Cytokines in osteoporosis and steroid induced osteoporosis

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WHO (1993) has defined osteoporosis "disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk".[1]
Osteoporosis is a serious public health problem second to cardiovascular diseases in global health care scenario. 1 in 3 women and 1 in 5 men over the age 50 experience osteoporotic fracture worldwide. Patients usually suffer from pain, limited range of motion, disability and deformity but osteoporosis becomes clinically apparent only after the fracture occurs. Psychosocial symptoms and loss of self-esteem are also associated.

Once a fracture takes place there is increased risk of subsequent fractures and hence, rise in subsequent mortality. There is 5 fold risk of second fracture after sustaining first fracture in subsequent months or years. One vertebral fracture in an osteopenic patient has 25 fold risks for getting second fractures.

Conventionally, importance of BMD in quantification of osteoporosis is being questioned and the bony trabecular strength is being put forward to be a better criteria for evaluation of osteoporosis as report of fracture in normal BMD patients is being reported. Hence quantification of osteoporosis should not only be restricted to BMD but also to CT vertebral imaging.

WHO FRAX Tool - WHO has developed an algorithm which provides 10 year probability of getting a fracture in a particular person.[2] In this assessment model available on any computer, all the risk factors including femoral neck BMD are as under:-

a. Current age
b. Gender
c. Prior osteoporotic fracture
d. Low BMI
e. Oral glucocorticoids for > 3 months
f. RA
g. Current smoking
h. Alcohol intake (3 or more drinks per day)
i. Parenteral history of hip fracture
j. Secondary causes of osteoporosis like untreated long standing hyperthyroidism, hypogonadism, premature menopause etc.

Normal bone homeostasis

The bone remodeling process is always operational and is a continuous rivalarly between osteoblast and osteoclast.[3] The heightened osteoblastic activities upto the age of 35 is responsible for peak bone mass and subsequently resting balance is maintained depending on various factors like food and physical exercise. With advancing age specially around 50 years, the osteoclastic activities supervene leading to osteoporosis. The life style factors responsible for osteoporosis are as under:-

a. Alcohol abuse
b. Smoking (active or passive)
c. Vitamin D insufficiency
d. Inadequate physical activity
e. Low calcium intake
f. Low BMI
g. High salt intake

Osteoporois is inherent to secondary causes like:-

a. Genetic diseases
b. Hypogonadal states
c. Endocrine disorders
d. GIT disorders
e. Hematologic disorders
f. Rheumatologic and autoimmune diseases
g. Respiratory diseases
h. Medications

Pathways regulating bone metabolism

Inflammatory milieu contributes to change in OPG/RANK/RANKL axis. Increased RANKL activity promotes osteoclastogenesis and hence osteoporosis.[3] There are 2 pathways regulating bone metabolism.

1st pathway

Osteoprotegerin (OPG) / Receptor Activator of Nuclear-Factor kappa B (RANK) / Receptor Activator of Nuclear-Factor kappa B Ligand (RANKL)

2nd Pathway

Wnt/β -catenin system. This Wnt signaling pathway works through osteoblast and has a role in bone formation – bone morphogenic protein (BMP).

In patients with osteoporosis, there is imbalance between the above two signaling pathways leading to:-

a. Elevated levels of RANK and RANK/OPG ratio
b. Up regulation of RANKL
c. Lower levels of OPG
d. Decreased activity of Wnt/β-catenin signaling
e. Elevated levels of matrix metalloproteinases

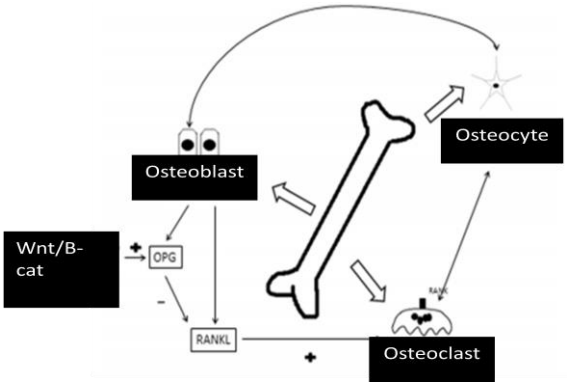

Fig. 1

Osteoprotegerin (OPG), also known as osteoclastogenesis inhibitory factor (OCIF), or tumor necrosis factor receptor superfamily member 11β (TNFRSF11 β), is a protein that in humans is encoded by the TNFRSF11 β gene.[5] Osteoprotegerin is a cytokine receptor, and a member of the tumor necrosis factor (TNF) receptor superfamily.

The discovery of the receptor activator of nuclear factor-kappaβ ligand (RANKL)/RANK/osteoprotegerin (OPG) system and its role in the regulation of bone resorption exemplifies how both serendipity and a logic-based approach can identify factors that regulate cell function.[6] Before this discovery in the mid to late 1990s, it had long been recognized that osteoclast formation was regulated by factors expressed by osteoblast/stromal cells, but it had not been anticipated that members of the tumor necrosis factor superfamily of ligands and receptors would be involved or that the factors involved would have extensive functions beyond bone remodeling. RANKL/RANK signaling regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling and in a variety of pathologic conditions. OPG protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to its receptor, RANK. Thus, RANKL/OPG ratio is an important determinant of bone mass and skeletal integrity. Genetic studies in mice indicate that RANKL/RANK signaling is also required for lymph node formation and mammary gland lactational hyperplasia, and that OPG also protects arteries from medial calcification. Thus, these tumor necrosis factor superfamily members have important functions outside bone. Although our understanding of the mechanisms whereby they regulate osteoclast formation has advanced rapidly during the past 10 years, many questions remain about their roles in health and disease. Here we review our current understanding of the role of the RANKL/RANK/OPG system in bone and other tissues.

Nuclear - factor Kappa β: NF-κβ (nuclear factor kappa-light-chain-enhancer of activated β cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival. NF-κβ is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens.[7-11] NF-κβ plays a key role in regulating the immune response to infection. Incorrect regulation of NF-κβ has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κβ has also been implicated in processes of synaptic plasticity and memory.[12-17]

Wnt/β: The Wnt/β signaling pathways are a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors. Three Wnt signaling pathways have been characterized: the canonical Wnt pathway, the non-canonical planar cell polarity pathway, and the non-canonical Wnt/calcium pathway. All three pathways are activated by binding a Wnt-protein ligand to a Frizzled family receptor, which passes the biological signal to the Dishevelled protein inside the cell. The canonical Wnt pathway leads to regulation of gene transcription, and is thought to be negatively regulated in part by the SPATS1 gene.[18] The non-canonical planar cell polarity pathway regulates the cytoskeleton that is responsible for the shape of the cell. The non-canonical Wnt/calcium pathway regulates calcium inside the cell. Wnt signaling pathways use either nearby cell-cell communication (paracrine) or same-cell communication (autocrine). They are highly evolutionarily conserved in animals, which means they are similar across animal species from fruit flies to humans.[19,20]

Wnt signaling was first identified for its role in carcinogenesis, then for its function in embryonic development. The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation and cell migration. These processes are necessary for proper formation of important tissues including bone, heart and muscle. Its role in embryonic development was discovered when genetic mutations in Wnt pathway proteins produced abnormal fruit fly embryos. Wnt signaling also controls tissue regeneration in adult bone marrow, skin and intestine.[21] Later research found that the genes responsible for these abnormalities also influenced breast cancer development in mice.

This pathway's clinical importance was demonstrated by mutations that lead to various diseases, including breast and prostate cancer, glioblastoma, type II diabetes and others.[22,23] Encouragingly, in recent years researchers reported first successful use of Wnt pathway inhibitors in mouse models of disease.[24]

Catenin System: Catenins are a family of proteins found in complexes with cadherin cell adhesion molecules of animal cells. The first two catenins that were identified became known as α-

catenin and β-catenin.[25] A-catenin can bind to β-catenin and can also bind actin. B-catenin binds the cytoplasmic domain of some cadherins. Additional catenins such as γ-catenin and δ-catenin have been identified. The name "catenin" was originally selected ('catena' means 'chain' in Latin) because it was suspected that catenins might link cadherins to the cytoskeleton.[26]

Bone morphogenetic protein: Bone morphogenetic proteins (BMPs) are a group of growth factors also known as cytokines and as metabologens.[27] Originally discovered by their ability to induce the formation of bone and cartilage, BMPs are now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body.[28] The important functioning of BMP signals in physiology is emphasized by the multitude of roles for dysregulated BMP signalling in pathological processes. Cancerous disease often involves misregulation of the BMP signalling system. Absence of BMP signalling is, for instance, an important factor in the progression of colon cancer,[29,30] and conversely, over activation of BMP signalling following reflux-induced esophagitis provokes Barrett's esophagus and is thus instrumental in the development of adenocarcinoma in the proximal portion of the gastrointestinal tract.

Recombinant human BMPs (rhBMPs) are used in orthopedic applications such as spinal fusions, nonunion and oral surgery. rhBMP-2 and rhBMP-7 are Food and Drug Administration (FDA)-approved for some uses. rhBMP-2 causes more overgrown bone than any other BMPs and is widely used off-label.

Any systemic inflammation in the body like rheumatoid arthritis, asthma, G. I. disorders etc. recruits cytokines, IL1B, IL-6, IL-18 and TNFα resulting in increasing of acute phase reactants like CRP and SAA titers.

Systemic inflammation produces osteopososis / osteopenia in the bones whereas the metabolic diseases like diabetes and obesity, cardiovascular diseases like IHD, CCF and hypertension, and there could be a psychotic ailment like as well.

Cytokines: Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. Their release has an effect on the behavior of cells around them. It can be said that cytokines are involved in autocrine signalling, paracrine signalling and endocrine signalling as immunomodulating agents. Their definite distinction from hormones is still part of ongoing research. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell.[31-33]

They act through receptors, and are especially important in the immune system; cytokines modulate the balance between humoral and cell-basedimmune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways.[33]

They are different from hormones, which are also important cell signaling molecules, in that hormones circulate in less variable concentrations and hormones tend to be made by specific kinds of cells.

They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction.

IL-1β: Interleukin 1 beta (IL1β) also known as leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor and other names, is a cytokine protein that in humans is encoded by the IL-1β gene.[34-37] There are two genes for interleukin-1 (IL-1): IL-1 alpha and IL-1 beta (this gene). IL-1β precursor is cleaved by cytosolic caspase 1 (interleukin 1 beta convertase) to form mature IL-1β.

IL-6: Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene.[38]

Interleukin 6 is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. IL-6 also plays a role in fighting infection, as IL-6 has been shown in mice to be required for resistance against bacterium Streptococcus pneumoniae.[39]

In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1 and activation of IL-1ra and IL-10.

IL-18: Interleukin-18 (IL18, also known as interferon-gamma inducing factor) is a protein which in humans is encoded by the *IL18* gene.[40,41] The protein encoded by this gene is a pro inflammatory cytokine.

IL-18 is a cytokine that belongs to the IL-1 superfamily and is produced by macrophages and other cells. IL-18 works by binding to the interleukin-18 receptor, and together with IL-12 it induces cell-mediated immunity following infection with microbial products like lipopolysaccharide (LPS). After stimulation with IL-18, natural killer (NK) cells and

certain T cells release another important cytokine called interferon-γ (IFN-γ) or type II interferon that plays an important role in activating the macrophages or other cells.

The combination of this cytokine and IL12 has been shown to inhibit IL-4 dependent IgE and IgG1 production, and enhance IgG2a production in B cells. IL-18 binding protein (IL18BP) can specifically interact with this cytokine, and thus negatively regulate its biological activity.[42]

TNFα: Tumor necrosis factor (TNF, tumor necrosis factor alpha, TNFα, cachexin, or cachectin) is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons.[43]

The primary role of TNF is in the regulation of immune cells. TNF, being an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, inflammation and to inhibit tumorigenesis and viral replication and respond to sepsis via IL1 & IL6 producing cells. Dysregulation of TNF production has been implicated in a variety of human diseases including Alzheimer's disease, cancer,[44] major depression,[45] psoriasis[46] and inflammatory bowel disease (IBD).[47] Though controversial, studies of depression and IBD are currently being linked to TNF levels.[48] Recombinant TNF is used as an immunostimulant under the INN tasonermin. TNF can be produced ectopically in the setting of malignancy and parallels parathyroid hormone both in causing secondary hypercalcemia and in the cancers with which excessive production is associated.

Acute-phase proteins are a class of proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the acute-phase reaction (also called acute-phase response).

CRP: C-reactive protein (CRP) is a blood test marker for inflammation in the body. CRP is produced in the liver and its level is measured by testing the blood. CRP is classified as an acute phase reactant, which means that its levels will rise in response to inflammation.

Vitamin D and Osteoporosis: A large human population is deficient of vitamin D. 2/3rd of COPD patients are known to have vitamin D deficiency.[3] Vitamin D deficiency is linked to increased risk of asthma attacks in children and in adults with asthma. Some of the patients of drug resistant tuberculosis start responding to the drugs on supplementation with vitamin D.

Smoking and osteoporosis: This known risk factor of smoking leads to increased free radicals and oxidative stress, inflammation and modulation of OPG/RANK/RANKL system leading to osteoporosis.

Anaemia and resultant hypoxia in COPD: The hypoxia leads to decreased expression of transcription factor (RUNX2), stimulates osteoclast formation and inhibits stem cell differentiation into osteoblast.[3]

RUNX2 is a key transcription factor associated with osteoblast differentiation. Runt-related transcription factor 2 (RUNX2) also known as core-binding factor subunit alpha-1 (CBF-alpha-1) is a protein that in humans is encloded by the RUNX2 gene. Parallel to RUNX2, osterix also inhibits stem cell differentitation osteoblast. Osterix (nasal kilen cell)-osteoblast-specific transcription factor osterix (Osx) is an upstream regulator of Satb2 during bone formation.

Osterix (Osx) is an osteoblast-specific transcription factor essential for osteoblast differentiation and bone formation. Osx knock-out mice lack bone completely. Satb2 is critical for osteoblast differentiation as a special AT-rich binding transcription factor. It is not known how Satb2 is transcriptionally regulated during bone formation. In this study, quantitative real-time RT-PCR results demonstrated that Satb2 was downregulated in Osx-null calvaria. In stable C2C12 mesenchymal cells using Tel-off system, overexpression of Osx stimulated Satb2 expression. Moreover, inhibition of Osx by SiRNA led to repression of Satb2 expression in osteoblasts. These results suggest that Osx controls Satb2 expression. Transient transfection assay showed that Osx activated 1kb Satb2 promoter reporter activity in a dose-dependent manner. To define the region of Satb2 promoter responsive to Osx activation, a series of deletion mutants of Satb2 constructs were made, and the minimal region was narrowed down to the proximal 130bp of Satb2 promoter. Further point mutation studies found that two GC-rich region mutations disrupted the Satb2 130bp promoter activation ob Osx, suggesting that these GC-rich binding sites were responsible for Satb2 activation by Osx. Gel Shift Assay showed that Osx bound to Satb2 promoter sequence directly. Chromating immunoprecipitation (ChIP) assays indicated that endogenous Osx associated with native Satb2 promoter in osteoblasts. Importantly, Satb2 siRNA significantly inhibited Osx-induced osteoblast marker gene expressions. Taken together, our finding indicate that Osx is an upstream regulator of Satb2 during bone formation. This reveals a new additional link of the transcriptional regulation mechanism that Osx controls bone formation.

Hypercapnia: COPD, Chronic CO_2 retention, Elevated CO2 and stimulates osteoclast activity.

Hypogonadism: Human sex hormones important in promoting bone formation and inhibiting resorption. 69% COPD patients found to have hypogonadism. There is decreased bone formation and increased bone resorption in hypogonadism.

Reduced BMI and Reduced Physical Activity: Mechanical loading is important in maintaining bone mass and integrity.

Sarcopenia, decreased physical activity, low BMI and low Fat Free Mass (FFM) and decreased mechanical loading are found in osteoporotic patients.[3]

Steroid induced osteoporosis: It is the most common form of secondary osteoporosis and first cause in young people. Use of glucocorticoids affects both the pathways. In the first pathway, it increases the RANKL and M-CSF are increased thereby activating osteoclasts which leads to osteoplastogenesis simultaneous decrease in apoptosis leads to increase bone resorption. This could be an early and transient response to use of glucocorticoids.

Glucocorticoids influencing the second pathway involves decreased Wnt signaling and simultaneously increased PPARγ 2 also activates caspase-3. These influence the osteoblasts to lessen the osteoblastogenesis and increased apoptosis. Activation of caspase-3 working through osteocytes again leads to increased apoptosis. These finally lead to decreased bone formation on a long term basis.

Peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG), also known as the glitazone receptor, or NR1C3 (nuclear receptor subfamily 1, group C, member 3) is a type II nuclear receptor that in humans is encoded by the *PPARG* gene.[49,51]

PPARG is mainly present in adipose tissue, colon and macrophages. Two isoforms of PPARG are detected in the human and in the mouse: PPAR-γ1 (found in nearly all tissues except muscle) and PPAR-γ2 (mostly found in adipose tissue and the intestine).[52,53]

PPARG regulates fatty acid storage and glucose metabolism. The genes activated by PPARG stimulate lipid uptake and adipogenesis by fat cells. PPARG knockout mice fail to generate adipose tissue when fed a high-fat diet.[54]

This gene encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes. Four subtypes of PPARs are known: PPAR-alpha, PPAR-delta, PPAR-beta and PPAR-gamma.

The protein encoded by this gene is PPAR-gamma and is a regulator of adipocyte differentiation. Alternatively spliced transcript variants that encode different isoforms have been described.[55]

Many naturally occurring agents directly bind with and activate PPAR gamma. These agents include various polyunsaturated fatty acids like arachidonic acid and arachidonic acid metabolites such as certain members of the 5-Hydroxyicosatetraenoic acid and 5-oxo-eicosatetraenoic acid family, e.g. 5-oxo-15(S)-HETE and 5-oxo-ETE or 15-Hydroxyicosatetraenoic acid family including 15(*S*)-HETE, 15(*R*)-HETE, and 15(*S*)-HpETE.[56-58] The activation of PPAR gamma by these and other ligands may be responsible for inhibiting the growth of cultured human breast, gastric, lung, prostate and other cancer cell lines.[59]

The colony stimulating factor 1 (CSF1), also known as macrophage colony-stimulating factor (M-CSF), is a secreted cytokine which influences hematopoietic stem cells to differentiate into macrophages or other related cell types. Eukaryotic cells also produce M-CSF in order to combat intercellular viral infection. It is one of the three experimentally described colony-stimulating factors. M-CSF binds to the colony stimulating factor 1 receptor. It may also be involved in development of the placenta.

Caspase-3 is a caspase protein that interacts with caspase-8 and caspase-9. It is encoded by the *CASP3* gene. *CASP3* orthologs[60] have been identified in numerous mammals for which complete genome data are available. Unique orthologs are also present in birds, lizards, lissamphibians, and teleosts.

The CASP3 protein is a member of the **c**ysteine-aspartic acid protease (caspase) family.[61] Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspases exist as inactive proenzymes that undergo proteolytic processing at conserved aspartic residues to produce two subunits, large and small, that dimerize to form the active enzyme. This protein cleaves and activates caspases 6 and 7; and the protein itself is processed and activated by caspases 8, 9, and 10. It is the predominant caspase involved in the cleavage of amyloid-beta 4A precursor protein, which is associated with neuronal death in Alzheimer's disease.[62] Alternative splicing of this gene results in two transcript variants that encode the same protein.

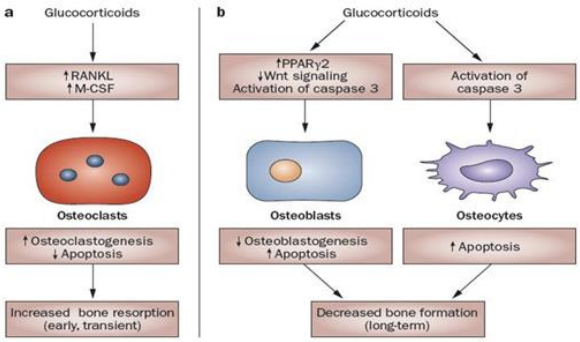

Fig. 2

Glucocorticoid inhibit vitamin D mediated, calcium absorption and hypercalciuria and results into secondary hyperparathyroidism. Inhibition of gonadotrophin secretion and decreased gonadal hormone secretion leading to hypogonadism is another

side effect of steroid use. Trabecular thinning and perforation are the changes in bone quality as an end result of steroid use leading to microarchitectural distruction, loss of strength and increased fracture risk. Finally, the steroids have the potential of bone cell aging and death leading to early aging and death of osteocytes and osteoblast with impaired formation and function. There is associated osteoclastic longevity and bone destruction.

Effects of excess of glucocorticoids can thus be summarized in the following chart. Finally leading to increased risk of fracture.

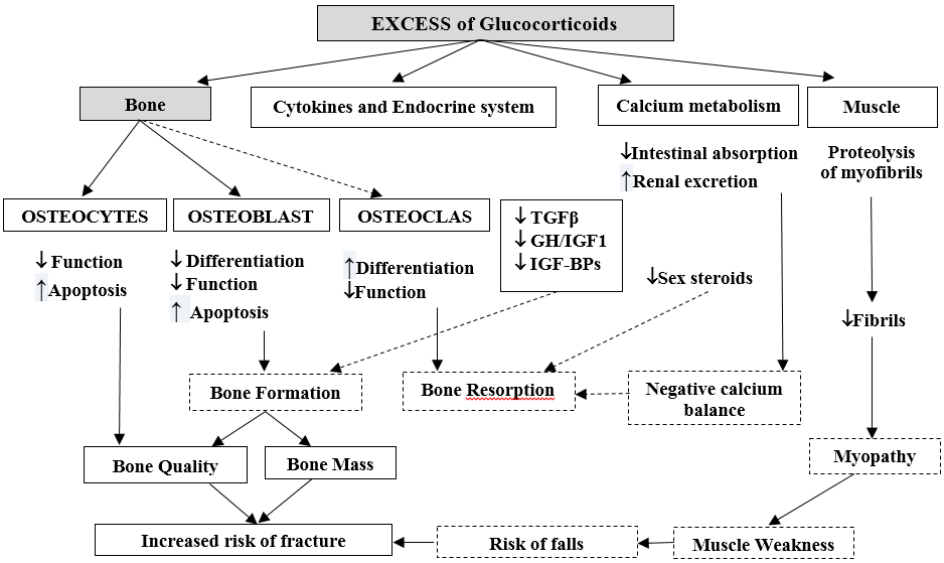

Fig. 3

Recommendation for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP)[4]

Initial fracture risk assessment within 6 months of GC Use

Glucocorticoid (GC) use: Dose, duration, pattern of use

Risk Factors:

a. Malnutrition
b. Significant weight loss or low body weight
c. Hypogonadism
d. Secondary hyperparathyroidism
e. Thyroid disease
f. Family history of hip fracture
g. History of alcohol use
h. Smoking

Physical examination:

a. Weight and height (without shoes)
b. Muscle strength
c. Assessment for undiagnosed fracture (i.e., spinal tenderness, deformity, reduced space between lower ribs and upper pelvis) as appropriate given patient's age.

All adults taking prednisone at a dose of ≥2.5mg/day for ≥3 months beginning long term GC treatment:

Calcium intake (800-1,000 mg/day)

Vitamin D intake (600-800 IU/day)

Lifestyle modifications

Balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1-2 alcoholic beverages/day.

Children ages 4-17 years treated with GCs for ≥ 3 months

Optimize calcium intake (1,000 mg/day) and vitamin D intake (600 IU/day) + lifestyle modifications.

Children ages 4-17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥ 0.1 mg/kg/day for ≥ 3 months.

Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) + calcium and vitamin D.

Recommendations for follow-up treatment for prevention of GIOP:

Adults age ≥ 40 years continuing GC treatment who have had a fracture that occurred after ≥ 18 months of treatment with an oral bisphosphonate or who have had a significant loss of bone mineral density (≥ 10% / year).

Treat with another class of OP medication (teriparatide or denosumab) or, consider IV bisphosphonate + calcium and vitamin D.

Adults age ≥ 40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture.

Continue active treatment with an oral bisphosphonate or switch to IV bisphosphonate or drugs from other class ((teriparatide or denosumab).

Adults age ≥ 40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at low risk of fracture.

Discontinue OP medication, continue calcium and vitamin D.

Adults age ≥ 40 years taking an OP medication in addition to calcium and vitamin D who discontinue GC treatment and are assessed to be at moderate-to-high risk of fracture

Continue treatment with osteoporosis medication in addition to calcium and vitamin D.

Management of Osteoporosis

General measures: General measures in management of osteoporosis are directed towards prevention of any future fracture and containment of osteoporosis itself. These measures include regular weight bearing, muscle strengthening exercises, prevention from fall, cessation of tobacco use and avoidance of excessive alcohol intake

Specific measures: Treatment of associated primary cause like rheumatoid arthritis, COPD & Asthma etc. for osteoporosis has to be achieved. Steroids wherever indicated should be used in lowest effective doses and for shortest possible duration of time with additional measures to prevent development of osteoporosis. Adequate calcium and vitamin D must be maintained.

Specific pharmacotherapy for management of osteoporosis has to be unhesitating initiated either as a preventive measure or as a therapy following a fracture. The drugs are raloxifene, bisphosphonates, teriparatide, denosumab. Romosozumab and odanacatib are the two new entrants with encouraging results.

Conclusion

a. Osteoporosis affects majority of the population.
b. The complexity of the mechanisms involved in osteoporosis and steroid induced osteoporosis have been simplified.
c. Effective strategies to prevent bone loss and/or to treat osteoporosis include calcium and vitamin D and bisphosphonate administration.
d. With an increased awareness by clinicians and increased use of preventive strategies, impact of osteoporosis should decrease.

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