

Bone rebuild in osteoporosis - a review

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Abstract

Introduction: Osteoporosis is a silent disorder characterized by a T score of less than -2.5 in bone densitometry. Bone loss starts from the age of 30 to 35 and progresses further after menopause. It can be alleviated by vitamin D and calcium supplement. More effective anti-osteoporotic medication has been marketed like Fosamax, Actonel and Evista. Despite the medical advance, wrist fractures, vertebral collapse and hip fractures are still common in Hong Kong.

Method: Bone response to compression is first confirmed by literature review. Then local statistics will be studied to point out the severity and the medical expenses on osteoporotic bone fractures. Finally, exercises with axial loading forces acting on radius, vertebrae and femur are proposed to strengthen bones and prevent osteoporotic fractures.

Results: Straight punch, weight lifting and breaststroke swimming style cause pulsatile axial compression of bone trabeculae of distal radius, vertebrae and femoral neck. Regular practice of these exercises will strengthen the bone architecture and prevent wrist, vertebral and hip fractures.

Conclusion: Suitable exercise is supplementary to medication in preventing osteoporotic bone fractures.

Key words: Osteoporosis, T-score, bone rebuild, compression force, bone trabeculae.

Introduction

Bone is a rigid organ that constitutes part of the vertebral skeleton supporting and protecting the various organs of the body. This active tissue is composed of different cells. Osteoblasts are involved

in the creation and mineralization of bone while osteocytes and osteoclasts in its reabsorption (Figure1). Bone undergoes continual formation and resorption [1,2]. New bone formation occurs at bone resorption sites to maintain the microarchitecture in bone remodeling.

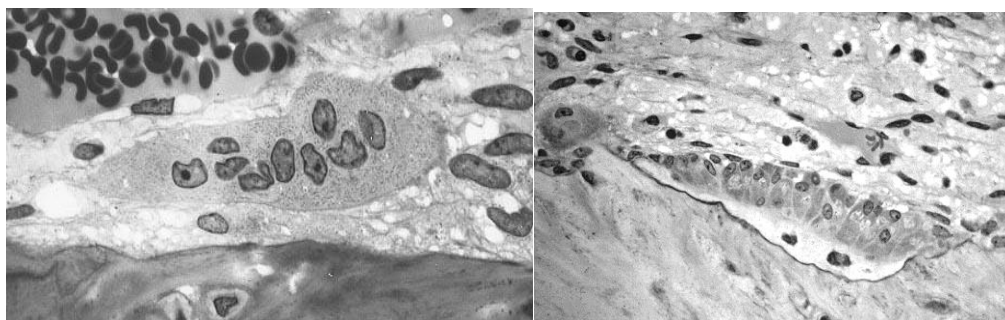


Figure 1. On the left, osteoclast displaying many nuclei within a "foamy" cytoplasm. On the right, osteoblasts lining bone (bottom) and actively synthesizing osteoid, containing two osteocytes.

TGF- β 1 and IGF-1 are released in response to osteoclastic bone resorption and induce the osteoblastic migration to that site. Osteoclasts secrete Semaphorin 4D that activates RhoA by binding to Plexin-B. RhoA facilitates the role of TGF- β 1 and IGF-1 in regulating osteoblast differentiation. Osteoblastic RANKL (receptor activator of nuclear factor-kappa B ligand) stimulates the production of Semaphorin 4D, that inhibits osteoblast

differentiation, thus achieving a balance between bone formation and resorption.

The whole bone strength is determined by bone mass, bone shape and microarchitecture and bone material properties [3]. The latter includes bone density, matrix mineralization, collagen trait and microdamage. Bone density refers to the amount of mineral matter per square centimeter of bones and is used in clinical medicine as an indirect indicator of

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osteoporosis and fracture risk.

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fractures. The pathogenesis is the consequence of genetic, hormonal, dietary, lifestyle and physical factors. Genetics influences bone accrual and bone mass, while systemic hormones (parathyroid hormone excess and withdrawal of estrogens) or local cytokines affect the bone remodeling balance [4,5]. Old age, sex steroid deficiency, lipid oxidation, decreased physical activity, use of glucocorticoids and a propensity to fall are the most critical determinants of increased fracture risk.

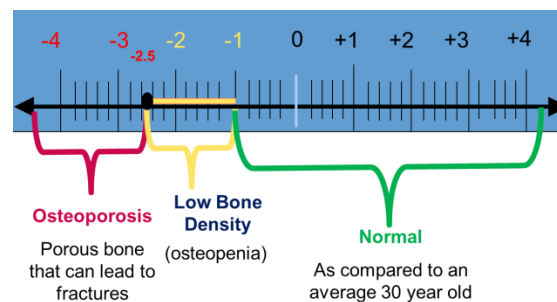


Figure 2. Osteoporosis and T score

Z-score instead, compares patient's bone density to the average bone density of people of same age. Low values suggest secondary osteoporosis. If Z-score is less than 2 standard deviations, it means that other illnesses or conditions coexist and contribute to osteoporosis such as glucocorticoid therapy, hyperparathyroidism, alcoholism or medications that may cause such unexpected bone density.

Fractures occur when loading exceeds bone strength. Bone trabeculae, as the basic building unit of bone, play an important role in osteoporotic fracture [7]. It is found that osteoporosis changes the amount of vertebral trabecular bone but not the vertebral load distribution. Computed tomography finite-element analyses of vertebrae showed osteoporosis had no effect on the vertebral load distribution, as compared to normal people, but the amount of trabecular bone at risk of fracture was increased from 1% to 16%.

Central DXA of spine and hip predict hip fracture risk and together with peripheral DXA of wrist, heel, finger or hand represent good screening tools. American Bone Health recommends further evaluation for patients with peripheral T-score < -1.0.

DXA scan reflects the bone mass, degree of mineralization but not the 3D distribution of bone mass nor the trabecular and cortical microarchitecture neither the intrinsic properties of the bone matrix.

Bone tissue shows structural adaptation to cyclical compressive stress. The magnitude of the bone remodeling response is site specific [8]. The contribution of vertebral trabeculae to vertebral strength was well documented [9]. Compression

T-score is a relevant measure to screen for osteoporosis, comparing a patient's bone density to that of a healthy thirty-year-old of the same sex and ethnicity, T-score values are as following (Figure 2):

- Normal condition is defined by a T-score of -1.0 or higher
- Osteopenia is defined as between -1.0 and -2.5
- Osteoporosis is defined by a T-score of -2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman (World Health Organization in 1994) [6].

increased the width of bone diaphysis in dog model [10]. Repeated axial loading caused bone hypertrophy and decreased osteoporotic bone fracture [8], [11,12]. Considering the direction of bone trabeculae, we identify the exercises with axial loading forces along our target bones.

The stability of modern building requires reinforced concrete and architectural design. Current medication focuses on the restoration of bone density without considering how to "thicken" the individual bone trabeculae. As bone fractures occurs across these trabeculae, trabecular hypertrophy will reduce the fracture risk. Bone is known to be a living tissue that can be hypertrophied on training and atrophied on disuse. Bone trabeculae particularly respond to on-axis compression force or tensile stress.

Slipped and fell usually result in bruise in normal people but it can cause bone fracture in elderly. Part and partial is due to osteoporosis especially in postmenopausal women. However, in the early stage of bone loss, there is no symptoms. In established osteoporosis, patients may have back pain, loss of height, a stooped posture due to vertebral collapse and fracture may result after trivial injury [13,14].

Osteoporotic hip fracture particularly attracts attention since it causes not only prolonged immobilization, but also nosocomial complications like pneumonia and venous thrombosis. Even with surgery and rehabilitation, patients may end up with a limping gait affecting their social life. Femoral head and neck are not arranged in a straight line (Figures 3 and 4).

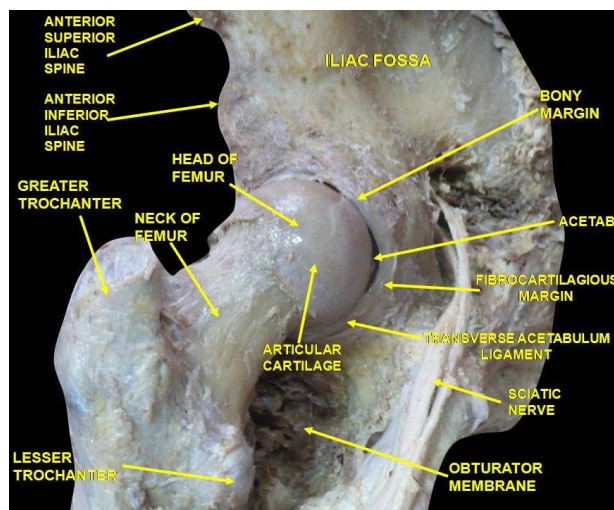


Figure 3. Postero-lateral view of left hip joint.

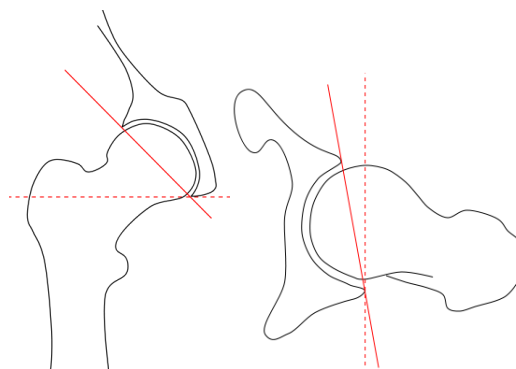


Figure 4. Transverse and sagittal angles of acetabular inlet plane. Note the anteversion of femoral neck on the right side.

The angle between femoral neck and femoral shaft also affects the arrangement of bone trabecular

pattern with coxa valga more compression trabeculae, and coxa vara more tension trabeculae (Figure 5).

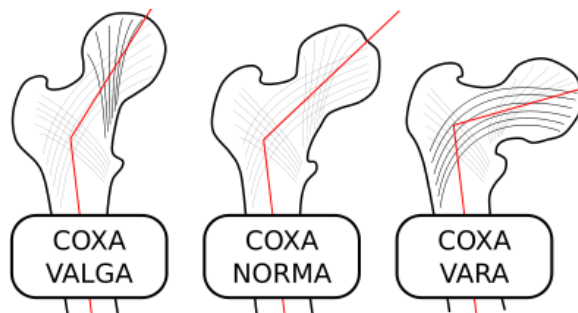


Figure 5. Changes in trabecular patterns due to altered caput-collum-diaphyseal angle.

Dietary and medication

Adequate dietary calcium and Vitamin D is required to prevent osteoporosis. Milk, cheese, yogurt are the natural sources of calcium. Animal foods rich in Vitamin D include beef liver, fish liver oil, egg yolk, tuna, mackerel and salmon. The Recommended Daily Allowance (RDA) [15] of calcium for age and gender is shown in Table 1.

Table 1. Recommended Daily Allowance (RDA) of calcium.

Target population	RDA of calcium
Females 51 to 70 years	1, 200 mg
Males 51 to 70 years	1, 000 mg
Males and females over 71 years	1, 200 mg
Pregnant and lactating women all ages	1,300 mg

Antiresorptive and bisphosphonate medications prevent loss of bone density and thus osteoporosis, but a recent study by the Food and drug administration (FDA) has shown that continued usage of bisphosphonate has little long term benefits. Post-menopausal women may benefit from estrogen hormone therapy taken in combination with

progesterone to prevent uterine cancer. However, long-term hormonal replacement therapy is not recommended due to the risks of stroke, cancer and venous thrombosis.

Consistent exercise maintains bone health. Walking, climbing stairs, light weight-lifting are advised. High impact physical exertion stimulates bone-rebuild. Research proves that smoking one pack of cigarettes daily leads to a loss of 5-10% in bone mass. Furthermore, smoking reduces the level of estrogen in women .

Bone densitometry of spine and hips are checked before anti-osteoporotic drug treatment, except for those patients with fractures after a simple fall. The densitometry is then repeated every 2 to 5 years. In highly equipped laboratory, blood and urine markers, like N-terminal telopeptides of type-I collagen are also checked and show bone renewal which reflects the consequent bone loss measured one year later.

Osteoporotic bones hold with difficulty the screws or implants during orthopedic surgery like Enders nailing, Austin Moore Arthroplasty, AO (Arbeitsgemeinschaft für Osteosynthesefragen) screws, dynamic hip screw, condylar blade plate, gamma nailing. As a result, the screws will cut through the femoral head. Furthermore, hospital

acquired pneumonia may cause mortality and some residual disability is inevitable after rehabilitation. Usually, bisphosphonate, parathyroid hormone, denosumab, raloxifene, micalcic, strontium ranelate, hormonal replacement therapy is given on top of calcium and vitamin D and the fracture risk is reduced in 6 to 12 months.

To reduce the complications, anti-osteoporotic medications is stopped after 3 to 5 years, so called the drug holiday. The residual beneficial effects of the medications last for few more years. So another cycle of anti-osteoporotic medication can be started every 8-10 years. However, T-scores wax and wane between treatment cycles leading to an increase in fracture risk. Furthermore, the medications cannot improve the trabecular architecture so it is logical to consider bone rebuild by means of suitable exercises.

Osteoporosis epidemiology in Hong Kong

The burden of osteoporotic bone fractures is part and partial reflected by the Clinical Data Analysis and Reporting System of Hospital Authority of Hong Kong. 13,674 patients, from 31st July, 2011 to 31st

July, 2015, were recruited. They had diagnosis of unspecified osteoporosis, senile osteoporosis, idiopathic osteoporosis, disuse osteoporosis, other osteoporosis or algo-neurodystrophy.

1,807 patients (13.21%) had hip fracture, mainly the femoral neck fracture and the trochanteric fracture. 691 patients (5.05%) had closed vertebral fracture, mainly affecting the lumbar spine and 203 patients (1.48%) got wrist fracture, mainly affecting the distal radius with or without distal ulnar bone. In other words, 20% of the osteoporotic patients will acquire a major bone fracture over a 4-year period despite the advance in anti-osteoporotic medications.

Scientific evidence of bone adaptation to compression

Bone adaptation is driven by dynamic loading, even for a short period of time. However, osteoblast-osteoclast concert system will soon accustom to the loading force making the cells less responsive to the loading signals[16]. So repeated or cyclical compressive stress is required for bone hypertrophy.

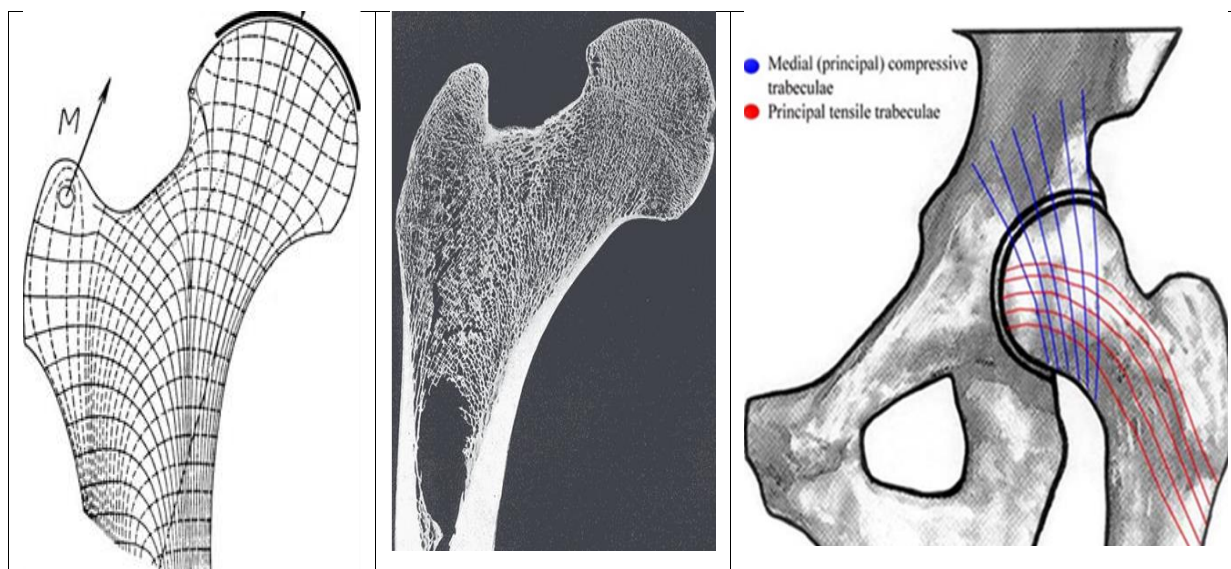


Figure 6. Stress trajectories (left) and trabecular architecture (middle) in the proximal femur (right) femoral neck trabeculae pattern

Wolff discovered that the bone architecture obeyed the mathematical laws. The thickness and number of trabeculae followed the distribution of axial mechanical stresses or compression. This principle was confirmed by Pauwels who demonstrated that the stress trajectories correspond to the trabecular architecture in the proximal femur [17,18].

Using high-resolution micro-computed tomography and micro-finite-element analysis, most vertebral strength was attributed to the bone volume fraction of vertical trabeculae rather than to all bone trabeculae during vertebral compression. This trend did not change after the removal of the cortical shell. Study of individual bony tissue compartment is possible by means of a custom script (IDL 6.2, ITT Visualization Information Solutions, Boulder,

CO,USA) where the bone tissue in the trabecular compartment was digitally isolated from the cortical shell and endplates [9].

In dog model, continuous compressive stress increased the cross-sectional area of mid-diaphysis of femur due to periosteal new bone apposition [10]. Repeated axial loading caused bone hypertrophy and decreased osteoporotic bone fracture through the effect on matrix protein expression, selective stimulation of osteopontin, bone sialoprotein and prostaglandin E₂ production [8], [11,12].

By similar reasoning, axial stresses acting in line with bone trabeculae in distal radius and vertebral bodies by punching and weight lifting exercise are effective to strengthen the radius and the vertebrae as shown in Figure 7.



Figure 7. Bone trabeculae arrangement in distal radius and vertebra. Boxing and weight lifting strengthen the corresponding bones.

Finding a suitable exercise to prevent hip fracture is difficult due to the complex femur anatomy as discussed above. The femoral neck extends inferolaterally from head to meet shaft of femur at an angle of 125° . The angle varies with age, stature and width of pelvis, being less in adult, in patients with short limbs and in women. This angle can be more than 135° (coxa valga) or less than 120° (coxa vara). The femoral neck is not in parallel to the plane of femur. The femoral head is anterior to midline of femoral shaft (anteverted). In adult, the femoral neck-shaft angle is 5 to 15° . It can be more than 15° (increased femoral anteversion) or less than 5° (femoral retroversion).

To strengthen the femur, straddling at around 130° is not enough. We need a backward component

of around 10° due to the femoral anteversion. Simple straddling can be achieved by dancing, yoga or kung-fu training but straddling back is only seen in breaststroke swimming style. The swimmer's head emerges from water for breathing at the end of straddling. The lower lumbar spine bends back making the force of straddling directed forward. Furthermore, the continuous motion of breaststroke straddling will strengthen surrounding bone trabeculae in direction to the greater and the lesser trochanters, along with the femoral neck and the whole sphere of femoral head.

In other words, breaststroke swimming style (Figure 8) essentially strengthens the principle tensile trabeculae as the lateral kick of legs creates a force directing through the bone trabeculae of femoral neck to the femoral head.



Figure 8. Breaststroke swimming style

Discussion:

As osteoporosis is a silent disorder, we need an assessment protocol to recognize it and to understand how the medication works increasing the bone density. So patients with osteoporosis can be identified and treatment can be offered. Osteoporosis is diagnosed by dual energy x-ray absorptiometry (DEXA scan). For osteopenia, doctors look for any previous low trauma fracture, current smoking history, steroid exposure, family of hip fracture, more than 2 units of alcohol intake daily, rheumatoid arthritis, increase in fall or frailty or loss of more than 2.4 inches in height. For high-risk osteopenia or osteoporosis, the collagen crosslinks parameters like deoxypyridinoline, collagen type 1 cross-linked amino or carboxyl terminal peptide are measured. For those who are in high risk of rapid bone loss,

anti-osteoporotic medication is started and reviewed at 3 to 6 months. If there is less than 20-40% change in bone markers patient should check for drug compliance (Table.2) and consider to change to another agent since biochemical bone markers predict the rapid bone loss [19]. Bone formation markers include serum bone-specific alkaline phosphatase, serum osteocalcin, serum type 1 procollagen. Bone resorption markers include urinary hydroxyproline, urinary pyridinoline, urinary deoxypyridinoline, urinary collagen type 1 cross-linked N-telopeptide, urinary or serum collagen type 1 cross-linked C-telopeptide, bone sialoprotein, tartrate-resistant acid phosphatase 5b [20]. Bone marker test and DEXA scan are repeated after 1 and 2 years, respectively.

Table 2. Mechanism of action and side effects of anti-osteoporotic medication.

Anti-osteoporotic drugs	Mechanism of action	Side effects
Bisphosphonate: Alendronate, neridronate, ibandronate, pamidronate, risedronate, and zoledronic acid	Inhibit osteoclastic bone resorption by attaching to hydroxyapatite binding sites on bony surfaces undergoing active resorption. Decreasing osteoclast progenitor development and recruitment	GI upset, rashes or photosensitivity, sore mouth, flu-like symptoms for oral drug, bone pain in iv preparation, muscle pain, headaches. Jaw osteonecrosis, tiny increase in esophageal cancer, partial fractures in upper outer femur below the hip (alendronate).
Teriparatide (PTH amino acid sequence 1 through 34)	Stimulates osteoblastic activity over osteoclastic activity, resulting in new bone formation	Nausea, reflux symptoms, palpitations, dizziness, headache, fatigue, depression, bone pain. Not in skeletal cancers, Paget's disease, post radiotherapy.
Denosumab (for osteoporosis, bone metastases, multiple myeloma, and giant cell tumor of bone)	Human monoclonal antibody reduces osteoclastic bone resorption by inhibiting RANKL, that activates RANK surface receptor expressed on osteoclast precursors	Joint and muscle pain, increased risk of infection (RANKL is expressed by T-helper cell), hypocalcemia, allergy, jaw osteonecrosis, hip fracture.
Riloxifene	Oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on uterus and breast	Hot flushes, leg cramps, swollen ankles and flu-like symptoms. Not used if there is history of deep vein thrombosis, uterine cancer or liver disease.
Miacalcic Nasal Spray	Inhibits osteoclasts, thereby decreasing the rate of bone breakdown, allowing the body to build bone naturally.	Nasal irritation, dryness, redness, itching, or bleeding
Strontium ranelate	Its nucleus has the same size as that of calcium, strontium incorporates into bones and tooth enamel. It stimulates differentiation of pre-osteoblast, osteoblasts secretion of osteoprotegerin that inhibits differentiation of pre-osteoclasts in relation to RANKL system.	Mild diarrhea, nausea or rashes or DVT. Not used if there is history of ischemic heart disease, stroke, thrombosis, uncontrolled hypertension.
Hormone replacement therapy: Conjugated estrogens like equine or synthetic, micronized 17 β estradiol, and ethinyl estradiol. Progestins like medroxyprogesterone acetate and norethindrone acetate.	Estrogen with or without progestogen to restore a woman's declining hormone levels after menopause	Complications include endometrial / breast/ ovarian cancer, hypertension, hyperlipidemia, gallbladder disease, DVT, heart attacks, strokes and memory impairment.
Calcium and vitamin D (D3 cholecalciferol) and D2 ergocalciferol)	Fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc.	Patients taking vitamin D for long periods of time in doses higher than 4000 units daily will have hypercalcemia with weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting.

The choice of anti-osteoporotic medication is based on the mechanism of action, side effects and limitations as shown in the following table. Suitable exercise for at least 30 minutes a day and 5 days a week will supplement the medication to improve the bone strength and reduce the osteoporotic fracture

Anti-osteoporotic medications have different characteristics and limitation. To use them well, we should have deep knowledge about them. Bisphosphonates can cause heartburn. Pamidronate and Zoledronate are given intravenously every three months and once a year, respectively. Ibandronate

can be given orally or intravenously every three months. Treatment is limited to 5 years. Regular dental checkup is required.

Teriparatide is injected to abdomen or thigh subcutaneously daily for 18 to 24 months. Denosumab subcutaneous injection twice a year is used in postmenopausal women who cannot take bisphosphonates and in men who undergo orchidectomy for prostate cancer. Raloxifene is given after osteoporotic vertebral fracture in postmenopausal women. Miacalcic nasal spray provides immediate pain relief after osteoporotic vertebral collapse. Strontium ranelate is a second line anti-osteoporotic medication.

Hormonal replacement therapy is a short-term therapy for women up to the age of 60 with increased fracture risk and troublesome menopausal symptoms. Calcium and vitamin D supplements are often given alongside with the other treatments for osteoporosis.

Conclusion and future study

Besides medications, bone rebuild by boxing, weight lifting, and breaststroke swimming improves the trabecular architecture. We proposed a cohort study to confirm the beneficial effect of on-axis loading exercise. Two groups will be evaluated: One group on anti-osteoporotic medication only another one on medication and regular breaststroke swimming for 30 minutes daily and 5 days weekly. These 2 groups should be age matched and demographically similar. After 8 weeks, the bone density and the trabecular architecture will be assessed by DEXA scan, high-resolution micro-computed tomography and micro-finite-element analysis. The expected result should be a better bone quality of the exercise group.

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