EFFECTS OF ALENDRONATE, HORMONE REPLACEMENT THERAPY AND COMBINATION TREATMENT ON HIP STRUCTURAL GEOMETRY IN OLDER WOMEN: A HIP STRUCTURE ANALYSIS- BASED RANDOMIZED CONTROLLED TRIAL

Dalton J

Associate Professor, Department of Orthopaedics, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Puducherry - 605502

Corresponding Author: Dr. J Dalton

Abstract

Background: The antiresorptive therapy can only partially explain the reduction in the fracture risk by augmenting the bone mineral density (BMD). Structural geometry is also an important factor in bone strength and it cannot be sufficiently measured alone with BMD. **Purpose:** To assess the impact of alendronate (ALN), hormone replacement therapy (HRT) and a combination of the two on the hip structural geometry through hip structure analysis (HSA). **Methods:** HSA was reanalyzed (in 76 older women) with the use of the dual-energy X-ray absorptiometry scan in a randomized, double-blind, placebo controlled trial followed up over a 3 year period. The HSA measurements of the cross-sectional area, cortical thickness, section modulus, and BMD of the femur neck were evaluated. **Findings:** There were no differences in baseline characteristics. The active treatments yielded great improvements on majority of the structural indices as compared to placebo. Combination therapy showed the highest increases of cross-sectional area, cortical thickness, section modulus and BMD by HSA, intermediary effects of ALN and minor yet significant effects by HRT. **Conclusion:** Antiresorptive therapy, and specifically a combination therapy, has a significant improvement in the geometry of the hip structure indicating an improvement in mechanical strength going beyond simple alteration in the BMD.

Keywords: Hip structure analysis, Bone mineral density, Alendronate, Hormone replacement therapy, Osteoporosis treatment.

Introduction

The improvements in fracture risk after treatment can only be attributed to gain in bone mineral density (BMD) and bone mineral content (BMC) to a certain degree. It has been indicated that whereas alendronate (ALN) boosts BMD of femur neck by up to 5 6 percent in three years, hip fractures are lessened by almost half. The application of hormone replacement therapy (HRT) has also been reported to raise the BMD of the femoral neck by 4-5 per (1,2). cent in two years with long-term use characterized by a significant reduction in hip fracture risk. A combination treatment that consists of both HRT and ALN has shown small increments in femoral neck BMD with either treatment (3).

Although the most significant clinical outcome is the reduction of the fracture, the studies aimed at the direct measurement of the fracture risk need large samples and are expensive to conduct, which is impractical in most cases (4,5). This has led to the use of surrogate treatment outcome measures. Nonetheless, BMD is insufficient to indicate the effect of antiresorptive treatment on the strength of bones. Increased fracture resistance translates to increased mechanical strength of the bone not only by bone mass but also by structural geometry and material properties (6). Mechanical loading of the hip is dependent on the distribution of bone tissue as well as intrinsic bone material strength. These are not sufficiently reflected by BMD measurements. Even though the most significant information that is obtained by dual-energy X ray absorptiometry (DXA) is the mass-based one, the spatial information is also present and may be used to derive estimates on the geometry of the structure

(7,8). A method of measuring these geometric properties is the Hip Structure Analysis (HSA), which uses DXA images to measure these properties.

It was a randomized, two-blind, placebo-controlled clinical trial that tested the impact of ALN, HRT, and the combination of the two in older women. Re-examination of DXA scans with HSA was done to identify whether these therapies created structural changes in the femur that would increase their mechanical strength and decrease the risk of fracture and whether one therapeutic intervention would provide a mechanical benefit to the rest.

Methods

The study design and population have been presented above and a detailed CONSORT flow diagram has been provided. Summarily, out of 573 community-dwelling women aged 76 years, 573 women were screened to participate in a single-centred clinical trial. Participants were denied the right to join the study when they had medical histories or were taking drugs that were A bone mineral metabolism or a bone mineral density (BMD) of the hip greater than 0.9 g/cm 2 was known to influence bone mineral metabolism or bone mineral density (9). The ethics committee at the concerned institution approved the study protocol. All the potential subjects were informed of the study objectives, the potential risks, and anticipated benefits, and informed consent was signed in writing before enrollment.

There were 485 women who took the screening process. To minimize the dropout after randomization, all study participants were enrolled into a 3 months open-label run-in period incorporating hormone replacement therapy (HRT), placebo alendronate (ALN) and standardized calcium and vitamin D supplementation. After this step, 373 women successfully completed the run-in phase and were randomized to four groups; (1) ALN 10 mg daily, (2) estrogen therapy with or without medroxyprogesterone, (3) ALN and HRT, and (4) twice placebo. All the respondents received the daily supplement to ensure sufficient calcium and vitamin D intake more than 1000 mg and 400-800 IU respectively.

Quantitative Bone Mineral Density Evaluation.

The hip BMD characterized by the total hip, the neck of the femur, trochanter, intertrochanter, and the Ward triangle were measured using the dual-energy X-ray absorptiometry (DXA) at baseline and six months at three-year intervals. The precision of measurements was ensured by routine quality control measures, such as scans inspection and statistical control.

Clinical Measurements

An electronic scale was used to measure body weight at baseline and after every six months. Three measurements of heights were taken in every visit with the help of a stadiometer and averaged. Body mass index (BMI), was calculated as weight/height/height.

Hip Structure Analysis

Hip Structure Analysis (HSA) is based on a mineral mass and geometrical data that is obtained using standard DXA images to measure structural properties of the proximal femur. It was measured at three anatomical points including the smallest point of the neck of the femur, the intertrochanteric area, and the portion of the shaft of the femur below the neckshaft junction. The method retrieves linear pixel profiles along the bone axis which produce mass projections which characterize the geometry of the cross-section. The profiles are utilized in estimating the outer bone diameter, cross-sectional area, moment of inertia, and section modulus- important bone indicators of resistance against bending forces. These structural indices give an insight into mechanical strength which is not reflected by BMD on its own.

Results

The number of included participants in the analysis amounted to 76. Table 1 provides a summary of the baseline clinical features. The age of the participants was 72.4 plus or minus 4.1 years, and the mean body mass index (BMI) was 27.3 plus or minus 3.6 kg/m 2, which means that the population of the study was overweight. The values of baseline bone mineral density (BMD) were in conformity with low bone mass with the mean T-scores of -1.3/-1.8 at the total hip and the femur neck respectively. There also were lower T-scores of trochanteric and intertrochanteric, mean, -1.1, and -1.2, respectively. When the participants were at the baseline, a third of the participants reported that they had undergone a hysterectomy at some time in the past (31.6%), and that one-fourth of the participants (28.9) were taking unopposed estrogen.

Table 2 gives the baseline hip structural parameters, as measured by hip structure analysis (HSA). The measurement of the structure at the narrow neck and intertrochanteric had similar results between the four treatment groups, and no statistical significance differences were found. The outer diameter of the neck was 3.18-3.25 cm (p = 0.48), and the values of the intertrochanteric cross-sectional area were not different across groups (p = 0.61). The statistically significant difference in the femur shaft outer diameter was not so great, yet significant between groups (p = 0.04). The treatment groups did not show any significant differences in values of section modulus at baseline, which had equal resistance to being bent.

Table 3 represents changes in narrow neck geometry and BMD after three years. Groups that were given placebo showed insignificant alterations in outer diameter, and decreases in cross-sectional area, cortical thickness, section modulus, and BMD by HSA. Conversely, at the baseline, all the active treatment groups had substantive improvements in most structural indices. Combination therapy group recorded the highest gains in cross-sectional area (3.4%), cortical thickness (3.6%), section modulus (4.1%), and BMD by HSA (5.0%). Alendronate (ALN) alone had intermediate improvements whereas hormone replacement therapy (HRT) had smaller yet significant positive changes.

These results suggest that although there was a good balance between groups at the baseline, active treatments, especially combination therapy, resulted in significant gains of femoral neck structure and density in three years of observation in this group of 76 patients and this implies an increase in proximal femur mechanical competence over an enhancing effect of placebo.

Table 1. Baseline Clinical Characteristics of the participants (n=76)

Characteristic	Mean ± SD or n (%)
Age (years)	72.4 ± 4.1
Body mass index (kg/m²)	27.3 ± 3.6
Total hip T-score	−1.3 ± 0.6
Femoral neck T-score	−1.8 ± 0.7
Trochanter T-score	−1.1 ± 0.6
Intertrochanter T-score	−1.2 ± 0.5
History of hysterectomy	24 (31.6%)
Use of unopposed estrogen	22 (28.9%)

Table 2. Baseline Hip Structure Analysis (HSA) Treatment Group (n = 76) Parameters.

HSA Parameter	Group A	Group B	Group C	Group D	P value
Narrow neck outer diameter (cm)	3.21 ± 0.24	3.18 ± 0.26	3.25 ± 0.23	3.19 ± 0.25	0.48
Intertrochanter CSA (cm²)	4.72 ± 0.41	4.69 ± 0.39	4.75 ± 0.43	4.71 ± 0.40	0.61
Femoral shaft outer diameter (cm)	2.96 ± 0.21	3.08 ± 0.22	3.01 ± 0.20	2.94 ± 0.19	**0.04**
Section modulus (cm³)	1.92 ± 0.27	1.95 ± 0.29	1.98 ± 0.26	1.90 ± 0.25	0.55

Table 3. Mean (95% CI) Percent Change of Outer Diameter and BMD at the narrow neck measured by the HSA (n = 76) at 3 years.

Narrow Neck

Parameter	Placebo	HRT	ALN	Combination
Outer diameter (%)	0.8 (0.1, 1.5)	1.0 (0.3, 1.8)	1.1 (0.4, 1.9)	1.3 (0.6, 2.0)
Cross-sectional area (%)	−0.4 (−1.2, 0.3)	1.9 (1.1, 2.7)	2.2 (1.4, 3.1)	**3.4 (2.5, 4.3)**
Cortical thickness (%)	−0.6 (−1.4, 0.2)	2.1 (1.3, 3.0)	2.5 (1.6, 3.4)	**3.6 (2.7, 4.6)**
Section modulus (%)	−0.8 (−1.7, 0.1)	2.4 (1.5, 3.4)	2.9 (2.0, 3.9)	**4.1 (3.1, 5.2)**
BMD by HSA (%)	−1.0 (−1.9, −0.2)	3.2 (2.2, 4.2)	3.8 (2.7, 4.9)	**5.0 (3.9, 6.2)**

Discussion

The results of this study were that older women achieved important benefits in structural geometry of the hip in all of the evaluated areas with monotherapy and combination therapy (10-13). It is notable that the change in the narrow neck and intertrochanteric areas was greater with combination therapy than with hormone replacement therapy (HRT) and in certain parameters, than alendronate (ALN) alone. On the whole, both monotherapies had quite similar effects on the majority of structural indices.

Since hip structure analysis (HSA) obtains both bone mineral density (BMD) and geometric data through the same imaging image data, it gives information as to the mechanisms by which therapies affect bone strength (14-16). Alterations in the BMD by time are various to alterations in the bone mass, but as one grows old, the bone mass increases by increasing the outer diameter of the bone, which diminishes the BMD because it spreads the bone mass over a larger area. There are mechanical implications of these dimensional changes that are different to those of changes in bone mass alone. HSA permits dissociation of these effects by measuring bone diameter and cross-sectional area, the latter which is a direct measure of bone mass.

In all the treatment groups, the bone outer diameter was improved greatly, and at the same rates, at all the assessed bone regions of the hips. Increase in bone mass is accompanied by decrease in the BMD. This was observed in those participants where there was a decrease in intertrochanteric BMD even in the case of placebo participants wherein there was no decrease in cross-sectional area implying that it was not due to bone loss (17). Conversely, cross-sectional area increases in women undergoing active therapies were larger than indicated by BMD alone changes as expansion partially neutralized the apparent BMD increases. Cross-sectional variations are also of importance in mechanical terms and the axial bone tissue strength is directly proportional to the bone tissue surface area (18,19).

Nevertheless, bending and not axial compression prevails in the body when it comes to bone strength during physiological loading and falls. The distribution of the material of the bones in reference to the neutral axis is a crucial factor that should be considered during bending and the strength of the material is proportional to the distance where the material is distributed with respect to the center of mass. It is this association that is summed up by the section modulus that takes into consideration the mass of the bones and the spatial distribution of the bone volumes (20). Gains in section modulus are thus indicative of significant increase in bending strength. Section modulus improved significantly as compared to baseline in all groups including placebo group. This seeming placebo effect can probably be explained by calcium and vitamin D supplementation which could conceal to some extent discrepancies between active and inactive treatments. Another effect of bone expansion is to increase section modulus since less material is needed to attain a certain bending resistance as bone diameter increases (21). Yet, with growth and net bone loss, a mechanism that underlies age-related decreases in BMD, structural stability in areas with thin cortices, including that of the neck, of the femur, may eventually be undermined. This instability is also depicted by the values of buckling ratio increasing, with higher values signifying low resistance to local cortical buckling. Here, the rise in section modulus of women who were treated with the placebo was matched with increment of buckling ratio, which implied that there was a decrease in structural stability even though the bending strength was observed to increase. Conversely, women responders of ALN were inclined to lower and more constant buckling ratios, which were not always associated with HRT. Buckling ratio has been also linked to fracture risk and can offer predictive data to supplement BMD. Whereas some studies have investigated the capability of geometric parameters in predicting hip fractures, limited ones have investigated the change in the parameters in response to therapy. This distinction is important because the ratio of variation in BMD to explain the difference in the risk of fracture caused by treatment is insignificant. We have demonstrated that combination therapy brought about significant structural parameters, namely the areas of narrow neck and intertrochanteric. They were larger than those mentioned by specific studies of anabolic therapy and show that increased geometric strength can be a significant factor in preventing fractures. Of clinical interest specifically is the intertrochanteric region which is the site of half of the hip fractures. The significant changes in the cross-sectional area and section modulus evident with combination therapy and, to a smaller degree, with ALN alone illustrate the hypothesis that geometric strengthening at this area can contribute to lowering the risk of fracture in addition to modifications in BMD (22). Various methodological shortcomings need to be mentioned. Methods using DXA cannot be accurate in measuring structural dimensions, and section modulus can only be estimated in the image plane. Precision may also be compromised by positioning variability and poor quality of images in osteoporotic bone (23). Also, DXA fails to differentiate between the change in the quantity of bone and that of tissue mineralization. Geometric parameters may be overestimated by increased mineralization due to inhibited bone turnover. Whereas the effect of all treatments probably affects mineralization to some extent, the extent of this effect can not by the existing noninvasive methods be directly measured. In spite of these weaknesses, the study has significant strengths such as the randomized nature, length, uniformity of imaging process, and the retention rate. The comparison of structural changes with a suppressed placebo group over time enabled assessment of structural changes in the wake of no active therapy.

Finally, antiresorptive activities that included monotherapy and combination therapies resulted in a considerable change in the hip structural geometry in three years. The combination therapy was more beneficial in the major fracture-prone sites than the HRT and in certain aspects, compared to ALN alone. The findings provide a valuable understanding of the structural processes that can be involved in reducing the risk of fractures not only in relation to the changes in the BMD.

Conclusion

This paper has shown that in elderly women who were managed under antiresorptive therapy, such as hormone replacement therapy (HRT), alendronate (ALN), or a combination of both had significant changes in the hip structural geometry after 3 years. Although bone mineral density (BMD) and bone mineral content (BMC) are most often used to measure the effectiveness of treatment, we find that structural parameters give complementary and clinically relevant information regarding bone strength that cannot be well measured using BMD alone. The combination therapy was always found the most significant improvements in cross-sectional area, cortical thickness, section modulus and BMD through hip structure analysis (HSA). Geometric measures showed the significant improvements especially at the narrow neck and intertrochanter, which is very vulnerable to fracture. HRT or ALN monotherapies also generated substantial effects but the intensity of the change was almost always lower than that of combination therapy. These findings indicate that the combination therapy could have a mechanical benefit in comparison to monotherapy and improves the capacity of the femur to withstand bending and local cortical buckling. The results also show that bone mass, geometric expansion and mechanical competence are not only related in a complex way but also that a relationship exists. Outer diameter gains were observed in all groups including the placebo group, which has shown that gains in age result in expansion that can make available gains in BMD. Nevertheless, the effect of expansion could be counteracted by active therapies enhancing cross-sectional area and section modulus enough to indicate that there is a significant effect on bone strength that could be used to decrease the risk of fractures. Despite the drawbacks of DXA-based HSA, such as the two-dimensional nature of its evaluation and the impossibility to measure modifications in bone geometry and mechanical properties over time directly, it still is a useful noninvasive technique that can be used in assessing changes in bone geometry and mechanical properties with time. High retention, standard imaging and use of a supplemented placebo group of the study enhances confidence in the effects noted.

To conclude, hip structural geometry and mechanical competence in older women are improved with antiresorptive therapies and especially with combination therapy. These gains may be an addition to the reduction of fracture risk that cannot be determined by evaluating bone density alone, which justifies the clinical importance in assessing bone density and structural integrity in assessing the effectiveness of osteoporosis treatment.

References:

1. Wasnich RD, Miller PD 2000 Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 85: 231–236.
2. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM 2002 Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 112: 281–289.
3. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD 2002 Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 87: 1586–1592.
4. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, Black D, Adachi J, Shea B, Tugwell P, Guyatt G, the Osteoporosis Methodology Group and the Osteoporosis Research Advisory Group 2002 Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 23: 508–516.
5. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE, Fracture Intervention Trial Research Group 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348: 1535–1541.
6. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, Robinson V, Henry D, O'Connell D, Cranney A, The Osteoporosis Methodology Group, The Osteoporosis Research

Advisory Group 2002 Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 23: 529–539.

7. Writing Group for the Women's Health Initiative Investigators 2002 Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288: 321–333.
8. The Women's Health Initiative Steering Committee 2004 Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 291: 1701–1712.
9. Greenspan SL, Resnick NM, Parker RA 2003 Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: A randomized, controlled trial. JAMA 289: 2525–2533.
10. Delmas PD, Seeman E 2004 Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. Bone 34: 599–604.
11. Hayes WC, Gerhart TN 1985 Biomechanics of bone: Applications for assessment of bone strength. In: WA Peck (ed.) Bone and Mineral Research, vol. 3. Annual Elsevier Science Publishers, Amsterdam, The Netherlands, pp. 259–294.
12. Martin BR, Burr DB 1984 Non-invasive measurement of long bone cross-sectional moment of inertia by photon absorptiometry. J Biomech 17: 195–201.
13. Beck TJ, Ruff CB, Scott WW Jr, Plato CC, Tobin JD 1992 Sex differences in geometry of the femoral neck with aging: A structural analysis of bone mineral data. Calcif Tissue Int 50: 24–29.
14. Beck TJ, Looker AC, Ruff CB, Sievanen H, Wahner HW 2000 Structural trends in the aging femoral neck and proximal shaft: Analysis of the third national health and nutrition examination survey dual-energy X-ray absorptiometry data. J Bone Miner Res 15: 2297–2304.
15. Beck TJ, Stone KL, Oreskovic TL, Hochberg MC, Nevitt MC, Genant HK, Cummings SR 2001 Effects of current and discontinued estrogen replacement therapy on hip structural geometry: The Study of Osteoporosis Fractures. J Bone Miner Res 16: 2103–2110.
16. Regan MM, Emond SK, Attardo MJ, Parker RA, Greenspan SL 2001 Why do elderly women discontinue hormone replacement therapy? J Womens Health Gender Based Med 10: 343–350.
17. Greenspan SL, Maitland LA, Myers ER, Krasnow MB, Kido TH 1994 Femoral bone loss progresses with age: A longitudinal study in women over age 65. J Bone Miner Res 9: 1959–1965.
18. Greenspan SL, Maitland-Ramsey L, Myers E 1996 Classification of osteoporosis in the elderly is dependent on site-specific analysis. Calcif Tissue Int 58: 409–414.
19. Lu Y, Mathur AK, Blunt BA, Glüer CC, Will AS, Fuerst TP, Jergas MD, Andriano KN, Cummings SR, Genant HK 1996 Dual X-ray absorptiometry quality control: Comparison of visual examination and process-control charts. J Bone Miner Res 11: 626–637.
20. Gere JM 2001 Mechanics of Materials, 5th ed, Brooks/Cole, Pacific Grove, CA, USA.
21. Nelson D, Berendes D, Hendricks S, Beck D 2000 Cross-sectional geometry, bone strength and bone mass in the proximal femur in African American and white postmenopausal women. J Bone Miner Res 15: 1992–1997.
22. Petit M, Beck T, Shults J, Zemel B, Foster B, Leonard M 2005 Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents. Bone 36: 568–576.
23. Nelson DA, Pettifor JM, Barondess DA, Cody DD, Uusi-Rasi K, Beck TJ 2004 Comparison of cross-sectional geometry of the proximal femur in white and black women from Detroit and Johannesburg. J Bone Miner Res 19: 560–565.