



ASSESSMENT OF PROXIMAL FEMUR BONE DENSITY AND GEOMETRY BY DXA IN JAPANESE PATIENTS TREATED WITH RISEDRONATE

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ABSTRACT

Hip structure analysis (HSA) and advanced hip assessment (AHA) can be used to evaluate proximal femur geometry based on dual energy X-ray absorptiometry scans of the hip. The purpose of this review was to reveal the effects of 1-year risedronate therapy on proximal femur bone mineral density (BMD) and geometry in Japanese patients with an increased risk for fractures. The relevant literature was searched using PubMed and two available clinical practice-based observational studies were identified. The HSA study revealed that the BMD increased at the intertrochanter and shaft, the cross-sectional area (CSA) and section modulus increased at the narrow neck, intertrochanteric, and shaft and the buckling ratio decreased at the intertrochanteric. The increase in section modulus was greater than the increase in BMD. The AHA study revealed that the total hip and femoral neck BMD, CSA, cross-sectional moment of inertia (CSMI), and femoral strength index (FSI) of the proximal femur increased. The increases in CSMI, CSA, and FSI were greater than the increases in femoral neck and total hip BMD. These results suggested beneficial effects of risedronate therapy on proximal femur geometry assessed by HSA and AHA in Japanese patients with an increased risk for fractures, indicating positive effects of risedronate on the structural properties in terms of bone quality.

Keywords: Risedronate; Geometry; Bone mineral density; advanced hip assessment (AHA); Hip structure analysis (HSA); proximal femur.

INTRODUCTION

Osteoporosis is a skeletal disease characterized by a decrease in bone strength and an associated increase in the risk for fractures [1]. The strength of bone depends on two factors, namely the bone density and bone quality [1]. Therefore, maintaining not only the bone mineral density (BMD) but also the bone quality may be important for the prevention of fractures. Bone quality depends on both structural and material factors, with structural factors including the macroscopic trabecular structure of cancellous bone and the porosity of cortical bone, and material factors including the extent of calcification, crystal size, collagen content, and microdamage [1].

Risedronate has been widely used as a first-line drug for the treatment of osteoporosis, because current data obtained according to the principles of evidence-based medicine suggest that it is both safe and effective for osteoporosis in postmenopausal women and men [2-6]. In particular, the Hip Intervention Program Study showed a significant reduction in the risk of hip fractures after 3 years of risedronate therapy among elderly women with osteoporosis [4].

In recent years, clinical assessment of bone geometry and microstructure has become possible because of marked progress in imaging technologies. Hip structure analysis (HSA) can be used to measure proximal femur geometry based on conventional dual energy X-ray absorptiometry (DXA) scans of the hip [7,8]. Software for advanced hip assessment (AHA) can be incorporated into DXA systems (Prodigy Advance; GE Healthcare, Madison, WI, USA) to noninvasively determine the structural geometry of the proximal femur [9]. HSA- and AHA-based analyses can be employed to assess the structural geometry in terms of bone quality. Thus, assessing the effects of risedronate on parameters of bone quality (structural geometric properties) as well as BMD could provide more evidence about the mechanism by which this drug prevents hip fractures. The purpose of this review was to reveal the effects of risedronate therapy on proximal femur BMD and geometry in Japanese patients with an increased risk for fractures.

Search of Studies:

To assess the effects of risedronate therapy on BMD and geometry of the proximal femur, PubMed was used to search the literature for studies regarding risedronate therapy and proximal femur BMD and geometry in Japanese patients with an increased risk for fractures. The following terms were used: risedronate; hip structure analysis (HSA); advanced hip assessment (AHA); and Japan. Non-English papers were excluded.

Identified Studies:

In total, four clinical practice-based observational studies were identified. No randomized controlled trials (RCTs) were found. One study showed the effects of 1-year risedronate therapy (17.5 mg weekly) on 181 Japanese women with osteoporosis (mean age: 70.6 years) using HSA. [10] The other studies showed the effects of 4-month, 1-year, and 3-year risedronate therapy (2.5 mg daily; 17.5 mg weekly) on 174 Japanese patients (9 men and 165 women; mean age: 67.8 years) with osteoporosis or osteopenia and clinical risk

factors for fractures using AHA. [11–13] The 3-year study [13] was an extension of the 4-month and 1-year studies. [11,12] Two of the studies, namely the 1-year studies using HSA and AHA, were processed for analyses.

According to the Japanese diagnostic criteria, [14,15] patients with a BMD <70% of the young adult mean (YAM) or 70–80% of the YAM together with a history of osteoporotic fracture were diagnosed as having osteoporosis, while patients with a BMD of 70–80% of the YAM and no history of osteoporotic fracture were diagnosed as having osteopenia. Patients with osteoporosis or osteopenia and at least one of the clinical risk factors for fractures are recognized to have a high risk of fractures and need to be treated with anti-fracture medicines. The clinical risk factors for fracture included current smoking, maternal history of hip fracture, alcohol intake of =2 units daily, age =75 years, lean physique (body mass index =18.5 kg/m²), and history of steroid use.

All patients were treated with risedronate (2.5 mg daily; 17.5 mg weekly). Previous studies have shown that the daily and weekly doses of risedronate used in the above studies were effective for Japanese patients. [17,18] The effects of daily and weekly risedronate on the BMD and bone turnover markers as well as the incidence of side effects were reported to be similar in postmenopausal Japanese women with osteoporosis. [18]

Hip Structure Analysis Hip (HSA):

The BMD and geometry parameters of the proximal femur were measured by DXA. Three measured sites were defined as follows (Figure 1): (1) narrow neck, traversing the narrowest width of the femoral neck; (2) intertrochanter, along the bisector of the shaft and femoral neck axes; and (3) shaft, at a distance of 1.5 times the minimum neck width, distal to the intersection of the neck and shaft axes. The outer diameter, cross-sectional area (CSA), section modulus, average cortex, and buckling ratio were assessed by the HSA method. [19,20] The outer diameter was defined as the distance (blur-corrected) between the outer margins of the cross-section. The CSA was defined as the surface area of bone tissue in the cross-section after excluding the soft tissue (marrow) spaces. The CSA is an index of resistance to forces directed along the long axis of the bone. The cross-sectional moment of inertia (CSMI) was measured directly from the mineral mass distributions using algorithms. [21,22] The section modulus is an index of resistance to bending forces, and was calculated as $CSMI/d_{max}$, where d_{max} is the maximum distance from either bone edge to the centroid of the profile. The average cortex is an estimate of the mean cortical thickness assuming a circular (narrow-neck or shaft) or elliptical (intertrochanter) annulus model of the cross-section for use in the estimated buckling ratio. The model assumes that 60%, 70%, and 100% of the measured bone mass is in the cortex for the narrow neck, intertrochanter, and shaft, respectively. The buckling ratio describes stable configurations of thin-walled tubes subjected to compressive loads, and is estimated as the ratio of d_{max} to the estimated mean cortical thickness. The buckling ratio is presented only for the narrow-neck and intertrochanter regions.

The precision errors (coefficients of variation) for the HSA parameters at the neck, intertrochanter, and shaft ranged from 0.8–4.7%, with an average of 2.2%.

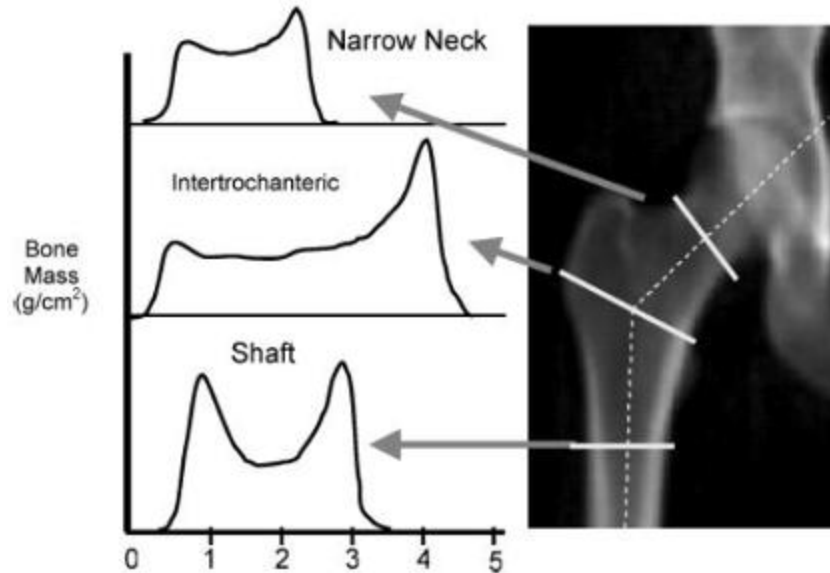


Figure 1: Hip structure analysis (HSA) of the proximal femur

Advance Hip Assessment (AHA):

The BMD and geometry parameters of the proximal femur (neck and total) were measured by DXA with a Prodigy Advance (GE Healthcare). The CSMI, CSA, and femoral strength index (FSI) were assessed using software for AHA incorporated into the DXA system (Figure 2). [9] The CSA was defined as the surface area of bone in a cross-section after excluding the soft tissue (marrow), and was derived from the integral of the bone mass profile. The CSA is an index of resistance to force directed along the long axis of the bone. The CSMI was calculated as the integral of the bone mass profile [23, 24] across the bone weighted by the square of the distance from the center of gravity. The FSI was defined as the ratio of the estimated compressive yield strength of the femoral neck to the expected compressive stress applied by falling on the greater trochanter. Thus, $FSI = \text{strength}/\text{stress}$, where $\text{strength} = 185 - 0.34 * (\text{age} - 45)$ for patients aged >45 years or 185 for those aged =45 years and $\text{stress} = \text{moment} * y / \text{CSMI} + \text{force} / \text{CSA}$. $\text{Moment} = d1 * 8.25 * \text{weight} * 9.8 * (\text{height} / 170)^{1/2} * \cos(180^\circ - \theta)$, $\text{force} = 8.25 * \text{weight} * 9.8 * (\text{height} / 170)^{1/2} * \sin(180^\circ - \theta)$, $d1$ = distance along the neck axis from the center of the femoral head to the section of minimum CSMI, y = distance from the center of gravity to the upper neck margin along the section of minimum CSMI, and θ = angle of the intersection between the neck and shaft axes. [9] As the FSI increases, the risk of hip fracture due to a fall on the greater trochanter decreases. [9]

The short-term precision was determined by duplicate measurements with repositioning between each scan. The precision error (coefficient of variation) of the BMD ranged from 0.7–2.2% for the proximal femur. [25,26] The precision errors of the femur strength variables ranged from 3.6–4.1% for the CSMI, 1.7–2.8% for the CSA, and 1.9–2.6% for the FSI. [25]

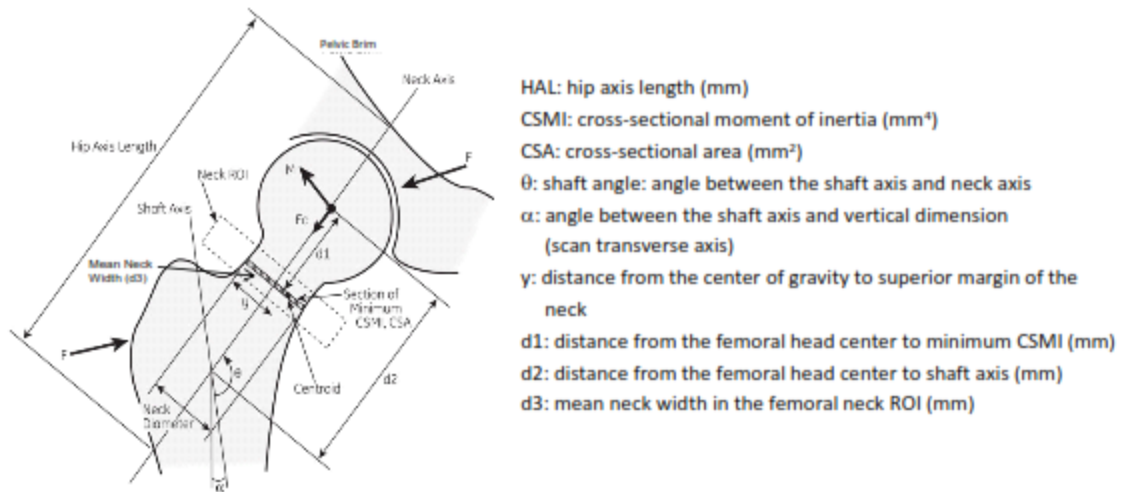


Figure 2: Advanced hip assessment (AHA) analysis of the proximal femoral geometry

RESULTS

Effects of risedronate therapy on BMD and HSA parameters (Figure 3) [10]

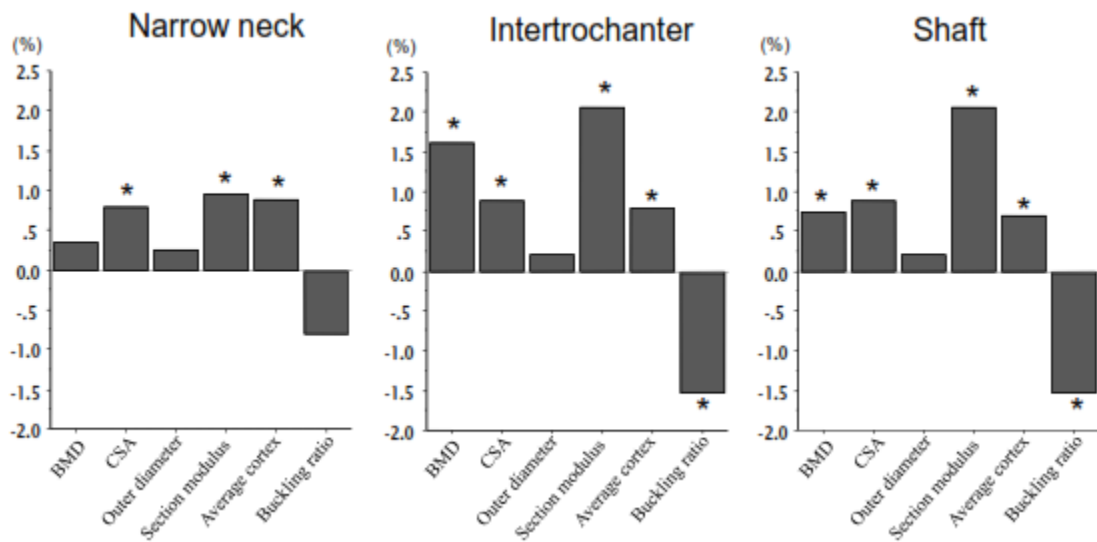
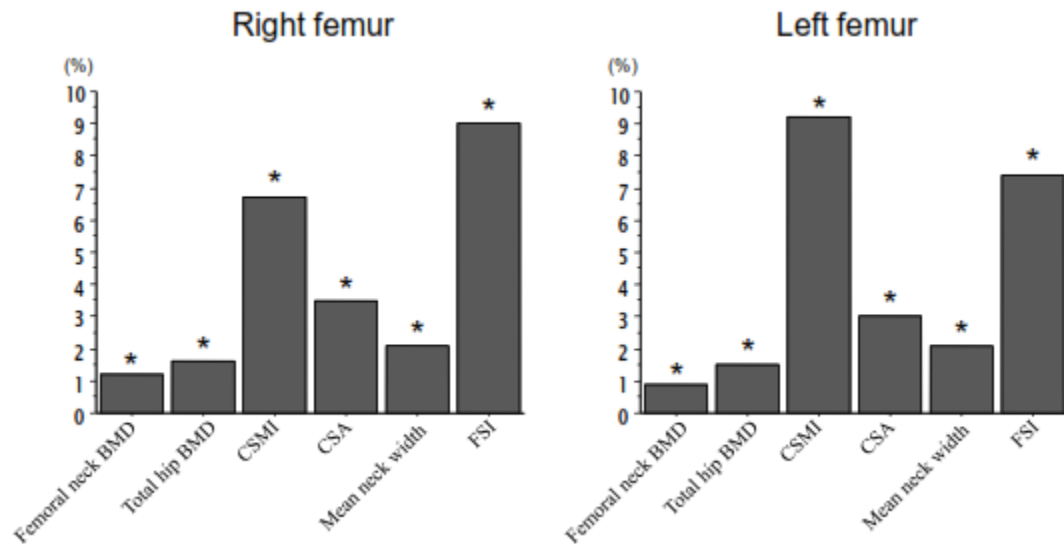


Figure 3: Mean changes in parameters assessed by HSA

The CSA, section modulus, and average cortex were significantly increased at the narrow neck. The BMD was slightly increased, but the increase was not significant. The BMD, CSA, section modulus, and average cortex were significantly increased, and the buckling ratio was significantly decreased at the intertrochanter. The BMD, CSA, section modulus, and average cortex were significantly increased at the shaft. The increase in section modulus was greater than the increase in BMD at the intertrochanter and shaft. The section modulus increased, but the BMD was not significantly increased at the narrow neck.

Effects of risedronate therapy on BMD and AHA parameters (Figure 4)**Figure 4:** Mean changes in parameters assessed by AHA

The right and left femoral neck and total hip BMD was significantly increased. The right and left CSMI, CSA, mean neck width, and FSI were significantly increased. The [12, 13] increases in CSMI and FSI were greater than the increases in the femoral neck and total hip BMD.

DISCUSSION

Two clinical practice-based observational studies were identified with respect to the effects of 1-year risedronate therapy on proximal femur BMD and geometry in Japanese patients with an increased risk for fractures. One study clarified the effects of 1-year risedronate therapy among postmenopausal women with osteoporosis using HSA, and the other revealed the effects of 1-year risedronate therapy among patients with osteoporosis or osteopenia and clinical risk factors for fractures using AHA. In the former study, the BMD at the intertrochanter and shaft, and the CSA and section modulus at the narrow neck, intertrochanter, and shaft were increased, and the buckling ratio at the intertrochanter was decreased. [10] In the latter study, the total hip and femoral neck BMD and proximal femur CSMI, CSA, and FSI were increased. [13]

The increase rates in the BMD, CSA, section modulus, and average cortex after 1-year risedronate therapy in the HSA study were 0.35–1.61%, 0.80–0.88%, 0.95–2.05%, and 0.79–0.89%, respectively. [10] The increase rates in the total and femoral neck BMD, CSMI, CSA, and FSI after 1-year risedronate therapy in the AHA study were 1.5–1.6%, 0.9–1.2%, 6.7–9.2%, 3.0–3.5%, and 7.4–9.0%, respectively. The effectiveness of risedronate therapy should be evaluated using the least significant change (LSC) of each parameter measured by DXA. The LSC represents the smallest difference between successive measurements of BMD that can be considered to be a real change and not attributable to chance. The LSC is derived from same-day in vivo BMD precision measurements. [27] The precision errors (coefficients of variation) for the HAS parameters at the

neck, intertrochanter, and shaft ranged from 0.8–4.7%, with an average of 2.2%. [23,24] The precision errors (coefficients of variation) for the AHA parameters ranged from 0.7–2.2% for the proximal femur BMD, 3.6–4.1% for the CSMI, 1.7–2.8% for the CSA, and 1.9–2.6% for the FSI. [25,26] Since AHA is based on the same concept as HAS, [28] it could be useful to evaluate the effects of anti-fracture therapy on the proximal femur geometry. However, it is certain that the increases in proximal femur CSMI, CSA, and FSI after 1-year risedronate therapy overwhelmed their LSCs in the AHA study, suggesting beneficial effects of risedronate therapy on geometry parameters [13] [10] [12,13] in Japanese patients with an increased risk for fractures.

The increase in section modulus after 1-year risedronate therapy was greater than the increase in BMD in the HSA study, [10] and the increases in CSMI, CSA, and FSI after 1-year risedronate therapy were greater than the increases in femoral neck and total hip BMD in the AHA study. [13] The changes in CSA and CSMI with risedronate therapy might be explained by the suppression of endocortical bone resorption. The FSI is the ratio of the estimated compressive yield strength of the femoral neck to the expected compressive stress applied by falling on the greater trochanter. Therefore, as the FSI increases, the risk of hip fracture from a fall on the greater trochanter declines. The beneficial effects of risedronate therapy for 1 year on the structural geometry as well as the BMD of the proximal femur support the efficacy of risedronate against hip fracture. [4]

One-year risedronate therapy decreased the buckling ratio by 1.53% at the intertrochanter in the HSA study. [10] The buckling ratio is estimated as the ratio of d to the estimated mean cortical thickness, where d is the maximum distance from either bone edge to the centroid of the profile. [19,20] Thus, the decrease in buckling ratio with risedronate therapy might be primarily explained by the suppression of endocortical bone resorption. However, this change might not be clinically significant considering the LSC. Thus, a longer duration of observation is needed to find an adequate change in buckling ratio among patients treated with risedronate.

Some limitations of this study should be noted. First, although HSA and AHA allow calculation of the bone geometry from DXA scans, we should keep in mind that DXA images are obtained from the mineral distribution pattern, and therefore the calculated geometric parameters do not necessarily reflect the true bone geometry. Second, because clinical practice-based observational studies were analyzed, there was no placebo control group, and the results might have been biased. Accordingly, a large-scale RCT would be needed to confirm the results of these two clinical practice-based observational studies.

In conclusion, both the HSA and AHA studies showed some positive effects of 1-year risedronate therapy on BMD and geometry parameters at the proximal femur in Japanese patients with an increased risk for fractures. The HSA study revealed that the increases in section modulus at the narrow neck, intertrochanter, and shaft were greater [9] than the increase in BMD, while the AHA study revealed that the increases in CSMI, CSA, and FSI were greater than the increases in femoral neck and total hip BMD. These results suggested beneficial effects of risedronate therapy on proximal femur geometry in terms of bone quality in patients with an increased risk for fractures.

DISCLOSURE

The authors have no funding sources. Yoshinori Suzuki is the product manager of Eisai Co. Ltd., Tokyo, Japan, who deals with risedronate.

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