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Review Article

The contribution of finite element analysis (FEA) in the assessment of pharmacological therapy outcomes in patients with postmenopausal osteoporosis: a literature review

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Abstract

The finite element analysis (FEA), is an engineering computational method of mechanical analysis for complicated structure and it has been employed for the study of the mechanics of human bone. QCT (Quantitative computed tomography) offers three-dimensional data concerning the geometry of bone and how the bone mineral is allocated in terms of space. Depictions acquired with quantitative CT can be utilized to create FE (finite element) models, which enable the analysis of how strong the bone is and how the mechanical stress is distributed, as well as the physical distortion. This methodology can be applied so that the various mechanical loading scenarios can be investigated (stance and fall arrangements) and for the estimation of the entire strength of the bone and the proportional mechanical assistance of bone parts. In this review we research the published literature concerning the effects of various pharmacological agents on parameters of bone strength as measured by FEA in patients with postmenopausal osteoporosis. After selection based on our inclusion and exclusion criteria we evaluated 17 original articles on various pharmacological agents (bisphosphonates, denosumab, teriparatide, PTH 1-84, romosozumab). Although not many studies are currently available an increased value of FEA is definitively seen.

Keywords: Finite Element Analysis, Osteoporosis, Treatment

Introduction

Osteoporosis is identified as a skeletal disorder which is featured by reduced bone strength and high risk of fracture. Bone strength is the sum of bone quantity and bone quality which includes bone geometry, microarchitecture and macroarchitecture, turnover and mineralization. Areal BMD measurements using DXA constitute the standard method through which osteoporosis can be diagnosed, in addition to the assessment of fracture risk and therapeutic outcomes.

However, spinal areal BMD has low sensitivity and only represents 50-80% of bone strength of individual bones in vitro. Measurements of areal BMD cannot adequately predict those individuals who will sustain fractures, as the vast number present in patients with osteopenia rather than osteoporosis. Although bone turnover markers may be helpful to predict changes of bone mass (i.e. bone resorption versus bone formation) these markers cannot be used for the estimation of fracture risk. A finite element analysis which relies on data from QCT has been proposed in order to identify more acutely subjects at risk either for femoral or for vertebral fracture. Quantitative CT based on FE method seems to contribute more to predictions of femoral strength than quantitative computed tomography or DXA alone and can calculate the approximate femoral fracture spot[1,2]. Nonlinear finite element analysis showed enhanced projections of femoral bone strength. Finite element analysis was utilized to examine vertebral strength also and cadaver studies have been conducted for the evaluation of the

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accuracy of FEA. The cadaver studies have confirmed that FEA, predicts fracture patterns and failure loads and can foresee ex vivo vertebral bone strength better than DXA and quantitative computed tomography[1].

Briefly, the method employs some small parts that can have a range of models, and that are associated with nodal points[3]. A model with substance properties is created and after that loads and border requirements are designated, and finite element analysis solver solves the model recreation. Afterwards, the results are transmuted into a helpful output data including fracture load, stress, fracture site and stiffness[4].

Although extensive research has been carried out for finite element analysis, there are not many studies for the evaluation of osteoporotic therapy in postmenopausal females in vivo. The reason obviously is ethical because QCT exposes females to radiation. In this review the focus is on those studies.

Material and Methods

We conducted a search of the published literature using the PubMed search engine. Our key words for the search were: Osteoporosis, Treatment, Finite Element Analysis. Our inclusion criteria were: original articles published in the English literature until September of 2020. Our exclusion criteria were in vitro, ex vivo, or animal studies. We also did not include reviews, case reports, or articles regarding surgical methods but only the most common pharmaceutical therapy for postmenopausal osteoporosis.

Results

Our original search provided 255 articles. Based on our inclusion and exclusion criteria, we included 17 articles in our review. Briefly 6 studies refer to alendronate, 3 studies for risedronate, 1 study for zoledronic acid, 3 studies for ibandronate, 3 studies for denosumab, 9 studies for teriparatide, 3 for PTH (1-84) and 2 for romosozumab. Some of those studies include analysis for more than one agent.

Bisphosphonates

Alendronate (ALN)

Imai K (2011), performed a study in Japanese women, whose purpose was the evaluation of vertebral fracture risk and the impact of ALN on osteoporosis employing FEA in vivo. Vertebral strength and fracture risk in 123 postmenopausal Japanese females was analyzed. Of them a subgroup of 33 females with osteoporosis, who were undergoing treatment with ALN (5 mg per day) for 18 months was examined. Fracture risk, therapeutic impacts on osteoporosis, and the mechanism of action of ALN were studied.

The average percentage increase from baseline to 3 months in vertebral strength index was 10.2% and 2.5% in the volumetric BMD of the second lumbar vertebra. After 6 months of therapy, average increases from baseline were 16.7% in vertebral strength index, 5.1% in L2 volumetric BMD and 3.7% in L2-4 areal BMD. After 12 months of therapy, average increases from baseline were 26.9% in vertebral strength index, 8.8% in the L2 volumetric BMD and 7.5% in L2-4 areal BMD. After 18 months of therapy average increases from baseline was 31.8% in vertebral strength index, 10.9% in L2 volumetric BMD and 9.5% in L2-4 areal BMD. Percent change in the vertebral strength index was statistically significant between baseline and 3, 6, 12 and 18 months ($p<0.0001$). Percent increase in L2-4 areal BMD were significant at baseline, 6, 12, and 18 months ($p<0.0001$). However volumetric BMD of L2 vertebra was not found to increase significantly ($p=0.0549$).

The outcomes in this study show that FEA gives more accurate results for vertebral fracture than DXA derived or QCT derived BMD. FEA can also detect ALN effects at 3 months. All osteoporotic females who were treated with ALN, displayed increased vertebral strength at 12 and 18 months from baseline[5].

Ward et al (2016) in another study including biopsies from iliac crest in 45 females with osteoporosis, assessed the effects of either alendronate (ALN) or risedronate, or ibandronate given for various durations up to 16 years. Micro-QCT imaging based FEA and statistical modeling was applied for trabecular bone.

Following adjustments for participants age and Bone volume-Total Volume (BV/TV), therapy with bisphosphonates for up to 7.3 years was related with an increase in bone stress and stiffness. When the therapy exceeded 7.3 years, decreases in stiffenes and failure stress were noted[6].

Risedronate

D. Anitha et al (2013) assessed 10 subjects treated with risedronate (RISE) for a period of more than 3 years. The local buckling ratio (BR), from quantitative computed tomography data in the femoral neck was estimated.

Bone strength was examined through FEA and significant fracture loads (F_{cr}) were obtained from sideways fall load simulations. The participants were placed into three subgroups based on the alteration in fracture loads: inadequate (−22%), adequate (+20%), and indefinite (−2%) RISE response subgroups. Lesser and greater ranges of local buckling ratio standards per year were found for adequate (min=2.14, max=8.04) and inadequate (min=1.72, max=11.38) risedronate response subgroups, correspondingly.

The participants in the inadequate drug response subgroup displayed increased local buckling ratio at the superoanterior and superoposterior regions. These increased local buckling ratio values corresponded with FEA predicted critical strain regions, whereas participants from the adequate drug response subgroup showed

considerably reduced strain regions.

The superiority of the combination of buckling ratio (geometry) with fracture loads(structure) over DXA measurements has been shown. The authors of this study suggest that geometrical parameters of the bone are significant in the estimation of hip fracture risk[7].

Ibandronate

In a randomized, double-blind, placebo-controlled outpatient study, E.M. Lewiecki et al (2009) evaluated effects of treatment with ibandronate (150 mg per os, once monthly), for 12 months, on hip and lumbar BMD. Bone strength calculated using FE models. In the study, 93 osteoporotic postmenopausal females were analyzed. The authors compared 47 females who received oral ibandronate versus 46 females who received placebo for a 12-month-period.

Ibandronate resulted in an increase of integral total hip BMD more than placebo at 12 months. Finite element analysis calculated hip strength to density ratio and femoral, peripheral, and trabecular strength increased with ibandronate vs. placebo (4.1%, p<0.001 versus 5.9%, p<0.001, versus 2.5%, p=0.011, versus 3.5%, p=0.003, respectively). Ibandronate led to the improvement of vertebral, peripheral, and trabecular strength and anteroposterior bending stiffness versus placebo (7.1%,p<0.001, versus 7.8% ,p<0.001, 5.6% ,p <0.023, versus 6.3% (p<0.001), respectively.

The researchers conclude that monthly oral ibandronate treatment resulted in improving hip and spine BMD and strength, as assessed by QCT and FE models[8].

Bisphosphonates and atypical fractures

Leung et al (2013) assessed a possible link between long-term bisphosphonate therapy and atypical femoral fractures. There was a comparison of BMD at hip and femoral midshaft, bone cross-sectional area, moment of inertia of both femurs and FEA calculated stress and stiffness among 28 osteoporotic postmenopausal females, with the minimum 4 years of treatment and control group of 37 females without treatment.

There was no no statistically significant difference between the bisphosphonate treatment group and control group at the total hip BMD and T-score. Yet, bisphosphonate treated patients turned out to have essentially lower BMC in the femoral shaft (P<0.05). Structural study showed lower cross-sectional area in subtrochanteric and mid-diaphyseal region and thus essentially smaller moment of inertia (P<0.01). HR peripheral QCT exhibited vitally lowered trabecular density, bone volume ratio, trabecular number but higher trabecular spacing in tibia and distal radius. FEA additionally verified significantly lower bone stress and stiffness in tibia[9].

Denosumab

FREEDOM

In FREEDOM, an international, randomized placebo controlled clinical trial with postmenopausal osteoporotic females, the effects of denosumab (DMAB) treatment for 36 months were evaluated. In a subset of patients, 48 females for the control subgroup receiving placebo drug and 51 for the DMAB subgroup, T. M. Keaveny et al (2014) performed QCT based FEM of hip and spine to assess hip and spine strength.

For the females given DMAB, hip strength increased significantly in comparison to baseline by 5.3% (p<0.0001) at 12 months and gradually over time up to 8.6% (p<0.0001) at 36 months. In contrast, subjects in the placebo group did not exhibited significant changes at 12 months concerning hip strength and actually were found with decreased bone strength up to 5.6% (p<0.0001) by 36 months in comparison to the baseline. After 36 months of therapy, hip strength for the DMAB subgroup was higher by 14.3% in comparison to placebo. At the spine, increases in strength were larger. Spine strength increased by 18.2%, comparing to baseline for the DMAB subgroup (p<0.0001) and decreased by −4.2 %(p=0,002) for the control subgroup at 36 months, corresponding to a relative increase in spine strength for the DMAB subgroup of 22.4% (p<0.0001) comparing to placebo.

The finite element analysis showed increases in strength in both trabecular and cortical bone compartments of hip and spine, for patients treatment with denosumab. Hip and spine strength for the control subgroup, declined from baseline through 36 months but further analysis showed that the strength correlated to the cortical compartment was protected[10].

FREEDOM - alternative smooth FEA methodology

P. Zysset et al., (2015) explored the effects of DMAB on vertebral and femoral strength during the FREEDOM trial through the use of an alternative smooth FEA methodology. This alternative and probably more precise approach is comprised of the use of smooth tetrahedral meshes of the trabecular compartment that is coated with a layer of cortical elements.

The effects on femoral strength in stance and fall stress model were also assessed. Quantitative computed tomography images for the proximal femur and L1 and L2 vertebra were evaluated by FEA methodology at baseline, 12, 24, and 36 months. 51 postmenopausal osteoporotic females treated with denosumab and 47 females were the control group. Quantitative computed tomography data were transformed into smooth FEA data to calculate vertebral strength. DMAB increased vertebral body strength by 10.8%, 14.0%, and 17.4% from baseline at 12, 24, and 36 months, correspondingly (p<0.0001). DMAB also enhanced femoral strength in the fall configuration by 4.3%,

5.1%, and 7.2% from baseline at 2, 24, and 36 months, in that order (p<0.0001). Similar improvements were noted in the stance configuration with increases of 4.2%, 5.2%, and 5.2% from baseline (p<0.0007).

Through the use of an alternative smooth FEA method, researchers verified the important advances in lumbar spine and femur strength that was formerly detected with denosumab[11].

Osteoanabolic treatment

Teriparatide (PTH 1-34) treatment for 24 months

In a stage-4, open-label randomized control trial, of M. Kleerekoper et al (2014), postmenopausal females with serious osteoporosis treated with PTH (1-34) (20 mg daily). Evaluations included prospective changes in vBMD at the spine and hip on QCT, projected alterations in spine strength and hip strength consistent with FE models of QCT data.

35 postmenopausal females with serious osteoporosis were registered. 30 females completed 18 months and 25 completed a not mandatory 6 months extension. At month 18, the increase from baseline in vBMD at the spine was 10.05% (p<0,001), and estimated spine strength (L3 vertebra) increased 17.43% (p<0,001). Total vBMD at the hip increased 2.22% (p=0,021), and estimated hip strength increased 2.54% (p=0,045).

The authors of this study conclude that PTH (1-34) increased hip and spine aBMD and vBMD. Femoral and vertebral strength calculated by FE method also improved. These outcomes through the 24 month period, coherent with the established osteoanabolic impact of TPTD[12].

Teriparatide - EUROFORS study

The EUROFORS HR QCT research is a substudy of a European, monitored, randomized, trial of osteoporotic postmenopausal females. C. Graeff et al., (2009) used FEA analysis–based strength processes, to evaluate PTH (1-34) treatment. In 44 osteoporotic females taking part in the EUROFORS study, FE analysis based on HR QCT of T_{12} were assessed after 0, 6, 12, and 24 months of PTH (1-34) therapy (20 mg per day). Strength and stiffness analysis calculated using FEA estimations for compression and bending were matched with volume BMD and app. BV/TV (apparent bone volume fraction), along with DXA-based aBMD of the lumbar spine.

Significant increase (p<0.0001) in all examined parameters at 6 months after beginning PTH (1-34) were noticed. 2 years later, bone strength in compression was increased by 28.1±4.7% (SE), in bending by 28.3±4.9%, whereas apparent bone volume fraction was increased by 54.7±8.8%, volumetric BMD by 19.1±4.0%, and aBMD of lumbar 1-4 by 10.2±1.2. FEA alterations were essentially greater than those of BMD and not distinct from apparent bone volume fraction. The size of regions at high risk for local failure exhibited important reduction. Therapy with PTH 1-34 leads to strength increases for various loading conditions of close to 30%. FEA variables showed a greater consistent response to alterations than densitometry estimates[13].

Effects of teriparatide in distal radius and tibia

MacDonald et al (2011) tried to evaluate the effects of PTH (1-34) in distal radius and tibia which were unclear earlier. They used high-resolution peripheral QCT, after 0,6,12 and 18 months of PTH (1-34) treatment (20 µg per day), to screen alterations in bone microstructure and bone strength at the distal radius and tibia, in 11 postmenopausal females with osteoporosis. The final analysis comprises of radius data for 9 females and tibia data for 11 females.

At 18 months, they detected a decrease in overall BMD (p=0.03) cortical BMD at the distal radius and a decline in at the distal radius (p=0.05) and tibia (p=0.01). The decrease in cortical BMD were combined with tendencies for enhanced cortical porosity at both sites. At the distal radius, 18 months of PTH (1-34) treatment was also related to trabecular thinning (p=0.009) and diminished trabecular bone volume ratio (p=0.08). They observed comparable trends at the distal tibia. The noted alterations in cortical bone structure are in conjunction with the effects of PTH (1-34) on intracortical bone remodeling. Despite these alterations in bone quality, bone strength was maintained from baseline at 6, 12, or 18 months.

The reserchers concluded that the decline in cortical BMD in this study was paired with enhanced cortical porosity both at the radius and tibia though, cortical porosity was only statistically distinct from baseline at the distal tibia after 12 months. FEA indicated that bone strength did not appear to be conceded with PTH (1-34) treatment, despite a more porous cortex[14].

Teriparatide compared with Alendronate

Finite element analysis performed by T.M. Keaveny et al (2012) for the evaluation of femoral strength from 48 osteoporotic postmenopausal females, who were a subset of the FACT study (Forteo Alendronate Comparator Trial). They used QCT after 0, 6, and 18 months, of teriparatide (PTH1-34) treatment of (20 µg per day) or alendronate (ALN) treatment (10 mg per day). The quantitative CT, gained at 0, 6, and 18 months, were investigated for vBMD of trabecular bone, the peripheral bone, and the integral bone (both trabecular and peripheral), and for complete femoral bone strength in response to a virtual sideways drop.

At month 18, the authors of this study reported that in the women that underwent treatment with PTH (1-34), trabecular vBMD increased versus baseline (+4.6%, p<0.001), peripheral vBMD reduced (−1.1%, p<0.05), integral vBMD (+1.0%, p=0.38) and femoral strength (+5.4%, p=0.06) did not exhibit significant alteration, but the ratio of strength to integral vBMD ratio improved (+4.0%, p=0.04). An increase in the ratio of strength to integral vBMD indicates that overall femoral strength, compared to baseline, increased more than integral density did.

For the females that underwent therapy with ALN, there were small (<1.0%) but non-significant alterations in comparison to the baseline in vBMD. The only important between-treatment difference was related to the alteration in trabecular vBMD (p<0.005); accordingly, there was also discovered that, for a given alteration in peripheral vBMD, femoral strength enhanced more for PTH (1-34) than for ALN (p=0.02).

It was concluded that, although there were different compartmental vBMD responses for these two remedies, it could not be detected any complete difference in alteration in femoral strength concerning the two therapies, although femoral strength increased more than integral((both trabecular and peripheral) vBMD after therapy with PTH (1-34)[15].

Teriparatide treatment after Alendronate or risedronate treatment

OPTAMISE study determines how prior treatment with Alendronate (ALN) or Risedronate (RISE) in osteoporotic postmenopausal females successive affects PTH (1-34) treatment. Postmenopausal females with osteoporosis who had been administered ALN ,10 mg per day or 70 mg per week (146 participants) or RISE ,5 mg per day or 30–35 mg per week (146 participants) for at least 24 months joined. Y. Chevalier et al (2010) used FE models to assess how former treatment with RISE or ALN in osteoporotic postmenopausal females impacts on the effectiveness of PTH (1-34).

Researchers used data from L1 vertebra developed before and after 12 months of treatment with PTH (1-34), from 171 participants. Bone volume/total volume, stiffness, and strength were calculated from QCT.

12 months of therapy with PTH (1-34) following former therapy with either ALN or RISE increased bone volume/ total volume, stiffness, and strength. Though, the outcomes of PTH (1-34) were more apparent in participants who were formerly treated with RISE. The average surge in stiffness was more in the prior RISE subgroup than the prior ALN subgroup (24.6±3.2% versus 14.4±2.8%, respectively; p=0.0073). Equally, vertebral strength increased by 27.2±3.5% in the prior RISE subgroup versus 5.3±3.1% in the prior ALN subgroup (p=0.0042).

This study indicates that while PTH (1-34) can be employed successfully on females who have formerly gotten therapy with ALN and RISE, it proved to have more anabolic impact in prior RISE patients[16].

Effectiveness of Teriparatide, PTH 1-84 and zoledronic acid in peripheral skeleton

Hansen and all (2013), in an open-label, nonrandomized research, employed HR peripheral QCT to provide details on density, and microstructure and also FE models for strength at the distal radius and tibia in postmenopausal females with osteoporosis, treated with teriparatide (PTH 1–34) (20 mg sc per day, 18 females) or PTH 1–84 (100 mg sc per, 20 women) for 18 months. A subgroup of postmenopausal females with osteoporosis receiving zoledronic acid (5 mg yearly, 33 females) was also incorporated.

Osteoanabolic treatment led to the increase of cortical porosity in radius (PTH 1–34 32±37%, PTH 1–84 39±32%, both p<0.001) and tibia (PTH 1–34 13±27%, PTH 1–84 15±22%, both p<0.001) with respective drops in cortical density. With teriparatide, increases in cortical thickness in radius and tibia were found. Zoledronic acid did not impact cortical porosity at either site but increased cortical thickness and cortical density in tibia as well as trabecular volume fraction in radius and tibia. Bone strength was maintained, but not increased, with teriparatide and zoledronic acid at both sites, whereas it decreased with PTH 1–84 in radius (2.8±5.8%, p<0.05) and tibia (−3.9±4.8%, p<0.001). Research needs to examine the declined strength with PTH 1–84 therapy[17].

Romosozumab compared with Teriparatide

In a stage II clinical trial, romosozumab (ROMO) increased BMD at the hip and spine of osteoporotic postmenopausal females. In a substudy of that clinical test, T.M. Keaveny et al (2017) investigated if those noted increases in BMD also led to advances in anticipated strength, as assessed by QCT based FE models. Females took ROMO s.c. (210 mg per month) or placebo, or PTH (1-34) (20 mg per day) for 12 months. QCT scans, attained at the lumbar spine (82 females) and proximal femur (46 females at baseline and month 12), were analyzed with FEA to estimate strength for a simulated compression overload for the spine (L1 vertebral body) and a sideways fall for the proximal femur.

It was found that, at month 12, vertebral strength improved more for ROMO compared with both PTH (1-34) (27.3% versus 18.5%, p=0.005) and placebo (27.3% versus −3.9%, p<0.0001). Alterations in femoral strength for ROMO showed similar but smaller alterations, increasing more with ROMO versus PTH (1-34) (3.6% versus −0.7%, p=0.027), and trending higher versus placebo (3.6% versus 0.1%, p=0.059). The findings of this research indicate that that ROMO is a new agent for osteoporosis that promotes vertebral and femoral strength[18].

Romosozumab therapy for 3 months

C. Graeff et al., (2015) in a phase 1b study, administered romosozumab (ROMO) or placebo to 32 osteoporotic females and 16 men for 3 months and an additional 3-month follow-up. Quantitative CT for 24 ROMO and 9 placebo participants at L1-L2 vertebrae and HR Quantitative CT for 11 ROMO and 3 placebo participants at Thoracic 12 vertebra were examined, at baseline, month 3, and month 6. FE models also created to measure the stiffness.

In comparison to placebo, the ROMO group showed improvements at month 3 for trabecular BMD by quantitative CT and high resolution QCT, high resolution QCT trabecular bone volume/total volume and separation,

density-weighted cortical thickness, and stiffness. At month 6, improvements from baseline were noted in quantitative CT trabecular BMD and stiffness, and in high resolution quantitative CT BMD, trabecular BV/TV (bone volume/total volume) and separation, density-weighted cortical thickness, and stiffness in the ROMO group. The average growth in high resolution quantitative CT stiffness with ROMO from baseline was 26.9%±6.8% and 35.0%±6.8% at months 3 and 6, correspondingly. Participants that were given placebo showed alterations of −2.7%±13.4% and −6.4%±13.4%, correspondingly.

Overall, ROMO given for 3 months led to rapid and significant advances in trabecular and cortical bone mass and structure including the entire bone stiffness that prolonged 3 months after the last ROMO dose[19].

Combination Therapy

PTH and Alendronate study

The "PTH and ALN" or "PaTH" study, equated the effects of PTH1-84 and/or alendronate (ALN) in 238 postmenopausal females with osteoporosis. T. M. Keaveny et al (2008) executed FEA on the quantitative CT data of 162 of these participants to provide understanding into femoral strength alterations correlated with the intake of those remedies. Participants were divided into either PTH (1-84), Alendronate, or their combination in year 1 and were exchanged to either Alendronate or placebo therapy in year 2.

Strength of the femoral bone was created for a sideways fall through the employment of FEA of the QCT tests. At year 1, the femoral strength switch from baseline was important from the statistic point of view for PTH1-84 (average, 2.08%) and Alendronate (3.60%), and at year 2, substantial alterations were observed for the PTH (1-84), Alendronate group (7.74%), Combination, PTH1-Alendronate (4.18%), and Alendronate- Alendronate (4.83%) therapy group but not for the PTH1-34, Placebo (1.17%) ones. The large divergence between the bone strength at year 2 amongst the PTH1-84,Placebo and PTH1-84,PTH1-34 groups underpins inferences concerning the significance of subsequent therapy with PTH by an antiresorptive agent to better maintain the benefits of the PTH therapy[20].

Teriparatide, Denosumab, or both at distal radius and tibia

Tsai JN et al. (2016) in an open label randomized monitored trial tried to identify the consequences of 2-years of combination treatment on bone geometry and anticipated potency. They completed HR pQCT at the distal tibia and radius in 94 postmenopausal females with osteoporosis randomized to 2 years of PTH (1-34) 20-mcg per day SC, denosumab 60 mg SC every 6 months, or both.

They used microFEA to estimate stiffness and strength at months 0, 12, and 24. Strength and stiffness increased comparably in all subgroups at the tibia. The increases in strength at the tibia were greater in the Combination subgroup than the Teriparatide subgroup (P=.045). At the radius, stiffness increased by 4.8±4.2% in the Combination subgroup (P<.001), by 4.0±4.7% in the Denosumab subgroup (P<.001) but didn't alter in the Teriparatide group. The upturns in stiffness in the Combination group were higher than those in the Teriparatide subgroup (P.050 vs Teriparatide). Likewise, strength at the radius grew by 4.9±3.8% in the Combination subgroup (P<.001), by 3.8±4.5% in the Denosumab subgroup (P<.001) and did not alter in the Teriparatide subgroup. The expansions in the Combination subgroup were greater than those in the Teriparatide subgroup (P=.026 vs Teriparatide).

The authors of this study determine that 2 years of PTH (1-34) and denosumab in combination enhances bone microstructure and project intensity more than the individual therapies, notably in cortical bone[21].

Adding Up versus shifting to teriparatide with prior alendronate or raloxifene

F. Cosman et al study, in the USA evaluate the outcomes of addition versus turning to PTH (1-34). Postmenopausal osteoporotic females taking alendronate 70 mg per week (91 females) or raloxifene 60 mg per day (77 women) for 18 months were at random given an addition or they altered to PTH (1-34) 20 mg per day. QCT were executed at the starting point, 6 months, and 18 months to evaluate alterations in volumetric BMD. Bone strength was calculated by FEA.

At the spine, average volumetric BMD and strength (L1 vertebral strength) improved from baseline in all subgroups (13.2% to 17.5%, p<0.01). There were no substantial differences between the Adding or Switching subgroups. In the Raloxifene group femoral volumetric BMD and intensity grew at 6 and 18 months in the Adding subgroup but only at 18 months in the Switching subgroup (Strength, Month 18: 2.7% Adding group, p<0.01 and 3.4% Switching subgroup, p < 0.05). In the alendronate group, femoral volumetric BMD increased in the Adding but not in the Switching subgroup (0.9% versus −0.5% at 6 months and 2.2% versus 0.0% at 18 months, both p≤0.004 group difference). At 18 months, femoral strength increased in the Adding group (2.7%, p<0.01) but not in the Switching group (0%). The disparity amongst subgroups was not important (p=0.076).

The authors of this study came to the conclusion that adding or switching to PTH (1-34) awarded comparable benefits on lumbar spine strength in osteoporotic females pretreated with alendronate or raloxifene. Escalations in femoral strength showed more variability. In raloxifene treated females, strength increased more quickly in the Adding group. In Alendronate treated females, an important increase in strength in comparison to the baseline was seen only in the Adding subgroup[22].

Combination of PTH (1–84) therapy and ibandronate

A.L. Schafer et al (2013) assessed bone microstructure and geometry with HR pQCT at the radius (a nonweight bearing site) and tibia (weight bearing) in postmenopausal females obtaining combination PTH (1–84) and ibandronate. Osteoporotic females (43 females) underwent therapy with 6 months of PTH (1–84) 100 μg per day, combined with ibandronate 150 mg per month over 2 years. High resolution peripheral QCT was executed before and after the therapy took place.

Trabecular BMD increased at both radius and tibia ($p<0.01$). Cortical thickness and BMD decreased at the radius ($p<0.01$), consistent with alterations in DXA, while these factors did not switch at the tibia ($p\leq0.02$ for difference between radius and tibia). In contrast, cortical porosity increased at the tibia ($p<0.01$) but not radius. Stiffness and strength dropped at the radius ($p<0.0001$) but did not switch to the tibia.

It was concluded that cortical and trabecular alterations responding to the PTH 1-84 and ibandronate treatment combinations that were employed in this research were different at the nonweight-bearing radius vs. the weight-bearing tibia, with more beneficial total variations at the tibia. Those conclusions imply the possibility that weight bearing might enhance the impacts of the treatment[23].

Conclusions

FEA method is a beneficial instrument for the assessment of osteoporosis therapy. With regards to bisphosphonates, finite element analysis can identify the therapeutic impact of alendronate(ALN) even at 3 months. In addition, therapy with bisphosphonates for up to 7.3 years was related with an increase in bone stress and stiffness. When the therapy exceeded 7.3 years, decreases in stiffenes and failure stress were noted. Ibandronate per os once monthly for 12 months led to the improvement of hip and spine strength. FE method also assesses local osteoporosis after risedronate therapy and the hazard of atypical fractures after long-term bisphosphonate.

The FE method in Hip and Spine strength indicates increase in all denosumab-treated participants. Analogous results can be found by the employment of an alternative smooth FEA methodology.

For PTH (1-34), FE method determines larger anabolic impact on in prior-risedronate females during 12 months of PTH (1-34) therapy. It also shows the significance of following therapy with PTH (1-34) by bisphosphonates to better conserve the benefits of the PTH (1-34) therapy. Vertebral and femoral strength increased with PTH (1-34) and highly important improvements at 6 months after starting PTH (1-34) were observed. At radius and tibia, although a more porous cortex, FEA showed that bone strength did not seem to be conceded with PTH (1-34) therapy. After therapy with PTH (1-34) femoral strength increased more than essential (both trabecular and peripheral) vBMD in comparison to therapy with ALN. At radius bone strength, is decreased with PTH (1–84) and preserved with PTH (1-34) or zoledronic acid.

Vertebral strength showed better results for romosozumab compared to the ones with PTH (1-34). Romosozumab given for 3 months led to rapid and significant increases in the overall bone stiffness, which sustained 3 months after the last romosozumab dose.

FEA also indicates the significance of subsequent therapy with PTH by an antiresorptive agent to better maintain the benefits of the PTH therapy. Furthermore, 24 months of combined PTH (1-34) and denosumab improves bone microstructure and assessed bone strength more than each agent separately. In combination with PTH 1–84 treatment and ibandronate, stiffness and stress declined at the radius but there was not an alteration at the tibia. Finally in females treated with Alendronate or Raloxifene, adding versus shifting to PTH (1-34) produced various responses.

References

1. 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.
2. Carpenter RD. Finite element analysis of the hip and spine based on quantitative computed tomography. Curr Osteoporos Rep 2013;11(2):156-162.
3. Burr DB. The use of finite element analysis to estimate the changing strength of bone following treatment for osteoporosis. Osteoporos Int 2016;27(9):2651-2654.
4. Imai K. Computed tomography-based finite element analysis to assess fracture risk and osteoporosis treatment. World J Exp Med 2015;5(3):182.
5. Imai K. Vertebral fracture risk and alendronate effects on osteoporosis assessed by a computed tomography-based nonlinear finite element method. J Bone Miner Metab 2011;29(6):645-651.
6. Ward J, Wood C, Rouch K, Pienkowski D, Malluche HH. Stiffness and strength of bone in osteoporotic patients treated with varying durations of oral bisphosphonates. Osteoporos Int 2016;27(9):2681-2688.
7. Anitha D, Kim KJ, Lim SK, Lee T. Implications of local osteoporosis on the efficacy of anti-resorptive drug treatment: A 3-year follow-up finite element study in risedronate-treated women. Osteoporos Int 2013;24(12):3043-3051.
8. Lewiecki EM, Keaveny TM, Kopperdahl DL, et al. Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 2009;94(1):171-180.
9. Leung KS, Tang N, Griffith J, et al. Structural, densitometric and biomechanical evaluations of Chinese patients with long-term bisphosphonate treatment. Chin Med J (Engl) 2013;126(1):27-33.
10. Keaveny TM, McClung MR, Genant HK, et al. Femoral and vertebral strength improvements in postmenopausal women with osteoporosis treated with denosumab. J Bone Miner Res 2014;29(1):158-165.
11. Zysset P, Pahr D, Engelke K, et al. Comparison of proximal femur and vertebral body strength improvements in the FREEDOM trial using an alternative finite element methodology. Bone 2015;81:122-130.
12. Kleerekoper M, Greenspan SL, Lewiecki EM, et al. Assessing the

effects of teriparatide treatment on bone mineral density, bone microarchitecture, and bone strength. J Bone Jt Surg - Am Vol 2014;96(11).
13. Graeff C, Chevalier Y, Charlebois M, et al. Improvements in vertebral body strength under teriparatide treatment assessed in vivo by finite element analysis: Results from the EUROFORS study. J Bone Miner Res 2009;24(10):1672-1680.
14. MacDonald HM, Nishiyama KK, Hanley DA, Boyd SK. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. Osteoporos Int 2011;22(1):357-362.
15. Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone 2012;50(1):165-170.
16. Chevalier Y, Quek E, Borah B, et al. Biomechanical effects of teriparatide in women with osteoporosis treated previously with alendronate and risedronate: Results from quantitative computed tomography-based finite element analysis of the vertebral body. Bone 2010;46(1):41-48.
17. Hansen S, Hauge EM, Beck Jensen JE, Brixen K. Differing effects of PTH 1-34, PTH 1-84, and zoledronic acid on bone microarchitecture and estimated strength in postmenopausal women with osteoporosis: An 18-month open-labeled observational study using HR-pQCT. J Bone Miner Res 2013;28(4):736-745.
18. Keaveny TM, Crittenden DB, Bolognese MA, et al. Greater Gains in Spine and Hip Strength for Romosozumab Compared With Teriparatide in Postmenopausal Women With Low Bone Mass. J Bone Miner Res 2017;32(9):1956-1962.
19. Graeff C, Campbell GM, Peña J, et al. Administration of romosozumab improves vertebral trabecular and cortical bone as assessed with quantitative computed tomography and finite element analysis. Bone 2015;81:364-369.
20. Keaveny TM, Hoffmann PF, Singh M, et al. Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans. J Bone Miner Res 2008;23(12):1974-1982.
21. Tsai JN, Uihlein A V., Burnett-Bowie SM, et al. Effects of two years of teriparatide, denosumab, or both on bone microarchitecture and strength (DATA-HRpQCT study). J Clin Endocrinol Metab 2016;101(5):2023-2030.
22. Cosman F, Keaveny TM, Kopperdahl D, et al. Hip and spine strength effects of adding versus switching to teriparatide in postmenopausal women with osteoporosis treated with prior alendronate or raloxifene. J Bone Miner Res 2013;28(6):1328-1336.
23. Schafer AL, Burghardt AJ, Sellmeyer DE, et al. Postmenopausal women treated with combination parathyroid hormone (1-84) and ibandronate demonstrate different microstructural changes at the radius vs. tibia: the PTH and Ibandronate Combination Study (PICS). Osteoporos Int a J Establ as result Coop between Eur Found Osteoporos Natl Osteoporos Found USA 2013;24(10):2591-2601.