia dell'Osteoporosi 2006 - SINOSSI - SIOMMMS (Società Italiana dell'Osteoporosis e delle Malattie del Metabolismo Minerale e Scheletrico).
3. Adami S, Giannini S, Giorgino R, Isaia G, Maggi S, Sinigaglia L, Filipponi P, Crepaldi G, Di Munno O. The effect of age, weight, lifestyle factors on calcaneal quantitative ultrasound: the ESOPO (Epidemiological Study On the Prevalence of Osteoporosis) study. Osteoporosis Int 2003;14:198-207.
4. Crepaldi G. L'invecchiamento nel XXI secolo. Atti del 2° Congresso Nazionale GISMO Napoli 9-11 febbraio 2006.
5. Maggi S, Noale M, Giannini G, Adami S, Defeo D, Isaia G, Sinigaglia L, Filippini P, Crepaldi G. Quantitative Ultrasound in a population-based study in Italy and its relationship with fracture history: the ESOPO study. Osteoporosis Int 2006;17:237-244.

6. Osteoporosi: Una Malattia Sociale - Sito web Ministero della Salute 21/10/2005.
7. Lunt M, Felsenberg D, Reeve J, Benevolenskaya L, Cannata J, Dequeker J, Dodenhof C, Falch JA, Masaryk P, Pols HA, Poor G, Reid DM, Scheidt-Nave C, Weber K, Varlow J, Kanis JA, O'Neill TW, Silman AJ. Bone density variation and its effects on risk of vertebral deformity in men and women studied in thirteen European centers: the EVOS Study. J Bone Miner Res 1997;12:1883-1894.
8. Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Delmas PD, Dequeker J, Dilsen G, Falch JA, Felsch B, Felsenberg D, Finn JD, Gennari C, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Marchand F, Masaryk P, Matthis C, Miazgowski T, Naves-Diaz M, Pols HA, Poor G, Rapado A, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, O'Neill TW.. Incidence of vertebral fracture across Europe: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int 2002 Jul;13:565-571.
9. Gehlbach SH, Bigelow C, Heimisdottir M, May S, Walker M, Kirkwood JR. Recognition of vertebral fracture in a clinical setting. Osteoporosis Int 2000;11:577-582.
10. Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, Delmas P, Falch JA, Felsch B, Hoszowski K, Johnell O, Diaz-Lopez JB, Lopez Vaz A, Marchand F, Raspe H, Reid DM, Todd C, Weber K, Woolf A, Reeve J, Silman AJ. Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). Osteoporosis Int 1998;8:291-297.
11. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O; European Vertebral Osteoporosis Study.. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the EVOS study. Osteoporosis Int 2003;14:61-68.
12. Kanis JA, Odén A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalization for vertebral fracture. Osteoporosis Int 2004;15(2):108-112.
13. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285(3):320-323.
14. Lindsay R, Burge RT, Strauss DM. One year outcomes and costs following a vertebral fracture. Osteoporos Int 2005;16(1):78-85.
15. NORA (National Osteoporosis Risk Assessment) study sounds alarm on risk of osteoporotic fractures. Dis Manag Advis 2002;8(2):17-21.
16. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785-795.
17. Pearson D, Horton B, Green DJ, Hosking DJ, Goodby A, Steel SA. Vertebral Morphometry by DXA: A Comparison of Supine Lateral and Decubitus Lateral Densitometers. J Clin Densitom 2006;9:295-301.
18. No Authors Listed. Behavioural modelling for design decomposition and design equations derivation. Osteoporosis Int 2006;17(Suppl 15):363-437.
19. Fracture Evaluation by Digital Radiographic Observational (FEDRO) Study, presented in Minneapolis 2003, American Society of Bone & Mineral Research Annual Meeting.
20. Angeli A, Guglielmi G, Dovio A, Capelli G, Defeo D, Giannini S, Giorgino R, Moro L, Giustina A. High Prevalence of asymptomatic vertebral fractures in post-menopausal women receiving chronic glucocorticoid therapy: A cross-sectional outpatient study. Bone 2006;39:253-259.
21. Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. How many women have osteoporosis? J Bone Miner Res 2005;20(5):886-892.
22. International Osteoporosis Foundation World Congress on Osteoporosis. Osteoporos Int 2002;13:A32-57.
23. Rossini M., Piscitelli P, Fitto F., Cambia P., Angeli A., Guida G., Adami S. Incidenza e costi delle fratture di femore in Italia. Reumatismo 2005;57:97-102.
24. Oleksik A, Lips P, Dawson A, Minshall ME, Shen W, Cooper C, Kanis J. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. J Bone Mineral Res 2000;15:1384-1392.
25. Adachi JD, Ioannidis G, Olszynski WP, Brown JP, Hanley DA, Sebaldt RJ, Petrie A, Tenenhouse A, Stephenson GF, Papaioannou A, Guyatt GH, Goldsmith CH. The impact of incident vertebral and non-vertebral fractures on health related quality of life in postmenopausal women. BMC Musculoskelet Disord 2002;3:11.
26. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S; Health-Related Quality of Life Subgroup of the Multiple Outcomes of Raloxifene Evaluation Study. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation. Study Arthritis Rheum 2001;44(11):2611-2619.
27. Documento sulla diagnosi e terapia dell'osteoporosi. Consiglio Superiore di Sanità 2003 - http://www.epicentro.iss.it/focus/osteoporosi/osteoporosi.htm.
28. Bouxsein ML, Kaufman J, Tosi L, Cummings S, Lane J, Johnell O. Recommendations for optimal care of the fragility fracture patient to reduce the risk of future fracture. J Am Acad Orthop Surg 2004;12(6):385-395.
29. Borah B, Ritman EL, Dufresne TE, Jorgensen SM, Liu S, Sacha J, Phipps RJ, Turner RT. The effect of risedronate on bone mineralization as measured by micro-computed tomography with synchrotron radiation: Correlation to histomorphometric indices of turnover. BONE 2005;37:1-9.

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