Clinical Management of Osteoporosis: An Overview

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ABSTRACT

Osteoporosis is characterized by low bone mass and micro architecture deterioration of bone tissue and severe osteoporosis characterized by a disease of high mortality and morbidity. Risk increases exponentially with age and decrease in bone mass density. For management a deep understanding of biomechanics of osteoporotic bone and medical optimization is required. Worldwide belief is in average 5 women 3 women are at risk of getting osteoporotic fracture as well as 1 in 5 men. India with the population of 1.2 billion, 10% population is affected with osteoporosis. It is categorized into primary and secondary osteoporosis. There are various risk factors like age, hormonal disturbance, secondary hyperparathyroidism, hereditary and poor lifestyle. Repeatedly some drugs intake increases the risk of osteoporosis like glucocorticoids, proton pump inhibitors. Risk if fracture is higher in patients with higher incidents of falls as in hemiplegia, lower limb dysfunction. Methods to determine bone density are single and dual X-ray absorptiometry, computed tomography. Pharmacological therapy including vitamin D and calcium supplements, hormonal replacement therapies, serum estrogen receptor modulators and bisphosphonates. This paper highlight sorts of osteoporosis, its risk factor, management, pathophysiology of bone loss and about management of fractures.

Keywords: Osteoporosis, osteonecrosis, bones, bone loss.

1. INTRODUCTION

Osteoporosis is characterized by low bone mass and micro architecture deterioration of bone tissue. It is basically the loss of ability of bone tissues to compensate the loss done by traumatic injury (Friedman et.al. 2014). Also the alteration or imbalance of bone remodeling that is increased breakdown of bone tissues done by osteoclast as compared to formation done by osteoblasts which result to pore formation and leading to increase the susceptibility of bone fracture. The imbalance of bone resorption and formation lead to widening of haversian canal, thinning of cortical bone and a lesser number of taberculae is left in bone which is basically a decrease in bone mass density. Bone mass density is a marker of osteoporosis and determined by DEXA and expressed in form of T-score. (Cumming et.al. 2002) The risk of osteoporosis increases exponentially with age and decrease in bone mass density. Osteoporosis can be seen as a huge loss of mortality, morbidity and cost. It can lead to disability and deterioration of quality time. The higher prevalence of obesity and low tobacco consumption habits improve the bone mass. (Alshareef et.al. 2018) For management and guidance by osteoporosis a deep understanding of biomechanics of osteoporotic bone and medical optimization are required and there is need to take care to prevent secondary fractures. In many cases osteoporosis remains undiagnosed until manifests low trauma fractures. Osteoporosis is not only the single cause of fractures but it delays the fixation of fractures or failures of fixation of fractures (Olsen et.al. 2013)

1.1 Epidemiology

Type I postmenopausal osteoporosis generally occurs before the age of 65 years and affect women, type II is universal after peak bone mass has been attained and is found in both men and women. Worldwide estimation is in average 5 women 3 women are at the risk of having osteoporotic fracture, as well as 1 in 5 men. India with population of 1.2 billion, 10% population is affected with osteoporosis. A study in Delhi estimated the prevalence of osteoporosis as 24.6% in men and 42.5%in women above 50 years of age. (Kadam et.al.2020) As per the estimations the prevalence of osteoporosis is less in men as compared to women, but the mortality in males post hip fracture is a high. Male osteoporosis largely remains undiagnosed and untreated and is revealed only after the occurrence of a fracture. As per WHO definitions based on T- score, the prevalence of osteoporosis at lumbar spine 14.5% and at hip 5.7% in men while in women 18% at lumbar spine and 12.7%. (Kadam et.al. 2020)

1.2 Types

Osteoporosis has been categorized into two categories; primary osteoporosis and secondary osteoporosis Primary osteoporosis is that the most typical style of the disease includes postmenopausal osteoporosis (type1) and senile osteoporosis (type2). Type 1 is related to hormonal

deregulations as loss of estrogen and androgen ends up in increase bone turnover that's the predominant loss of trabecular bone compared to cortical bone. Type 2 represents gradual related bone loss found in both sexes caused by senescence with a predominat loss of cortical bone. (Miller et.al. 2015)

2. RISK FACTORS

2.1 Age specific changes in BMD

Age related bone loss is greater in female than man as in first years after menopause there is rapid loss of bone largely in trabecular compartment and lead to loss of entire trabeculae. (Nieves et.al 2005) Cortical bone loss is also acclerated. In men trabecular bone loss consist of thinning of trabecular region rather than loss of entire content. (Aaron et.al. 1987)

2.2 Hormonal disturbance

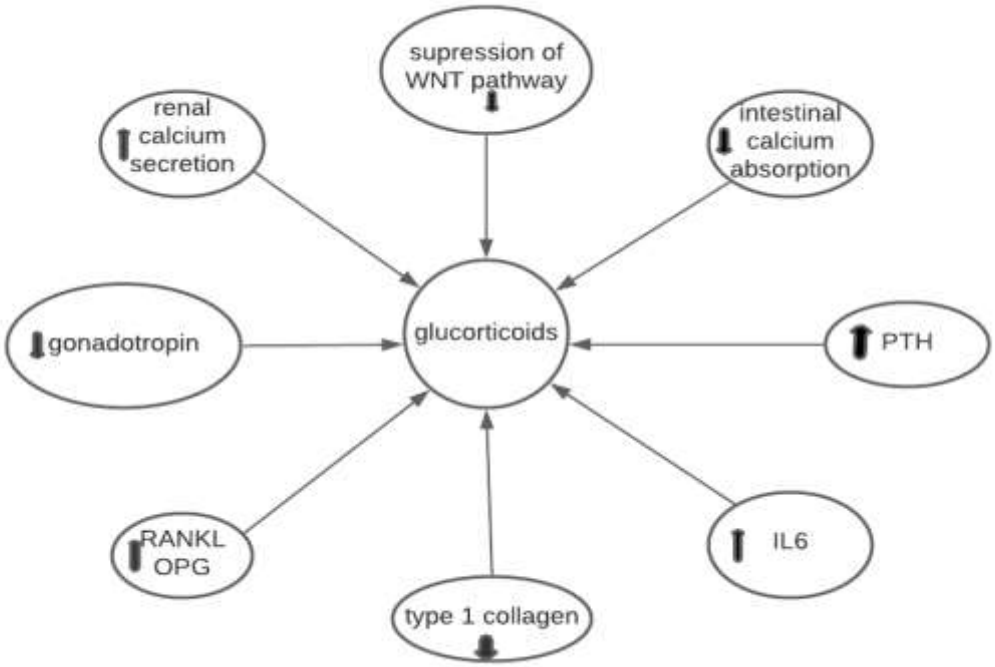
A rapid decrease is seen in 17β- estradiol secretion and enhanced the secretion of cytokines that activates osteoclast, RANKL, interleukins and tumor necrosis factor (Kaufman et.al 2005). Hence, increase in bone resorption. Men with lowest 17β-estradiol levels possess low BMD and higher level of biochemical bone turnover makers and are at higher prevelence of vertebral fracture and major hip fracture. (Khosla et.al. 2008)

2.3 Secondary hyperparathyroidism

Secondary hyperparathyroidism occurs due to less consumption and availability of vitamin D and calcium. The secretion of parathyroid hormone is increased and it stimulates the bone resorption at cortical bone.

2.4 Other risks

Other risks may include hereditary factors. Lifestyle factors such as alcohol abuse, smoking, low calcium intake, and lack of physical activity. Some disease also increases the risk of osteoporosis, hyperthyroidism, cushing's disease, primary biliary cirrhosis, hypogonadism, beta-thalassemia, and disease of digestive tract as crohn's disease, coealic disease. (kanis et.al. 2005) Some drugs intake increase the risk of osteoporosis as glucocorticoids, thyroid hormone excess, anti-androgen treatment, loop diuretics, proton pump inhibitors and some drugs used in AIDS (tenofovir, protease inhibitors) (Eisman et.al 1999) (Richard et.al 2009) Risk of fractures is also higher in patients with higher incident of falls as in hemiplegia, lower limb dysfunction, Parkinson's disease, orthostatic hypotension and among the patients treated with neuroleptics, antidepressants and antihypertensives.



3. GENERAL PATHOPHYSIOLOGY OF BONE LOSS

Bone remodeling is that the process by which old bone is replaced by new bone. The traditional bone remodeling carries with it five phases; resting, activation, resorption, reversal, formation.

- In the activation phase of remodeling, osteoclast are recruited to the surface of bone
- In the resorption phase, osteoclast generated an acidic microenvironment in between the cells and the surface of the bone, dissolving or resorbing the mineral content of bone.
- In the reversal phase, osteoclast undergo apoptosis and osteoblasts are recruited to bone surface
- In the formation phase, osteoblast then deposit collagen; that is mineralized to form new bone. (Christopher et.al. 2014)

At menopause osteoclastic resorption activity is increased without any corresponding increase in osteoblastic activity due to estrogen deficiency.

Bone resorption is stimulated by RANKL production via cells of osteoblastic lineage. Binding of RANKL to its specific RANK receptor activates the complex intracellular pathway including NF-Kβ and results in induction of osteoclastogenic genes. OPG forestalls the official of RANKL to RANK. So the OPG/RANKL is the key factor to maintain normal bone turnover. Several hormones, growth factors (TGF-β, IGF-1), cytokines (IL-1, IL-6, TNFα) influence the OPG/RANKL ratio (Sandhu et.al. 2011)

4. MEASUREMENT OF BONE MINERAL CONTENT

4.1 Single and dual x ray absorptiometry

Single and dual x ray absorptiometry are used to assess mineral content of entire skeleton and that of specific sites. These provides two-dimensional areal picture not true volumetric density. Presence of osteocalcin can be a complication that is caused by poor nutrition can result in underestimation of bone mass. DXA can also be visualize lateral images of the spine from T4 to L4 to detect deformities of vertebral bodies.

4.2 Computed tomography

Computed tomography is most useful for assessment of cancellous bone density as this technique provides the true volumetric density rather than just areal adjusted result. Computed tomography can also be used to check the effect of treatment and this technique avoids the effect of degenerative disease.

4.3 Threshold; a cutoff for BMD

Bone density values in individual are expressed in relation to a reference population in **standard deviation (SD) units.** This method reduced the ability of difficulty arise due to calibration of instruments. In T score, SDs are used in relation to young healthy people.

Diagnostic criteria for women by WHO and international osteoporosis foundation.

- Normal- hip BMD greater than 1 SD Below the young adult female reference mean
- Low bone mass- hip BMD greater than 1 SD but less than 2.5 SD from Below younger adult female reference
- Osteoporosis – hip BMD 2.5 SD or more below the young adult female mean
- Severe osteoporosis – hip BMD 2.5 SD or more below the young adult female mean in the presence of one or more fragility fractures.

For diagnosis hip is the gold standard in terms of site, since it has higher predictive value for hip fractures, which is most severe complication of osteoporosis and predicts risk of all fractures. BMD measurement is for indicative prospective; normal BMD does not ensure any guarantee that fracture will not occur, it means risk is reduced. If BMD is in osteoporotic range, then fractures are more likely to happen.

BMD T-score	**Diagnosis**
T-score ≥ -1	Normal
-1> T-score > -2.5	Low bone mass
T-score ≤ -2.5	Osteoporosis
T-score ≤2.5 with existing fracture	Severe osteoporosis

5. BIOCHEMICAL ASSESSMENT

Biochemical assessment of risk factors can also be done through checking the markers of resorption and markers of formation. Bone formation markers are total alkaline phosphatase, the bone isoenzyme alkaline phosphatase, osteocalcin, and the procollagen peptides of type 1 collagen. The most widely used markers of bone resorption are hydroxyproline, pyridinium crosslinks and their associated peptides. After menopause an increase in number of these markers can be seen and studies reveal that rate of bone loss varies according to the marker value. In elderly women with values for resorption markers that exceed the reference range for premenopausal women, fracture risk is increased about two folds after adjustment for BMD.

6. FRAX

FRAX is a computer-based calculation that figures the long-term likelihood of a significant break (hip, clinical spine, humerus, wrist fracture) and the 10 years probability of hip break. Fracture risk is calculated from age, body mass index and risk factors, parental history of fracture, tobacco smoking, long term use of glucocorticoids, arthritis and other causes of secondary osteoporosis. Fracture risk is computed taking both the things risk of fracture and risk of death into account. The use of risk factors with BMD improves sensitivity of risk of fracture prediction.

Interventional threshold

The use of FRAX demands a consideration of fracture probability at which to intervene for treatment are categorized under interventional threshold. This threshold uses the local factors such as health, economical assessment, willing to pay for health care and access to DEXA.

6.1 Assessment threshold for BMD testing

These are the assessment threshold for recommendation for the measurement of BMD. There are two assessment thresholds;

- A threshold probability below which neither treatment nor a BMD test should be considered; low assessment threshold
- A threshold probability above which treatment may be recommended irrespective of BMD; upper assessment threshold

6.2 Assessment of fracture risk with FRAX with limited admittance to BMD

- Fracture risk should be accessed in postmenopausal women with one or more clinical risk factors
- Women with prior fracture might be considered for treatment without further assessment through BMD
- In women without prior fracture, the 10-year probability of fracture should be determined by FRAX without BMD
- Those with probability above the lower assessment threshold but below the upper assessment threshold be considered for testing BMD

In case of unavailability of BMD assessment should be done by FRAX only treatment should be considered directly in those who lie under thresholds categories (Brid et.al 2013)

7. MANAGEMENT OF FRACTURES

Common anatomical areas of fragility fractures include spine, proximal femur, distal femur, distal radius and proximal humerus

7.1 Sarcopenia

Sarcopenia is defined as the loss of skeletal muscle mass and strength that occur with ageing. These are the changes occurring to the muscle at the cellular level including weakening of factors that promote anabolism and increased expression of inflammatory factors that contribute to catabolism. Diagnosis of sarcopenia can be done with imaging and non-imaging techniques. Non-imaging techniques include questionnaire and physical performance tools that measure gate speed, repeated chair rise and balance testing. Imaging techniques include DXA, sonography, MR, CT. Sonography is useful in screening of appendicular skeleton using size and echo intensity parameters. MR accurately quantify cross sectional area and display pathological features of muscle including fat content. CT allows measurement of cross-sectional area and density of muscle using axial cuts.

Sarcopenia and osteoporosis are discrete entities but are associated in the elderly secondary to the relationship of bone and muscle. (Marley et.al 2001)

7.2 Biomechanical principles of fragility fracture management

When fracture failure occurs at level of hardware, failure in fixation of fracture at osteoporotic bone it typically occurs at the interface of implant and bone

Structural differences in bone are reason for this failure such as decreased axial and torsional strength due to decreased BMD and increased incidence of comminuation despite low injury mechanism and also increased healing time in osteoporotic bone

7.3 Implants

Implant selection is most important. As a general principle atleast three bicortical screw should be placed on either side of fracture in osteoporotic bone. (freeman et.al 2010)

Locking plates provide a greater biomechanical advantage in bone with low BMD by creating a fixed angle between screw and plate. (Bottlang et.al 2009)

7.4 Nails

An intermedullary nail is a load sharing device which promotes secondary bone healing and preserves surrounding soft tissue and fracture hematoma. It is the gold standard of treating long bone fragility fractures, including proximal and distal fractures. Different stratergies have been planned to counteract the loss during screw fixation that are use of washers, use of interlocking screws in multiple planes, use of blades and locking screw. (Bogunovic et.al 2013) (Kammerlander et.al 2013)

7.5 Augmentation

Bone augmentation is one strategy to add to construct stability. Tricalcium phosphate and polymethylmethacrylate are two bone cement augment that helps in increasing implant fixation when screws are placed. They provide resistance against the thread of screw. (Fliri et.al 2012)

8. TYPES OF FRACTURES AND THEIR MANAGEMENT

8.1 Distal radius

Distal radius fractures are the second most common osteoporotic fracture. There is no significant increase in risk of mortality by distal radius fracture alone it can be a predictor of other fragility fractures. (Cumming et.al 1989)

In non-operative management consist of closed reduction and splint or cast immobilization. In operative management open reduction and internal fixation with volar plate is done. External fixation and intermedullary fixation can also be done. (Oyen et.al 2011)

8.2 Proximal humerus

Proximal humerus fractures are another commonly encountered fractures. They can be managed non operatively. Sling immobilization followed by gentle range of motion is preferred in non-operational management. Surgical treatment is based on fracture severity and overall health status of patient and the choice is based on surgeon preference. Surgical methods include closed reduction and precutaneous fixation, plate fixation, intermedullary nailing, and arthroplasty. Where percutaneous fixation is only reserved for minimal comminuted fracture patterns. In highly comminuted fractures arthroplasty should be considered. In case of deficient rotator cuff, reverse total shoulder arthroplasty is viable option. (Kancherla et.al 2017) (Kannus et.al 2009)

8.3 Proximal femur

Proximal femur are the fragility fractures with high mortality and morbidity. These fractures are associated with low energy injuries. Proximal fractures are divided into two main groups; intracapsular fractures and intertrochanteric fractures. Fractures can also be classified as stable and unstable. For unstable percutaneous cannulated screws are the treatment of choice. For unstable arthroplasty and hemiarthroplasty are considered. Hemiarthroplasty is most recommended in elderly patients as it is less invasive and more stable option. Total hip arthroplasty is recommended in youngsters or active individuals with arthritis. For extracapsular proximal femur fractures, the sliding hip screw and cephalomedullary nail are used. (Abrahamsen et.al.2009)

8.4 Spine

Spine fractures are the most common fragility fractures. These fractures have decrease the fixation strength in osteoporotic bone. Bisphosphonates and anabolic agents are used to manage. Bisphosphonates show negative impact on fusion while adjuvant anabolic agents significantly increase the rate of bony union and decrease pedicle screw loosing. Vertebroplasty is invasive method of stabilization and pain control. Spinal fusion and fixational failure may occur due to instrumentation failure and proximal junctional kyphosis.

For improving the strength of fixation various techniques are used such as increasing point of fixation, cross linking segmental pedicles, cement augmentation and screw design modification. (Casareo et.al.2015) (Harvey et.al.2017)

9. PHARMACOLOGICAL INTERVENTIONS

Initiation of pharmacotherapy is a significant step to prevent secondary fractures. Early diagnosis of patient injury and its distinguishing as fragility fracture and initiating a pharmacotherapy is crucial step for preventation of secondary fracture. Pharmacological interventions include calcium and vitamin D Supplements, hormonal replacement therapy, bisphosphonates, PTH and PTH agonists, and RANKL inhibitors. (Richard et.al. 2019)

9.1 Vitamin D and calcium

Vitamin D and calcium supplements are the first line pharmacological therapies. Active metabolites of vitamin D are used for treatment of osteoporosis. These metabolites show decrease in incidence of fragility fracture in patients who were not treated with glucocorticoids. (O' Donnell et.al. 2008) Low vitamin consumption did not reduce the risk of fracture a high amount of it should be given for efficacy and calcium supplements ranges from 1000 to 1200mg per day as per deficiency is seen. (Hollis et.al.2005)

9.2 Hormonal replacement therapy

Hormonal replacement therapy may only contain estrogen or in combination with progestin. HRT reduces the bone turnover rate and shows an increase in BMD at all skeletal sites in early and postmenopausal women. HRT decreased the fragility rate, but discontinuation of HRT lead to acceleration of bone turnover rate and decrease in BMD which is eventual loss of anti-fracture efficacy. (Torgerson et.al.2001) HRT can induce vaginal bleeding, breast tenderness and may increase the risk of myocardial infractions and ovarian cancer. (Cauley et.al.2003)

9.3 Selective estrogen receptor modulator

Selective estrogen receptor modulators are synthetic molecules that bind to estrogen receptors and act as estrogen agonists and antagonists depending upon target organ. (Siris et.al.2005) Raloxifene (60-120mg) slows down the bone turnover and increase BMD by 2 to 3% at the lumbar spine and femoral neck and also reduces the incidence of vertebral fracture. (Barret et.al.2006) Bazedoxifene (20-40mg) decrease BTM level as same extent as raloxifene and increase BMD and prevent bone loss at the total hip. It decrease the risk of vertebral as well as nonvertebral fractures. (Miller et.al.2008)

9.4 Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and inhibit the activity of osteoclast. Bisphosphonates bind to bone mineral, have long skeleton retention and variety of dosing regimens and types exist. The inhibitory effect of bisphosphonates may inhibit intramembranous fracture healing which leads to increased rate of delayed or non-union. Alendronates decrease bone resorption and increase BMD and reduce incidence of fracture to 30-50%. It decreases the risk of hip fracture to 45%. In early postmenopausal women small dose of 5mg is also significantly effective. In men, alendronate increase BMD at lumbar spine and hip and decrease the incidence of vertebral fractures and effective in treatment of glucocorticoid induced osteoporosis. (Black et.al.2006) Risedronate decrease incidence of new vertebral and peripheral fractures in women with low BMD. Risedronate is also effective in glucocorticoid induced osteoporosis. (Harris et.al.1999) Ibandronate is given as once monthly therapy and reduce the vertebral fracture (Delmas et.al.2004) Zolendronic acid is administered intravenously at low dose to postmenopausal women once a year and induce a decrease in bone turnover. Zolendronic acid increase BMD at hip, decrease incidence of clinical fractures. (Black et.al.2007) Osteonecrosis of jaw is the adverse effect of long-term consumption of bisphosphonates and high risk of atrial fibrillation is associated with long term consumption of bisphosphonates. (black et.al.2007)

9.5 Salmon calcitonin

Salmon calcitonin is a nasal spray, which is basically a 32 amino acid peptide secreted by C cells of thyroid. It inhibits the activity of osteoclast but only a slight increase in BMD. Nasal salmon in un-effective on non-vertebral fractures. It reduces the pain caused by acute vertebral fractures and it is safe from allergic reactions. Nasal salmon is not used as first line therapy because of its low or limited antifracture efficacy. (Chesnut et.al.2008)

9.6 Antibody to rank ligand: denosumab

Denosumab inhibit the receptor activator of nuclear factor RANKL to receptor activator of nuclear factor rank on the cells of osteoclastic lineage. This inhibits the activation, differentiation, and survival of osteoclast. Denosumab is human monoclonal antibody with high affinity and specificity. Denosumab decreased the risk of vertebral fracture in postmenopausal osteoporotic women. It improves BMD and slows down the bone turnover in older men receiving androgen deprivation therapy for prostate cancer. Denosumab in combination with terparatide are more effective rather than alone. (Smith et.al.2009)

9.7 Anabolic agents; PTH and teriparatide

Recombinant 1-34 fragment of human parathyroid hormone (teriparatide) and recombinant human intact parathyroid hormone (PTH1-84) are effective stimulators of bone formation. They increase the formation of bone and a slight increase in bone resorption. They strongly increase BMD in the trabecular compartment so the major increase of BMD at lumber spine can be observed. The increase in cortical bone volume at radius and femoral can is also seen. The therapeutic effect of PTH can be obtained by less frequent administration of PTH with alendronate. These medications are given to those patients who continuously loss bone mass despite of anti-resorptive therapy. (Hodsman et.al.2005) They are contraindicated in patients with sarcoma or having history meta-stative bone disease. Long term therapy may show adverse effects.

9.8 Strontium ranelate

Strontium ranelate slightly inhibit bone resorption, slightly stimulate bone formation, and increases BMD on basis of doses given. (Meunier et.al. 2009) It decreases the incidence of vertebral fracture in younger postmenopausal women. It decreases the risk of hip fracture in high-risk elderly women with severe osteoporosis (Reginster et.al. 2008)

Sr. no	DRUG	SIDE EFFECT
1	Bisphosphonates (alendronate (po), risedronate (po), ibandronate (po/iv), zolendroic acid (iv))	Atypical femoral fracture osteonecrosis of jaw, esophageal cancer
2	Calcitonin (sc/im/ins)	Nausea, hot flushes,calcitonin antibody formation, prostate cancer
3	Raloxifene (po)	Uterine stimulation, deep venous thrombosis, hot flushes
4	TSEC (conjugated estrogen 0.45mg/ bazedoxifene 20mg)	Abdominal pain, nausea, muscle spasms, dizziness
5	teriparatide	Hypercalcemia and hypercalciuria osteosarcoma

10. NEW DRUGS

Cathepsin k inhibitors that belongs to cysteine protease family and are responsible for pathological and physiological degradation of connective tissue. Several CATK inhibitors have been developed. CATK is vital target for drug development (Awasthi et.al.2018) Src kinase inhibitors modulates the cytoskeleton changes in the osteoclast to facilitate resorption activity. (Awasthi et.al. 2018) Nitrates are shown to be effective in post-menopausal women as it regulates osteoclast activity by OPG/RANK pathway (Himilton et.al.2013)

11. CONCLUSION

In the above as we stated that osteoporosis is major issue arise due to low bone mass highly impact the quality of life and cost or may lead to death. Women are at the high risk of having it due to hormonal deregulations and low bone mass. Even it is serious problem but only less or a portion of cases are identified so it is need of time to focus on identification of such patients. A proper guidance about its risk factors can help in many ways of identification of patients. DXA is most preferred technique to diagnose osteoporosis. In case BMD measurement is not assessable a case finding approach could also be done. After facing primary fracture, you need to be very careful to avoid secondary fracture. Another major concern is initiation of medical treatment. Bisphosphonates are first line drugs for glucocorticoid induced osteoporosis. Some preventive measures could also be made such as doing certain exercise and increase physical activity and taking proper calcium diet.

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