Review Article

GLUCOCORTICOID INDUCED OSTEOPOROSIS

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ABSTRACT

Osteoporosis is a skeletal disorder characterized by low bone mass, increased bone fragility, and susceptibility to fracture. It is of mainly into two types. Glucocorticoid induced osteoporosis occurs mainly due to the usage of glucocorticoids for prolonged periods. Glucocorticoid induced osteoporosis ranks third in importance as a risk factor for osteoporosis. It is mainly diagnosed by blood and urine estimations. The first choice of drugs for the treatment of glucocorticoid induced osteoporosis is bisphosphonates.

Keywords: osteoporosis, glucocorticoids, diagnosis, bisphosphonates.

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by low bone mass, increased bone fragility and susceptibility to fractures most commonly involving the hip, vertebrae and distal radius[1]. This disorder usually affects trabecular bone in the first instance but, compact bone may also be involved [2]. This disease is most frequently defined as the most prevalent metabolic bone disease in the world[3] and is a painful public health problem which increases as the population ages[4] Osteoporotic fractures are an important cause of morbidity and mortality, particularly in elderly women who often suffer multiple fractures[5].

WHO has defined osteoporosis based on bone mineral density into several types:

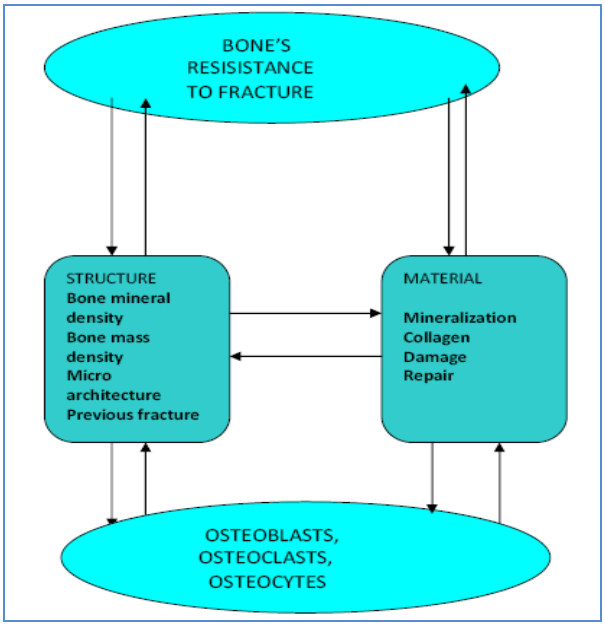
Table 1: World Health Organization Definition of Osteoporosis [6]

Bone Disorder	Bone Density in standard deviation (below the young adult mean)
Normal	>1
Osteopenia	1-2.5
Osteoporosis	>2.5
Severe Osteoporosis	>2.5 with fracture

Glucocorticoids (GCs) are the drugs used in the management of a wide range of autoimmune diseases including pulmonary, rheumatologic, bowel, and skin disorders as well as being an important component of standard protocols in preventing graft rejection post-organ transplantation. Although glucocorticoid therapy is life saving, important side effects are frequent, particularly with extended treatment. One important adverse effect is bone loss, which significantly increases fracture risk[7]. Glucocorticoids use ranks third in importance as a risk factor for osteoporosis; only proceeded by postmenopausal bone loss and age-related bone loss [8]. The other side effects that the glucocorticoids show are diabetes, hypertension, cataracts, thinning of the skin, and the characteristic appearance of Cushing's syndrome[9]. Apart from glucocorticoids, the other drugs that may increase the risk of osteoporosis are heparin or warfarin (prolonged use), thyroid replacement therapy, anticonvulsants (phenytoin, phenobarbital, gabapentin), antacids (specifically aluminum containing products; prolonged use), methotrexate, cyclophosphamide, cyclosporin A, other immunosuppressants, cholestyramine, goserelin, leuprolide (gonadotropinreleasing hormones) [10]. Among these use of glucocorticoids is the leading cause of drug-induced osteoporosis[8]. An estimated 50% of patients taking glucocorticoids for longer than 6 months will develop secondary osteoporosis. The absolute risk for glucocorticoid-induced osteoporosis is higher in patients aged 65 years or older given their baseline age-related fracture risk, although the relative risk of fracture related to glucocorticoid use may be even higher in patients under 65. A review of several studies over the past 10 years reveals that less than 50% of patients receiving long-term glucocorticoids have been evaluated for osteoporosis, and less than 25% have been treated[11].

With the use of glucocorticoids for short or longer time periods, an uncoupling between bone resorption and bone formation occurs. Chronic use of glucocorticoids increases resorption and decrease bone formation; which leads to the development of osteopenia and fractures [12]. The most serious clinical complication of osteoporosis is osteoporotic fracture. These fractures typically occur at the spine, hip and distal forearm [13]. Osteoporotic fractures are associated with pain, functional limitations, dependency, and fear of falling, which further augment bone loss, fall risk and are a serious threat for reduced quality of life[14].

Figure 1: Factors that relate to bone fracture



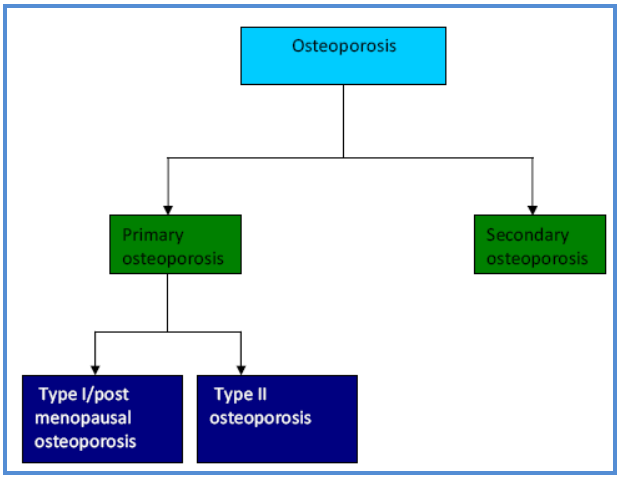
Bone resistance to fracture is related to structure and material characteristics of bone and also to the activity of osteoblasts, osteoclasts and osteocytes.

TYPES OF OSTEOPOROSIS

Osteoporosis is mainly of two types. They are:

1. Primary osteoporosis
2. Secondary osteoporosis

Figure 2: Types of osteoporosis



1. Primary osteoporosis

It occurs in both genders at all ages but often follows menopause in women and occurs late in life in men.

(i). Primary osteoporosis Type I (or) Postmenopausal osteoporosis

It is characterized by an increased bone resorption that primarily affects trabecular bone and is directly linked to the decreased production of estrogen that coincides with menopause. Rapid bone loss is osteoclast-mediated and occurs in women within the first 5 to 10 years after menopause.

(ii). Primary osteoporosis Type II

Proportionate loss of trabecular and cortical bone occurs usually due to a decrease in bone cell activity accompanying aging. This type of osteoporosis predominately afflicts men and women over the age of 70 years and is called senile osteoporosis [15, 16].

2. Secondary osteoporosis

Secondary osteoporosis is a condition where osteoporosis occurs as a result of an identifiable cause [17]. There are several causes for secondary osteoporosis which include

(i). Endocrine disorders: Acromegaly, adrenal atrophy in addison disease, cushing syndrome.

(ii). Eating disorders: Endometriosis, gonadal insufficiency (primary or secondary) hyperparathyroidism, hyper prolactinemia, hyperthyroidism, hypogonadism, Type 1 diabetes mellitus.

(iii). Nutritional disorders: Tumor secretion of parathyroid hormone–related peptide, gastro intestinal disease.

(iv). Alcohol-related liver diseases: Celiac disease, chronic active hepatitis, chronic cholestatic diseases, gastrectomy, inflammatory bowel disease, jejunoileal bypass.

(v). Malabsorption syndromes: Pancreatic insufficiency, parenteral nutrition, primary biliary cirrhosis, severe liver disease.

(vi). Marrow-related disorders: Amyloidosis, hemochromatosis, hemophilia, leukemia, lymphoma, mastocytosis, multiple myeloma, pernicious anemia, sarcoidosis, sickle cell anemia, thalassemia.

(vii). Organ transplantation: Bone marrow, heart, kidney, liver and lung.

(viii). Miscellaneous causes: Ankylosing spondylitis, chronic obstructive pulmonary disease, congenital porphyria, epidermolysis bullosa, hemophilia, idiopathic hypercalciuria, idiopathic scoliosis, multiple sclerosis, rheumatoid arthritis.

(ix). Genetic disorders: Hypophosphatasia, osteogenesis imperfecta [18].

PROCESS OF BONE REMODELLING

Bone is metabolically active organ where in around 10% of bone is normally and constantly replaced. Bone constitutes the trabecular or spongy bone (25%) and cortical or compact bone (75%). Trabecular bone is metabolically active and forms the internal support of the bone. The outer capsule is made up of cortical bone and is particularly present in the shafts of long bones. The primary cells partaking in the formation of bone include the osteoclasts, derived from blood (haematopoietic) stem-cell precursors and osteoblasts which differentiate from stromal-cell precursors. The role of osteoblasts is to manufacture a complex extra cellular matrix, which is capable of undergoing mineralization [19]. Bone strength is

a combination of the amount of bone, bone structure, and other aspects of bone quality, which include localized material properties, non mineralized matrix proteins, and bone turnover [20].

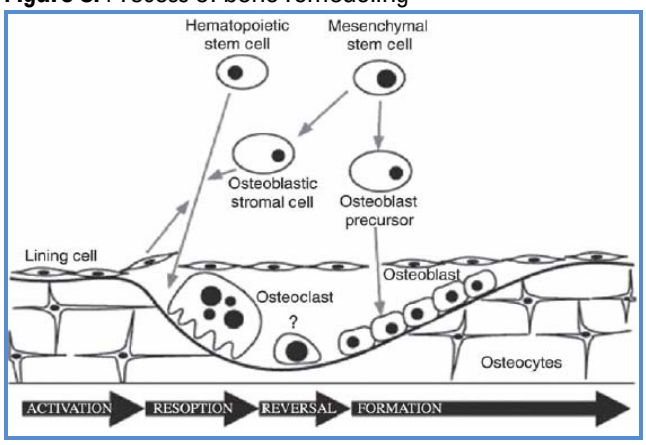
Bone turnover is a cyclic process of destruction and reconditioning of bone as a result of the concerted effects of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells). The objective is to replace micro damage and to adapt bone shape and density to patterns of usage and the attendant forces exerted. These cell types occur in areas referred to as bone remodeling units (BMUs)[21]. Each BMU is geographically and chronologically separated from other packets of remodeling[1]. Bone remodeling is initiated with the destruction of old bone by osteoclasts and the deposition of osteoid (unmineralized bone) by osteoblasts. Finally, the organic extracellular matrix is mineralized [21]. Initiation of bone remodeling can be monitored by mechanical stress that can alter the bone architecture. More recently it has been shown that mechanical stress can be sensed by osteocytes and these cells secrete paracrine factors like insulin like growth factor (IGF)-I in response to mechanical forces.

The sequences of events in the bone remodeling cycle are

1. Osteoclastic bone resorption
2. Reversal phase followed by
3. The osteoblastic bone formation to repair the defect.

The final step of bone resorption and initiation of bone formation in the resorption lacunae occurs through a coupling mechanism which ensures that equal amount of bone is laid down following the previous resorption phase. To play a pivotal role in this process growth factors and proteinases have been found. Osteoclasts release local factors from the bone during resorption which inhibit osteoclast function and stimulate osteoblast activity. Osteoclasts release factors that negative impact their activity and promote osteoblastic function. When osteoclasts complete the resorptive cycle, they secrete proteins which serves as substrates for osteoblastic attachment.

Figure 3: Process of bone remodeling



Bone resorption is a programmed event involving removal of both mineral and organic constituents of bone matrix by osteoclasts aided by osteoblasts [1]. Micro damage can serve as a triggering factor for bone resorption, however the exact cause is not known. Osteoclasts when activated produce a local decrease in pH which facilitates the dissolution of mineral. Exposure of the matrix can cause degradation of collagen by enzymes. Several signals might be responsible for termination of bone resorption and initiation of bone formation such as liberation of components of the matrix-embedded, insulin-like growth factor (IGF) system-IGF-I, IGF-II, and their binding proteins may induce this shift[22].

Parathyroid hormone, vitamin D, calcitonin, thyroid hormones, growth hormone and IGF-1, gonadal and adrenal sex steroids, insulin, leptin are some of the systemic factors monitoring bone remodeling.

The local factors include cytokines, interleukins (IL-1, IL-6, IL-11, IL-18), tumor necrosis factors (TNF-a), transforming growth factors (TGFb, FGF), colony-stimulating factors (M-CSF), insulin-like growth factors, prostaglandins (PG E2) and nitric oxide [23]. After the maximum eroded depth has been achieved by osteoclasts, there is reversal phase of bone. Bone formation is a complex cascade of events that affect the proliferation of primitive mesenchymal cells, differentiation into osteoblast precursor cells, maturation of osteoblasts, formation of matrix and mineralization [1].

Main causes of glucocorticoid induced osteoporosis

Glucocorticoid induced osteoporosis is thought to occur by four main reasons

- By direct action on bone causing the decrease in the production of osteocalcin and transforming growth factor β.
- Acting on enteric canal and affecting calcium absorption in the digestive tract.
- Acts on the kidneys resulting in an increase in the amount of calcium infiltration.
- Glucocorticoids facilitate the secretion of endocrine hormones producing decreased secretion of estradiol, testosterone, dehydroepiandrosterone and increased absorption of bone [24].

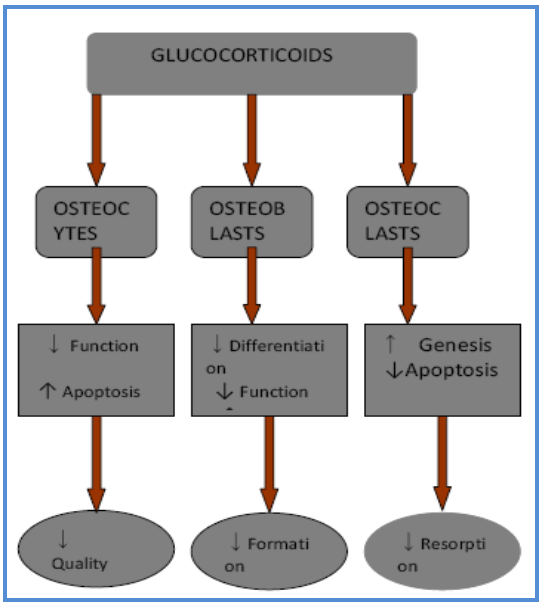
Glucocorticoid induced osteoporosis

Glucocorticoid-induced osteoporosis is the result of a combination of systemic effects on mineral metabolism and local effects on bone quality. An important effect of glucocorticoids on bone is its ability to reduce the number of osteoblasts and alter their functional capacity. Glucocorticoids stimulate the action of osteoclast and stimulate bone resorption[25].

Glucocorticoids exert direct effects on the bone cells

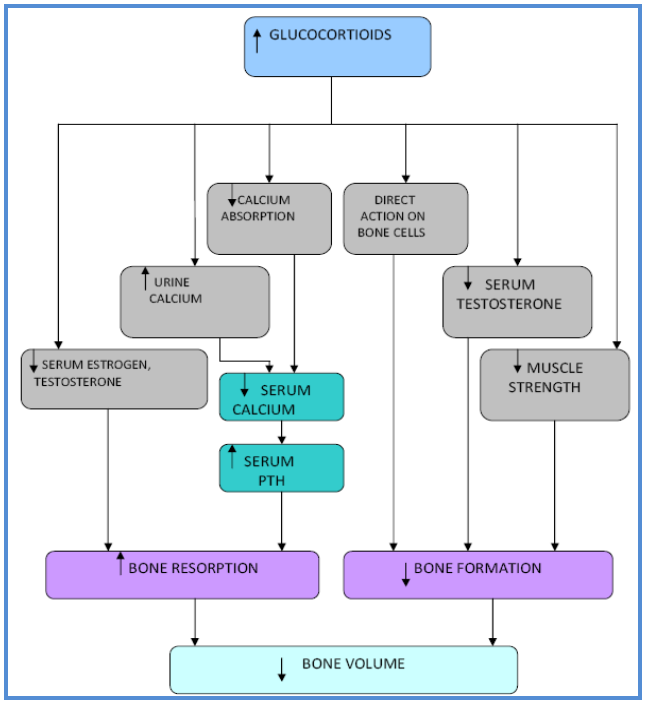
- Decrease of osteoblasts proliferation and activity
- Increase of osteoblast and osteocytes apoptosis
- Increase of osteoclasts life-span and activity

Figure 4: Effect of Glucocorticoids on Bone Cells



The effects of glucocorticoids on bone and mineral metabolism lead to rapid acceleration of bone loss. Prolonged exposure to super physiologic doses inhibits collagen synthesis and differentiation of osteoblasts, reducing bone formation. In the osteoclasts, physiologic concentrations of glucocorticoids enhance late stages of differentiation and function. The effect of glucocorticoids on bone resorption may also be mediated in part by secondary hyperparathyroidism. Glucocorticoids might also alter the production of prostaglandins, cytokines, and growth factors. Glucocorticoids inhibit the production of prostaglandins, such as prostaglandin E2, which normally stimulate collagen and non collagenous protein synthesis[18]. Glucocorticoids decreases intestinal calcium absorption and increases urinary calcium excretion[26].

Figure 5: High dose of glucocorticoids effect on bone cells



A measurable rise in immunoreactive serum parathyroid hormone (PTH) is the consequence of decreased intestinal calcium absorption and increased urinary calcium excretion. Both tend to lower serum calcium levels and thus increase PTH. Glucocorticoids may also directly stimulate PTH release. The effect of glucocorticoids to decrease bone formation appears to be attributed to at least three major mechanisms. First, glucocorticoids directly inhibit collagen production by bone cells. This may be a consequence of reduced bone cell production of insulin-like growth. Second, glucocorticoids may have a systemic action to reduce bone formation by reducing serum levels of testosterone, a potent bone anabolic agent, in both male and female patients. Third, decreased physical activity due to glucocorticoid-induced myopathy may further depress bone formation [27].

DIAGNOSTIC MARKERS

Calcium, phosphorous levels of both serum and urine, urinary creatinine and deoxypyridinoline levels and alkaline phosphatase levels in serum are commonly measured in osteoporotic patients [28]. Osteocalcin (OC) and the N- and C- telopeptides of collagen cross-links are the biochemical markers that provide information about the bone turnover [29]. Biochemical markers of bone remodeling are divided into markers of bone formation, usually measured in serum and markers of bone resorption, determined in serum or urine. Biochemical evaluation of bone metabolism should also include assessment of blood ions (calcium and phosphorus) and calcium-regulating hormones such as intact parathyroid hormone, 25-OH vitamin D, 1, 25-$(OH)_2$ vitamin D and calcitonin [23].

BIOCHEMICAL MARKERS OF BONE REMODELLING [23]

Table. 2(a). Biochemical markers of bone formation

S. NO	MARKER	COMMENTS
1	Alkaline phosphatase	Bone-specific alkaline phosphatase (bAP) is a constituent of osteoblast membrane. Its principal role is phosphate hydrolysis, which permits growth of hydroxyapatite crystals.
2	Osteoclacin (OC)	Sensitive and specific marker of bone formation. OC is synthesized by osteoblasts and odontoblasts and incorporated directly into bone matrix, but some circulates in blood.
3.	Procollagen I extension peptides	N-terminal and C-terminal extension peptides are cleaved during the extra cellular processing of type I collagen, prior to fibril formation. Procollagen I carboxy-terminal peptide can be measured in plasma and correlates with growth velocity and with bone mineral acquisition.

Table 2(b). Biochemical markers of bone resorption

S. NO	MARKER	COMMENTS
1.	Tartrate-resistant acid phosphatase	Enzyme present in the osteoclasts and released during osteoclastic activity, however serum TRAP is not bone- specific.
2.	Hydroxyproline (HP)	HP is a product of post-translational hydroxylation of proline in the procollagen chain and reflects bone resorption. HP is not specific for bone collagen, and non- collagenous proteins and dietary proteins may be a source for urinary HP. Urinary HP is very high during periods of rapid growth such as infancy and puberty.
3.	Collagen pyridinium cross-links	Pyridinoline (pyr) and deoxypyridinoline (Depyr) are generated from hydroxylisine during post-translational modification of collagen. Pyr and DPyr are released during matrix resorption and are excreted in urine. DPyr is more specific for bone. A marked age-related variation in urinary Pyr and DPyr occurs in children and adolescents and correlates with growth velocity.

TECHNIQUES TO MEASURE BONE MINERAL DENSITY

1. Radiographic Absorptiometry (RA)

It is a simple, low-cost, low-risk, technique for determination of BMD and for use as a screening tool for osteoporosis. Improvement and further investigation of RA will possibly increase its utility in diagnosing and monitoring osteoporosis.

2. Single-photon absorptiometry (SPA)

This is one of the older methods still in use but it remains a reliable, relatively inexpensive and relatively precise method. SPA also involves very low radiation exposure. SPA measures the bone mineral content of the radius, ulna or calcaneus. SPA cannot distinguish cortical bone (radius, ulna) from trabecular bone and it cannot be used to measure bone mass at the hip or spine.

3. Dual photon absorptiometry (DPA)

It has largely replaced SPA as a standard procedure but has itself been displaced by the development of dual energy X-ray absorptiometry. DPA is relatively accurate with low radiation exposure. It is particularly useful for the lumbar spine and the femoral inter trochanteric locations, two areas quite susceptible to fractures. DPA is relatively time consuming compared to some other methods.

4. Quantitative computed tomography (QCT)

The refinements of QCT allow for the separate assessment of trabecular and cortical densities within the same bone. QCT is relatively unaffected by the presence of soft tissue calcifications and other artifacts. It may be preferable to dual energy X-ray absorptiometry (DEXA) for lateral spinal bone mineral density (BMD) measurement[30]. In this the bone density is measured in grams per cubic centimeter [3]. It has certain distinct clinical disadvantages however, such as greater radiation exposure and higher cost[30].

5. Dual-energy X-ray absorptiometry (DEXA)

Screening for low BMD by using dual energy x-ray absorptiometry (DXA), the gold standard diagnostic tool for osteoporosis, is a widely accepted strategy for identifying increased risk of fracture [31]. Dual energy X-ray absorptiometry (DXA) is the most widely used technique to assess bone mass. Although great importance is often given to DXA, it should be remembered that there is no evidence that densitometric data can predict the likelihood of fracture or improve the management of children with chronic illness. Bone mineral density (BMD) as accessed by DXA is not a true volumetric density, but rather, it is the mass of bone mineral per projection area (grams/cm^2) and is given the term 'areal BMD' (aBMD). Areal BMD is a size-dependent measure [32].

6. Ultrasonography

The ultrasound (US) technique has not yet gained widespread use in this field and, to some extent, is still at an experimental stage[30].

7. Peripheral quantitative computed tomography (pQCT)

Peripheral quantitative computed tomography (pQCT) is an emerging technique that is useful to assess cortical and trabecular bone in the limbs and lateral spine. X-ray remains an excellent modality to image vertebral morphology [32].

8. Quantitative Ultrasonography (QUS)

Quantitative Ultrasonography (QUS) measures bone density in peripheral sites using parameters of ultrasound transmission. QUS is the easiest and the most affordable screening approach, less expensive than DXA, does not use ionizing radiation and the machine can be portable [29]. It is recently introduced to evaluate skeletal integrity at easily accessible peripheral sites and currently it is performed on the calcaneus, patella, tibia, finger and forearm [30].

TREATMENT OF GLUCOCORTICOID INDUCED OSTEOPOROSIS

Pharmacological treatment

1. Bisphosphonates: These are mainly two types [22]:

(i). Nitrogen-containing bisphosphonates: Alendronate, Risedronate, Ibandronate, Zolendronate/

(ii). Non-nitrogen-containing bisphosphonates: Etidronate, Tiludronate, Clodronate.

The first choice of drugs for the treatment and prevention of glucocorticoid induced osteoporosis are

bisphosphonates which increases bone mineral density and reduces the incidence of spine and hip fractures. Bisphosphonates, such as alendronate, risedronate, ibandronate, and more recently zoledronate, regulate bone resorption by reducing the number of osteoclasts in the bone remodeling units and induce their apoptosis[21]. Bisphosphonates are potent anti resorptive agents that disrupt the osteoclastic activity with interference of the mevalonate pathway of cholesterol biosynthesis[33].

Side effects of bisphosphonates: causes gastrointestinal irritation, including esophageal erosions in those with gastro-esophageal reflux[34].

2. Calcitonin

Calcitonin is a second line agent used for treatment of glucocorticoid induced osteoporosis[35]. Calcitonin acts as an endogenous inhibitor of bone resorption by decreasing osteoclast formation. It is available for delivery as a subcutaneous injection or nasal spray; both formulations are developed from salmon calcitonin, which is about 10 times more potent than naturally produced human calcitonin.

3. Calcium and Vitamin D

Calcium and vitamin D in combination is the accepted baseline treatment for osteoporosis and also is used as a preventive measure, particularly for elderly patients [22]. Their use in the management of osteoporosis is further limited by the risk of hyper calcaemia and hyper calciuria, and the need for regular monitoring.

4. Anabolic agents

Anabolic agents have the potential to increase BMD, restore micro-architecture, and restore fracture risk to a greater extent than the anti resorptives

Fluoride was the first anabolic agent to be used in the treatment of osteoporosis. Growth hormone, IGF, and more recently the lipid lowering statins have been proposed, but side effects and inability to target these agents to the skeleton have limited their use. Anabolic steroids and calcitriol may have modest anabolic effects on bone, but their utility is also limited by adverse effects. More recently, strontium ranelate and parathyroid hormone (PTH) have emerged as promising osteo-anabolic agents[36]. PTH exerts most of its effects on bone through the PTH 1 receptor, which it shares with the PTH receptor protein (PTH r P)[37].

5. Selective estrogen receptor modulators

Selective estrogen receptor modulators, such as raloxifine block conformational changes of the estrogen receptor[22].

Adverse events include an increase in thromboembolism, hot flushes, and leg cramps.

6. Estrogen replacement therapy

Treatment of women affected by osteoporosis with estrogen replacement therapy to prevent fracture has been controversial.

7. Tibolone

Tibolone is a synthetic steroid with estrogenic, androgenic, and gestagenic properties, which exerts its effect by binding to the estrogen receptor. Tibolone relieves climacteric symptoms without causing menstrual bleeding and with less breast tenderness than is caused by hormone replacement therapy [22].

8. Teriparatide (PTH1-34)

Intermittent, low-dose PTH administration causes rapid stimulation of bone formation resulting in a marked increase in bone mass, size and strength, as well as improvement in trabecular micro-architecture and cortical geometry.

Side effects of teriparatide have been limited to occasional nausea, headaches, and leg cramps [38].

Table 3: Side effects of drugs available for the treatment of osteoporosis

SL.NO	DRUG	SIDE EFFECTS
1.	Etidronate	Gastrointestinal irritation
2.	Calcium and Vitamin D	Hyper calcaemia, hyper calciuira
3.	Fluoride	Interferes with the normal mineralization of bone in bone crystal at high concentrations.
4.	Selective estrogen receptor modulators	thromboembolism, leg cramps and hot flushes
5.	Estrogen replacement therapy	Breast tenderness
6.	Teriparatide	nausea, pain in the limbs, headache and dizziness

HERBAL TREATMENT FOR OSTEOPOROSIS

Godanti bhasma and Kukkutandatvak bhasma that are well known for their bone remineralization properties as these are rich natural forms of calcium. *Terminalia arjuna* is extensively used to treat osteoporosis and other bone related disorders as it improves the synthesis and secretion of female hormones. *Withania somnifera* is considered a rejuvenator in Ayurveda. It helps in relieving pain associated with osteoporosis, nervous exhaustion and muscular pains. *Commiphora wightii* helps in remineralization of the bones, thus reversing the process of osteoporosis. *Sida cordifolia* has natural phytosterol and phytoestrogens which improves bone density. *Vanda roxburghii* possesses anti-inflammatory properties and relieves joint pains in osteoporosis[39].

DEVELOPMENT OF NEW DRUGS

Within the next few years, several more new drugs are likely to be licensed for use in osteoporosis. Unfortunately, the process of drug discovery and development is slow. It usually takes at least 10 years from the discovery of a new compound for it to be

studied experimentally, for its safety to be established, and for clinical trials to be completed. Even the clinical trial stage for drugs in osteoporosis may require 3 years or more from start to finish, in order to meet the current regulatory requirement for demonstrating a reduction in fractures. As a result, only those drugs already undergoing clinical trials can be expected to be approved in the next few years [19].

CONCLUSION

Glucocorticoids are indispensable for the treatment of several diseases however the adverse effects which ensue should not be ignored. Osteoporosis leads to significant morbidity and therefore caution should be undertaken in the usage of such drugs for prolonged periods of time.

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