# Challenges of Estimating Fracture Risk with DXA: Changing Concepts About Bone Strength and Bone Density

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**INTRODUCTION:** Bone loss due to weightlessness is a significant concern for astronauts' mission safety and health upon return to Earth. This problem is monitored with bone densitometry (DXA), the clinical tool used to assess skeletal strength. DXA has served clinicians well in assessing fracture risk and has been particularly useful in diagnosing osteoporosis in the elderly postmenopausal population for which it was originally developed. Over the past 1–2 decades, however, paradoxical and contradictory findings have emerged when this technology was widely employed in caring for diverse populations unlike those for which it was developed. Although DXA was originally considered the surrogate marker for bone strength, it is now considered one part of a constellation of factors–described collectively as bone quality–that makes bone strong and resists fracturing, independent of bone density. These characteristics are beyond the capability of routine DXA to identify, and as a result, DXA can be a poor prognosticator of bone health in many clinical scenarios. New clinical tools are emerging to make measurement of bone strength more accurate. This article reviews the historical timeline of bone density measurement (dual X-ray absorptiometry), expands upon the clinical observations that modified the relationship of DXA and bone strength, discusses some of the new clinical tools to predict fracture risk, and highlights the challenges DXA poses in the assessment of fracture risk in astronauts.

**KEYWORDS:** Bone density, bone strength, bone quality, astronauts, fracture risk, DXA, space medicine, weightlessness, probabilistic risk assessment, digital astronaut.

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Bone loss from weightlessness is a major concern for fracture risk of astronauts on mission and upon their return to Earth. This problem is identified by using dual energy X-ray absorptiometry (DXA), the technology that changed the medical landscape for diagnosing osteoporosis and fracture risk because it could identify bone deficiency years before it was visible on a standard skeletal X-ray.[56] DXA was originally developed to assess the risk of fractures from osteoporosis in a very specific population of patients, namely postmenopausal, elderly, Caucasian women in whom the incidence of this disease was quite high.[45] It provided an estimate of bone mineral density (BMD) from two-dimensional imaging of the skeleton that was referenced to a normative data base, which provided a statistical deviation of a patient's value from the reference mean, the T-score. Large negative deviations of this score implied greater fracture risk from the disease osteoporosis.[45] The wide availability of the technology, however, helped extend its use beyond the original population of patients for which it was developed. Clinicians used DXA to diagnose a high risk for fragility fractures in patients of all genders, races, and ages and with various other diseases; and as a result, they sometimes found paradoxical results between bone density and patients' clinical histories. For example, patients with osteopetrosis have high bone density but weak fragile bones.[53] Some patients chronically using glucocorticoids have high fracture risk despite nearly normal bone density.[29,34,35] Sodium fluoride, an old therapy for primary osteoporosis, markedly increases bone density but also the risk for peripheral fractures.[39] Diabetes mellitus increases risk of peripheral fractures despite normal to high BMD in the spine.[33,48,52] About 15% of healthy premenopausal

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women have low T-scores (-1.0 to -2.5 SD) and low risk of fracture.[40] Such observations shifted the perception that additional skeletal factors, collectively called bone quality, impacted skeletal strength and fracture risk besides traditional measurements of DXA. Hence, present day clinical practice is searching for measurements of mechanical strength rather than bone density.[42] This paper reviews the historical backdrop of this paradigm shift, presents some of the new technologies that can assess bone strength and quality apart from bone density, and addresses new ideas how fracture risk in the astronaut population may be evaluated.

### Historical Background

Many clinical observations about drug therapy and skeletal physiology challenged traditional orthodoxy about bone density and skeletal strength (**Table I**). One of the most important concepts was that age predicted fracture risk independently of bone density. The discordance between density and facture risk due to age alluded to skeletal properties that were transparent to DXA. The pharmaceutical studies of therapy for osteoporosis revealed several observations that questioned the traditional mechanisms of drug action on bone strength and density. All antiresorptive drugs reduced spinal fractures similarly but produced disparate changes in density that explained only a small part of the reduction in fracture risk. Moreover, these drugs reduced fractures before demonstrable changes in bone density – a finding attributed to decreases in osteoclastic activity before osteoblastic processes were discernible. Other favorable effects were noted on bone mineral, collagen, microarchitecture, and porosity. The transparency of routine DXA to all these qualitative and quantitative changes prompted new approaches to estimating bone strength and fracture risk.

### New Approaches for Assessing Bone Quality and Bone Strength

Several promising techniques are available to assess bone quality and strength[21] apart from routine clinical DXA. They include QCT and its variation three-dimensional (3D) QCT, finite element analysis (FEA), and hip structure analysis (HSA) and trabecular bone score (TBS). Studies show QCT and FEA significantly correlate with bone strength[21] with r-values between 0.6 and 0.9. QCT is better than DXA alone[2] and FEA is better than DXA and QCT.[13] Despite the theoretical advantage of FEA, QCT is the method clinically available today and offers advantages over DXA. It predicts hip fracture risk in patients better than DXA alone,[7] differentiates hip strength in women and men,[36] measures spinal bone density more accurately,[25] quantifies greater age related bone loss than DXA,[36] and shows larger therapeutic differences in bone density in clinical trials than assessed by DXA alone.[32,37,41]

HSA and TBS use density information from DXA to analyze strength. HSA estimates strength from a two-dimensional slice of cross-sectional femoral neck area and calculates the variables (moments of inertia, buckling ratios, moduli).[3] It has a high correlation to QCT[49] but not QCT/FEA.[38] In clinical studies, it improves estimates of fracture risk from 66 to 81%[14] and shows better therapeutic improvement in strength than DXA.[54,55] Trabecular bone score (TBS) evaluates vertebral bone microarchitecture and its contribution to compressive strength. Ex vivo studies of vertebrae show a strong correlation between microcomputer tomography and TBS but not DXA.[10] TBS has greater discriminatory power to separate samples with similar bone density but different microarchitecture.[17] Cross-sectional studies show TBS discriminates patients with and without fractures; better segregation may arise by combining it with DXA.[8,18,47] Another report suggests combined technology can discriminate fracture risk in patients with only low bone density.[60]

### Risk Assessment Tools

The astronaut corps may at times have healthy members with low density or changing BMD. Does this predictably reflect poor bone strength? Present clinical methods do not adequately estimate fracture risk in this young healthy population whether it be DXA or its popular fracture risk assessment tool called FRAX.[58,59]

**Table I.** Observations Confounding the Estimation of Bone Strength from Bone Density.

| | OBSERVATIONS | REFERENCES |
|---|---|---|
| **PHARMACOLOGICAL DATA** | | |
| Alendronate, risedronate, raloxifene, calcitonin | Similar reduction in vertebral fractures (33–50% avg) but disparate increases in bone density (1–7%) | 1,4,5,12,15,22,28,51 |
| Alendronate, risedronate | Bone density explains about 16% reduction in fracture rates | 15,57 |
| Alendronate, risedronate, raloxifene | Reduction in fracture rates before discernible increase in bone density | 5,23,27,43 |
| Alendronate, risedronate | Early decreases in bone turnover markers correlate with fracture reduction before changes in bone density | 23,24,26,50 |
| Sodium fluoride | Large increases in bone density and increased rates of fractures | 16,39 |
| Alendronate, risedronate, raloxifene, pamidronate, teriparatide | Alteration in structure unseen by DXA | 6,9,11,19,31,62 |
| **CLINICAL DATA** | | |
| Age dependency of fracture | Similar bone density in young and old does not carry same risk of fracture | 20 |
| | Fracture incidence in women ≤ 85 yr old 45% but DXA diagnosis of osteoporosis only 12% | 30 |
| | Low bone density in 15% healthy premenopausal women and no fractures | 40 |
| Diabetes mellitus type 2 | Increased bone density with increased fracturing | 33,48,61 |
| Osteopetrosis | High bone density with increased fractures | 53 |
| Glucocorticoids | Fractures occur with mild decreases or normal bone density | 29,34 |

The World Health Organization (WHO) developed FRAX, in part to address the conundrum of what to do for young healthy people with low bone density and no fractures who were over-treated with drug therapy. It has important application in refining fracture prediction for older high risk individuals. It combines DXA data (BMD / T-score) and clinical risk factors related to bone quality, such as age, family history, secondary medical problems, etc., into an algorithm that calculates a fracture probability (an intervention threshold) over a 10-yr period. This unique value helped guide clinical decisions about pharmaceutical intervention. For the astronaut population, FRAX has limited application. This model is not generated from a population as healthy and fit as astronauts. The clinical risk factors generating the model are for the general populace and not for astronauts. Those unique risk factors for astronauts such as microgravity, mission activity, etc., are not part of FRAX. The intervention threshold, although a decision tree for therapy, can be viewed as a surrogate marker of strength, but it is a point estimate with as yet no information on its variance. Moreover, this estimate is projected over a 10-yr time horizon that is not useful for short term predictions in space mission-related activity.

Another probabilistic risk assessment tool was developed to overcome these shortcomings. It is a physics-based model for prediction of fracture risk at any gravitational environment that uses a blend of clinical factors such as bone density, gender, body mass index, etc., and biomechanical factors from mission-specific loading activities and space related changes on skeletal physiology.[44] The model forecasts spinal, hip, and wrist fractures from intra- and extra- vehicular loading scenarios such as lifting heavy objects, falling, or exploratory activity like jumping on short or long Lunar or Martian missions. It predicts greater likelihood of fractures in the wrist and spine on missions to Mars. Although the boundaries of uncertainty are large and the mean fracture probability is low by terrestrial standards (slightly less than 1% to slightly more than 2%), such an event could be catastrophic to crew and mission and likely will need more consideration. In the future a more precise estimate will arise as this error boundary shrinks with the addition of new validated variables, possibly derived from the technologies discussed above.

### Discussion

Three major questions still remain unresolved for astronauts. Is it safe for healthy qualified individuals with low bone mass (or osteopenia) to enter the corps? What happens to fracture risk from weightlessness? What is the fracture risk upon return to Earth after prolonged space travel? The data presented in this article indicate that DXA alone is not adequate to provide the answers. It overestimates fracture risk in young healthy astronaut candidates since their age alone favors better bone quality and structure than DXA predicts. As a result, a low bone density may not disqualify a young candidate who has no other clinical risk factors. The more challenging issue is what may happen to such a person exposed to weightlessness. DXA shows small decreases in BMD for some, but not all, astronauts. This small BMD change and individual variability may not be accurate. QCT is a better surveillance tool than DXA.[46] In the hip, it detects changes in BMD better and when coupled with finite element analysis, can estimate strength.[46] Apart from these technologies, fracture risk prediction in active duty astronauts should be explored with the physics-based probabilistic risk assessment algorithm cited above.[44] A useful feature of this model is the ability to refine predictions by incorporating new variables such as QCT, finite element analysis, or even trabecular bone score and hip strength analysis.

In summary, the use of areal DXA will likely continue for the near future despite the limitations cited above. Research and development costs of new technologies will, in part, drive this, as well as the fact that vast amount of DXA information exists about terrestrial and astronaut populations which cannot be easily replaced with new technology. How best to use what exists is the challenge. The existing terrestrial DXA data will well serve the medical care of retiring astronauts as they assume the clinical characteristics of the general population. Fracture prediction using DXA seems reasonable. But for active corps members, DXA alone is not accurate and should be enhanced with technology about bone strength such as QCT and FEA or the emerging DXA-derived tools TBS and HSA. Until such time a clinical technology emerges to directly measure bone strength and not density, multiple tools will be needed to monitor skeleton health of active duty astronauts.

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## REFERENCES

1. Agnusdei D, Iori N. Raloxifene: results from the MORE study. J Musculoskelet Neuronal Interact. 2000; 1(2):127–132.
2. Belavy DL, Beller G, Ritter Z, Felsenberg D. Bone structure and density via HR-pQCT in 60 d bed-rest, 2 years recovery with and without countermeasures. J Musculoskelet Neuronal Interact. 2011; 11(3):215–226.
3. Beck TJ. Extending DXA beyond bone mineral density: understanding hip structure analysis. Curr Osteoporos Rep. 2007; 5(2):49–55.
4. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, et al. fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. J Clin Endocrinol Metab. 2000; 85(11): 4118–4124.
5. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, et al. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. Bone. 2006; 39(2):345–352.
6. Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. Bone. 2004; 34(4):736–746.
7. Bousson VD, Adams J, Engelke K, Aout M, Cohen-Solal M, et al. In vivo discrimination of hip fracture with quantitative computed tomography: results from the prospective European Femur Fracture Study (EFFECT). J Bone Miner Res. 2011; 26(4):881–893.
8. Sornay-Rendu E, Boutroy S, Hans D, Vilayphiou N, Winzenrieth R, Chapurlat R. Trabecular bone score improves fracture risk prediction

in non-osteoporotic women: the OFELY study. J Bone Miner Res. 2013; 28(7):1679–1687.
9. Brennan TC, Rizzoli R, Ammann P. Selective modification of bone quality by PTH, pamidronate, or raloxifene. J Bone Miner Res. 2009; 24(5):800–808.
10. Briot K. DXA parameters: beyond bone mineral density. Joint Bone Spine. 2013; 80(3):265–269.
11. Byrjalsen I, Leeming DJ, Qvist P, Christiansen C, Karsdal MA. Bone turnover and bone collagen maturation in osteoporosis: effects of antiresorptive therapies. Osteoporos Int. 2008; 19(3):339–348.
12. Chesnut 3rd, CH Silverman S, Andriano K, Genant H, Gimona A, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med. 2000; 109(4):267–276.
13. Cody DD, Gross GJ, Hou FJ, Spencer HJ, Goldstein SA, Fyhrie DP. Femoral strength is better predicted by finite element models than QCT and DXA. J Biomech. 1999; 32(10):1013–1020.
14. Crabtree NJ, Kroger H, Martin A, Pols HAP, Lorenc R, et al. Improving risk assessment: hip geometry, bone mineral distribution and bone strength in hip fracture cases and controls. The EPOS Study. Osteoporos Int. 2002; 13(1):48–54.
15. Cummings SR, Karf DB, Harris F, Genant HK, Ensrud K, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med. 2002; 112(4):281–289.
16. Farley D, Panczer G, Rey C, Delmas PD, Boivin G. Mineral maturity and crystallinity index are distinct characteristics of bone mineral. J Bone Miner Metab. 2010; 28(4):433–445.
17. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg M-A. correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. J Clin Densitom. 2011; 14(3):302–312.
18. Hans D, Goertzen GL, Krieg M-A, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: The Manitoba Study. J Bone Miner Res. 2011; 26(11):2762–2769.
19. Dufresne TE, Chmielewski PA, Manhart MD, Johnson TD, Borah B. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. Calcif Tissue Int. 2003; 73(5):423–432.
20. Duncan R, Francis RM, Jagger C, Kingston A, McCloskey E, et al. Magnitude of fragility fracture risk in the very old- are we meeting their needs? The Newcastle 85+ study. Osteoporos Int. 2015; 26(1):123–30.
21. Engelke K. Assessment of bone quality and strength with new technologies. Curr Opin Endocrinol Diabetes Obes. 2012; 19(6):474–482.
22. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA. 1999; 282(7):637–645.
23. Garnero P. Biomarkers for osteoporosis management utility in diagnosis, fracture risk prediction and therapy monitoring. Mol Diagn Ther. 2008; 12(3):157–170.
24. Garnero P The contribution of collagen crosslinks to bone strength. BoneKEy Reports 1. 2012:182.
25. Genant HK, Lang T, Fuerst T, Pinette KV, Zhou C, et al. Treatment with raloxifene for 2 years increases vertebral bone mineral density as measured by volumetric quantitative computed tomography. Bone. 2004; 35(5):1164–1168.
26. Greenspan SL, Parker RA, Ferguson L, Rosen HN, Maitland-Ramsey L, Karpf DB. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res. 1998; 13(9):1431–1438.
27. Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004; 74(2):129–135.
28. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999; 282(14):1344–52.
29. Hayashi K, Yamamoto M, Murakawa Y, Yamauchi M, Kaji H, et al. Bone fragility in male glucocorticoid-induced osteoporosis is not defined by bone mineral density. Osteoporos Int. 2009; 20(11):1889–1894.
30. Hui SL, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest. 1988; 81(6):1804–1809.
31. Hordon LD, Itoda M, Shore PA, Shore RC, Heald M, et al. Preservation of thoracic spine microarchitecture by alendronate: Comparison of histology and micro-CT. Bone. 2006; 38(3):444–449.
32. Imai K, Ohnishi I, Matsumoto T, Yamamoto S, Nakamura K. Assessment of vertebral fracture risk and therapeutic effects of alendronate in postmenopausal women using a quantitative computed tomography-based nonlinear finite element method. Osteoporos Int. 2009; 20(5):801–810.
33. Ishii S, Cauley JA, Crandall CJ, Srikanthan P, Grendale GA, et al. Diabetes and femoral neck strength: findings from the hip strength across the menopausal transition study. J Clin Endocrinol Metab. 2012; 97(1):190–197.
34. Kaji H, Yamauchi M, Chihara K, Sugimoto T. The threshold of bone mineral density for vertebral fracture in female patients with glucocorticoid induced osteoporosis. Endocr J. 2006; 53(1):27–34.
35. Kalpakcioglu BB, Engelke K, Genant HK. Advanced imaging assessment of bone fragility in glucocorticoid induced osteoporosis. Bone. 2011; 48(6):1221–1231.
36. Keaveny TM, Kopperdahl DL, Melton III, LJ Hoffmann PF, Amin S, et al. Age-dependence of femoral strength in white women and men. J Bone Miner Res. 2010; 25(5):994–1001.
37. Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. J Bone Miner Res. 2007; 22(1):149–157.
38. Khoo BC, Brown K, Zhu K, Pollock M, Wilson KE, et al. Differences in structural geometrical outcomes at the neck of the proximal femur using two-dimensional DXA-derived projection (APEX) and three-dimensional QCT-derived (BIT QCT) techniques. Osteoporos Int. 2012; 23(4):1393–1398.
39. Kleerekoper M, Balena R. Fluorides and osteoporosis. Annu Rev Nutr. 1991; 11:309–324.
40. Lewiecki EM. Low bone mineral density in premenopausal women. South Med J. 2004; 97(6):544–550.
41. Lewiecki EM, Keaveny TM, Kopperdahl DL, Genant HK, Engelke K. Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis. J Clin Endocrinol Metab. 2009; 94(1):171–180.
42. Lochmüller EM. Burklein D. Kuhn V. Glaser C. Muller R, et al. Mechanical strength of the thoracolumbar spine in the elderly: prediction from in situ dual-energy X-ray absorptiometry, quantitative computed tomography (QCT), upper and lower limb peripheral QCT, and quantitative ultrasound. Bone. 2002; 31(1):77–84.
43. Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. Arch Intern Med. 2002; 162(10): 1140–1143.
44. Nelson ES, Lewandowski B, Licata AA, Myers JG. Development and validation of a predictive bone fracture risk model for astronauts. Ann Biomed Eng. 2009; 37(11):2337–2359.
45. NIH Consensus Statement. Osteoporosis prevention, diagnosis, and therapy. Washington (DC): National Institutes of Health; 2000; 17(1): 1–52.
46. Orwoll ES, Adler RA, Amin S, Binkley N, Lewiecki EM, et al. Skeletal health in long-duration astronauts: nature, assessment, and management recommendations from the NASA bone summit. J Bone Miner Res. 2013; 28(6):1243–1255.

47. Pothuaud L, Barthe N, Krieg MA, Mehsen N, Carceller P, Hans D. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. J Clin Densitom. 2009; 12:170–176.
48. Pritchard JM, Giangregorio LM, Atkinson SA, Beattie KA, Inglis D, et al. Association of larger holes in trabecular bone at the distal radius in postmenopausal women with type 2 diabetes mellitus compared to controls. Arthritis Care Res (Hoboken). 2012; 64(1):83–91.
49. Ramamurthi K, Ahmad O, Engelke K, Taylor RH, Zhu K, et al. An in vivo comparison of hip structure analysis (HSA) with measurements obtained by QCT. Osteoporos Int. 2012; 23(2):543–551.
50. Riggs BL, Melton III JL. Bone turnover matters: the raloxifene treatment paradox of dramatic decreases in vertebral fractures without commensurate increases in bone density. J Bone Miner Res. 2002; 17(1): 11–4.
51. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000; 11(1):83–91.
52. Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos Int. 2010; 21(2):195–214.
53. Stark Z, Savarirayan R. Osteopetrosis. Orphanet J Rare Dis. 2009; 4:5.
54. Uusi-Rasi K, Semanicka LM, Zanchettab JR, Bogadob CE, Eriksen EF, et al. Effects of teriparatide [rhPTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone. 2005; 36(6):948–958.
55. Uusi-Rasi K, Beck TJ, Semanick LM, Daphtary MM, Crans GG. Structural effects of raloxifene on the proximal femur: results from the multiple outcomes of raloxifene evaluation trial. Osteoporos Int. 2006; (4):575–586.
56. Wahner HW, Dunn WL, Riggs BL. Assessment of bone mineral. Part 2. J Nucl Med. 1984; 25(11):1241–1253.
57. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004; 7(3):255–261.
58. Watts NB, Lewiecki EM, Miller PD, Sanford B. National Osteoporosis Foundation 2008 clinician's guide to prevention and treatment of osteoporosis and the World Health Organization fracture risk assessment tool (FRAX): What they mean to the bone densitometrist and bone technologist. J Clin Densitom. 2008; 11(4):473–477.
59. WHO Study Group on Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis. Report of a WHO Study Group, Geneva, World Health Organization Tech Report. 1994; 84(3):1–129.
60. Winzenrieth R, Dufour R, Pothuaud L, Didier H. A retrospective case–control study assessing the role of trabecular bone score in postmenopausal caucasian women with osteopenia: analyzing the odds of vertebral fracture. Calcif Tissue Int. 2010; 86(2):104–109.
61. Yamaguchi T, Sugimoto T. Bone metabolism and fracture risk in type 2 diabetes mellitus. Endocr J. 2011; 58(8):613–624.
62. Zebaze RM, Libanati C, Austin M, Ghasem-Zadeh A, Hanley DA, et al. Differing effects of denosumab and alendronate on cortical and trabecular bone. Bone. 2014; 59(2):173–179.