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Review Article

Internal Medicine Section

Endocrine Causes of Secondary Osteoporosis in Adults: Mechanisms and Evaluation

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ABSTRACT

Osteoporosis and fragility fractures are a major public health issue. Secondary osteoporosis is characterised by the presence of an underlying disease, deficiency, or use of a drug. Conditions that increase speculation for secondary osteoporosis include fragility fractures amongst the younger men or premenopausal women, markedly decreased Bone Mineral Density (BMD) values, and fractures despite conforming to anti-osteoporotic therapy. Since the emphasis is on the treatment of the primary disorder, a diagnosis of osteoporosis and thus the opportunity of preventive intervention can be missed. With this review, the authors objective is to emphasise the importance of secondary osteoporosis, discuss the causes and their mechanism and summarise treatment options.

Keywords: Fragility fractures, Hyperparathyroidism, Hyperthyroidism, Hypogonadism induced osteoporosis, Steroid-induced osteoporosis

INTRODUCTION

Osteoporosis is a affliction characterised by decreased bone mass and mineral density with poor bone quality predisposing to fracture in both men and women and is the most common bone disease [1]. The presence of fragility fractures predominates the clinical features of severe osteoporosis. Osteoporosis and the resulting fragility fractures are major public health burdens both humanly and economically. Prevention remains the priority as once fractures occur; associated morbidity also becomes a concern. Due to the absence of warning signs before a fracture, patients usually do not receive effective therapy during the initial phase of osteoporosis to prevent fracture morbidity [2].

The classification of osteoporosis into primary and secondary forms is whimsical. Secondary Osteoporosis is described as an underlying disorder, deficiency, or medication causing the bone fragility or reduced bone mass, whereas osteoporosis in women with natural menopause and older men with is called primary osteoporosis [1]. Incidence of secondary causes of osteoporosis has been reported to be ranging from 30%-60% in men, more than 50% in pre-menopausal women, and about 30% of post-menopausal [3]. Secondary osteoporosis remains a challenge for the endocrinologist as it usually affects younger men and women where a diagnosis of osteoporosis is not usually suspected. The diagnostic challenges also include the myriad of underlying disorders that are diverse and rare and require specific diagnostic tests [4,5]. [Table/Fig-1] enumerates the causes of secondary osteoporosis. Diabetes mellitus- both type 1 and 2, Acromegaly, Growth Hormone (GH) deficiency, Hyperparathyroidism, Hyperthyroidism, hypercortisolism including Cushing syndrome, Hypogonadism both primary and secondary, hyperprolactinemia, Pregnancy, lactation, and hyperaldosteronism are the endocrinopathies associated secondary osteoporosis.

Hence, the present study aims to summarise the current knowledge regarding the endocrine causes of secondary osteoporosis.

Underlying disorders	Causes
Endocrinopathies	Diabetes mellitus (both type 1 and 2), Acromegaly, GH deficiency, Hyperparathyroidism, Hyperthyroidism, hypercortisolism including Cushing syndrome, Hypogonadism -both primary and secondary, hyperprolactinemia, Pregnancy and lactation, hyperaldosteronism
Congenital/ genetic conditions	a) Structural collagen and connective tissue defects: Osteogenesis imperfecta, pseudoxanthoma elasticum, Ehlers-Danlos syndrome, Marfan syndrome, Menkes syndrome. b) Disrupted phosphate and/or calcium homeostasis: idiopathic hypercalciuria, hypophosphatasia. c) Metabolic/ storage disorders: Gaucher disease, cystic fibrosis, glycogen storage diseases, haemochromatosis, porphyria
Autoimmune disorders	Rheumatoid Arthritis (RA), Lupus erythematosus, Multiple sclerosis, Ankylosing spondylitis
Neoplastic and Hematologic disorders	Leukaemia; haemophilia, sickle cell anaemia, thalassaemia, metastatic disease; myelofibrosis, lymphoma; multiple myeloma; systemic mastocytosis; monoclonal Gammopathy of unknown significance. Breast and prostate cancer
Gastrointestinal Disorders	Coeliac disease, Weight loss surgery, Gastrectomy and other causes of malabsorption including chronic pancreatitis; liver cirrhosis; Inflammatory bowel disease, chronic biliary tract obstruction and alcohol related malnutrition
Nutritional deficiency and disorders	Deficiency of minerals such as calcium, magnesium, protein and/or vitamin D; parenteral nutrition; scurvy, anorexia nervosa, bulimia nervosa, malnutrition
Neurologic and psychiatric disorders	Stroke, Parkinson disease, multiple sclerosis, depression, eating disorders, Spinal cord injuries, post-polio syndrome
Drugs	Acid suppression therapies: omeprazole, pantoprazole etc. Anti-coagulants: warfarin, heparin Anti-convulsants: valproate; phenytoin; carbamazepine Anti-depressants: selective serotonin reuptake inhibitors Anti-hormonal therapies: aromatase inhibitors Anti-manic therapies: lithium Anti-psychotic therapies Anti-retroviral drugs: tenofovir Contraceptives: progesterone Cytotoxic drugs (chemotherapy): cyclosporine, tacrolimus, methotrexate Diuretics: furosemide Glucocorticoids Gonadotrophin-releasing hormone analogs: buserelin; goserelin; cyproterone acetate Lipase inhibitors: orlistat Thiazolidinediones: rosiglitazone; pioglitazone Thyroid hormone: L-thyroxine Unfractionated heparins: dalteparin; enoxaparin; tinzaparin
Infective	HIV/AIDS, poliomyelitis
Chronic illness	Liver disease, kidney disease, COPD
Others	Organ transplant, weight loss, female athletic triad

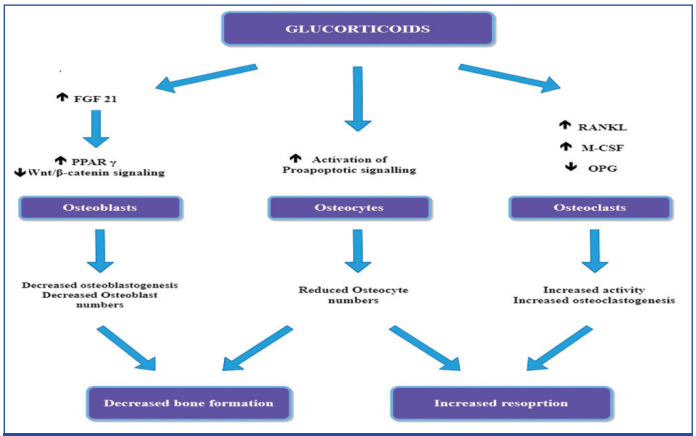
[Table/Fig-1]: Causes of secondary osteoporosis.
HIV: Human immunopdeficiency virus; AIDS: Acquired immunodeficiency syndrome; COPD: Chronic obstructive pulmonary syndrome

MECHANISMS

Glucocorticoid-Induced Osteoporosis (GIO)

The most pertinent cause of secondary osteoporosis is glucocorticoid-induced osteoporosis, which is usually results from the use of various steroids for treatment of inflammatory or autoimmune disorders [6]. Glucocorticoids are frequently given to patients with inflammatory and autoimmune disorders, and these primary diseases themselves are frequently associated with bone loss and osteoporosis. Systemic release of inflammatory cytokines has significant effects on bone remodeling and is associated with bone loss in Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD) and Systemic Lupus Erythematosus (SLE). Glucocorticoids increase, due to whether endogenously over-production or administered systemically, produces profound skeletal effects. The usual presentation of GIO is often a fragility fracture, occurring in 30-50% of patients [7]. Doses >7.5 mg/day lead to a 5 fold increased risk and even low-dose prednisolone (2.5-7.5 mg/day) correlates with a 2.6-fold increase in vertebral fractures [8]. There is significant bone improvishment and escalated marrow adipogenesis as marrow stromal cells transform to the fat lineage on prolonged exposure to pharmacologic doses of glucocorticoids. Both the osteoclast and osteoblast are affected directly, and secondary hypogonadism, secondary hyperparathyroidism, impaired vitamin D metabolism, muscle atrophy, and hypercalciuria occur during glucocorticoid therapy. All of these aspects lead to an expeditious and prolonged bone loss during the initial duration of steroid therapy [9,10].

[Table/Fig-2] illustrates the direct effect of glucorticoids on bone. Glucocorticoids effects on the bone formation are mediated mainly through FGF-21 mediated increased expression of Peroxisome Proliferator-Activated Receptor-Gamma Receptor (PPARγ) [11] and the Wnt/β-catenin signaling pathway [12,13]. The PPARγ mechanism causes the divergence of pluripotent precursor cells to adipocytes in preference to osteoblasts, causing a decrease in the numbers of osteoblasts. Glucocorticoids also directly affect the bone resorption, escalating the production of macrophage colony-stimulating factor (M-CSF) and Receptor activator of nuclear factor kappa-B ligand (RANKL) and reducing the production of Osteoprotegerin (OPG) by osteoblastic cells and osteocytes,



[Table/Fig-2]: Direct effects of glucocorticoids on bone.
FGF 21: Fibroblast growth factor 21; OPG: Osteoprotegenrin; RANKL: Receptor activator of nuclear factor kappa-B ligand; PPARγ: Peroxisome proliferator-activated receptor-gamma receptor; M-CSF: Macrophage colony-stimulating factor

increasing both in the number and activity of osteoclasts.

The variation in bone effect severity may be due to pre-receptor changes in glucocorticoid activity by 11 beta-hydroxysteroid dehydrogenase enzyme and polymorphisms in the glucocorticoid receptor [14,15]. Glucocorticoids have a strong adverse effect on bone formation by curbing the expression of Insulin-Like Growth Factor-1 (IGF1) in bone cells and by causing the transformation of marrow stromal cells into the fat lineage rather than into the osteoblast differentiation pathway [16]. Other factors that may be additive to GIO include hypogonadism, diminished physical activity due to myopathy, increased renal and intestinal losses of calcium, impaired production of growth hormone, and IGF1 Binding Protein (IGF-BP) [17]. Glucocorticoid excess also has negative effects on muscle mass and function, leading to myopathy and subsequent risk of falls [18].

Trabecular Bone Score (TBS) is a measure of trabecular bone architecture which is obtained from dual-energy X-ray absorptiometry (DXA) of the L1-L4 lumbar spine and can predict fracture independent of BMD [19]. In a study of 64 postmenopausal women taking prednisolone in a doses of ≥5 mg daily for >3 months, TBS was markedly reduced than the controls, although there was not much difference in the lumbar spine BMD T-scores [20]. A study on 416 patients on long-term predisolone (≥5 mg daily for 3 months) reported similar findings, with the reduction in TBS being most marked in men and those with a fracture [21]. These findings may provide evidence that steroids adversely affects the spine bone microarchitecture and these effects are independent of Bone Mineral density and may be a factor in the increased fracture risk.

GIO occurs at an indistinguishable frequency in men and women and various ethnic groups but is more incessant in elderly patients and in those with underlying inflammatory disorders, low BMI, and/or pre-existing impaired bone density [7]. The risk of fractures at all sites was nevertheless rapidly reversed after stopping glucocorticoids. The accruing dose may be less important than the daily dose [22].

Hyperthyroidism, Thyroid Hormone Replacement, and Suppressive Therapy

The clinical impact of thyrotoxicosis on bone health was first demonstrated in the 19th century as 'worm-eaten' long bones found postmortem in patients deceased due to primary thyrotoxicosis. Hyperthyroidism reduces the bone remodeling cycle duration increasing the resorption and causing increased bone turnover state with more bone resorption and formation rates. There is an elevation in the frequency of initiation of bone remodeling. Bone formation and mineralisation are reduced to a greater extent than bone resorption. This leads to decreased bone mineralization, a net 10% decrease in bone in each remodeling cycle, causing osteoporosis [23]. Depressed serum TSH levels and hyperthyroidism are correlated with an increased risk of hip and vertebral fractures with additive effects of increased falls due to decreasing muscle strength and coordination [24-26]. Besides, any current therapy with thyroid hormone replacement is inversely associated with BMD and propogates the probability of fractures even in the presence of euthyroidism [27].

Thyrotoxicosis causes increased elimination of calcium and phosphorus in both urine and stool; with subsequent elevation in bone turnover. Presence of vitamin D deficiency [28] and myopathy in graves may predispose to increased chances of osteoporosis. Thyroid hormone (T3) accelerates the activity of the osteoclasts via its nuclear receptors and this effect may explain these widespread changes. Local actions of TSH which may normally balance thyroid hormone action on osteoclasts and enhance osteoblast activity may also have a role. This effect is absent in hyperthyroidism [25,29-32].

Primary Hyperparathyroidism

Primary Hyperparathyroidism (PHPT) leads to an elevated expression of RANKL by the osteoblast lineage and an elevation in osteoclast-mediated bone resorption. Although there is an increase in osteoblast activity and associated bone formation, it is not enough to supplant the enhanced bone resorption. Bone turnover markers are in usual range or mildly elevated. In PHPT the cortical bone is mostly involved

while the trabecular bone is preserved comparatively. Excess parathyroid hormone results in cortical thinning due to endosteal bone resorption while there is no effect on trabecular bone, so that BMD in the distal forearm and the hip are reduced more [33,34].

Diabetes

While both Type 1 (T1DM) and Type 2 diabetes (T2DM) puts the patient at an elevated risk of fragility fractures, the risk is more with type I than with type II DM and peculiar differences exist between bone disorders in T1DM and T2DM [35,36]. There is bone loss in T1DM and it is recognised as a risk factor for osteoporosis and bone fractures. In T2DM, bone mass is preserved or increased providing evidence that the bone quality instead of quantity is the main causative reason affecting bone strength in this disorder. Also, the drugs used in the treatment of diabetes may cause bone loss and osteoporosis.

The peculiar difference in the secretion of growth factors and adipokines between T1DM and T2DM certainly is another point to be taken into consideration. T1DM is usually associated with low serum levels of IGF1, whereas this is not part of the hormonal alterations in T2DM. T2DM also predominantly exhibits an inflammatory profile in adipokine secretion by the white adipose tissue that is represented by increased levels of leptin, chemerin, resistin, Tumour Necrosis Factor (TNF), and Interleukins (IL), whereas adiponectin is reduced. Leptin and adiponectin have many complex effects on bone, and there are still no conclusive results about their ultimate effects on bone [37].

Thiazolidinediones are exogenous agonists of PPARs that lead to bone marrow mesenchymal stromal cells differentiation into adipocytes, inhibiting osteoblastogenesis via decreasing the Runx2 transcription factor, as well as IGF1 and Wnt signaling pathways. Thiazolidinediones also lead to osteoclast differentiation and bone resorption, and patients may experience bone loss and low BMD leading to an increased risk of fractures [38-42].

In older patients with a prolonged duration of T1DM and poor diabetic control, because there are increased vascular complications which may lead to reduced bone mass and increased fracture risk. Men with T1DM seem to be especially susceptible to osteopenia or osteoporosis [43]. Among patients with recent-onset T1DM, the impaired bone formation has been hypothesized to be due to the bone anabolic effects of insulin and amylin [44].

Type 2 DM patients are at an elevated risk of fracture with even normal or increased BMD [45]. This apparent conundrum may be interpreted by decreased bone quality in patients with T2DM, as a consequence of hyperinsulinemia, deposition of end-products from advanced glycosylation, renal failure, hypercalciuria, microangiopathy, and/or reduced serum levels of IGF-1. Fracture risk in T2DM might be increased by visual complications, muscle wasting, neuropathy, and impaired balance, leading to a greater risk of falls [43].

Hypogonadism

Hypogonadism, whether primary, secondary or drug-induced is associated with decreased BMD and osteoporosis, hypogonadism is the primary physiological cause of osteoporosis. Conditions such as premature menopause and drugs, such as aromatase inhibitors and gonadotropin hormone-releasing hormone (GnRH) analogs which cause hypogonadism, lead to reduced BMD, and increase the risk of fractures. While estrogen deficiency is major factor in the development of osteoporosis in both men and women, it is more of a factor causing postmenopausal osteoporosis.

Osteoblasts have androgen receptors, and testosterone and 5α- DHT (5α- dihydrotestosterone) both stimulate osteoblast to differentiate [46]. Testosterone may also increase skeletal and circulating IGF1 and stimulate bone formation, thus its decrease may be one of the additional causes that leads to bone loss in hypogonadal men [47].

Testosterone and 5α-DHT regulate gene expression in osteoblasts leading to inhibition of the resorptive capacity of isolated osteoclasts. In addition, sex hormones affect the release of a various cytokines and growth factors including Macrophage Colony Stimulating Factor (MCSF), and the proinflammatory molecules Interleukin-1 (IL-1), Interleukin-6 (IL-6) and TNF-α, RANKL, and OPG, which modulate the effects of androgens on bone remodeling [48-51].

Growth Hormone Deficiency (GHD) and Acromegaly

GH increases bone formation directly via action on the GH receptors in osteoblasts and via local production of IGF1. GHD leads to delayed skeletal maturation and reduction in BMD amongst patients with isolated GHD and in patients with multiple pituitary deficiencies, mainly through reduced bone formation [52].

Acromegaly is associated with elevated bone remodelling, when the skeleton is exposed to an increased levels of IGF-I for long duration, changes in bone microstructure may occur with a consequent reduction in bone strength and patients with acromegaly have a markedly higher prevalence of vertebral fractures, which is associated with the duration of the disease and serum IGF-1 levels. The hypercalciuria has been noticed in acromegaly patients and is traditionally linked to enhanced intestinal calcium absorption driven by calcitriol, as well as to the elevated bone turnover induced by GH excess and thus may be considered a marker of skeletal fragility [53,54].

Pregnancy and Lactation

Changes in bone mass in association with both pregnancy and lactation have been reported in several studies. At the lumbar spine, longitudinal studies show losses of 3-5% over pregnancy and 3-10% over six months of lactation with the recovery of the bone mass demonstrated over 6-12 months, thereafter, even in the setting of continued lactation. Over six months of lactation, a bone loss of 2-4% has been documented at the hip. The amount of bone loss during lactation is directly proportional to longer durations of lactation and postpartum amenorrhea [55-59].

There are several hypotheses regarding the cause of osteoporosis of pregnancy and lactation. These include the release of PTHrp (parathyroid related peptide) [60], increased transfer of calcium from bone to central circulation to provide calcium needed for lactation and fetal bone [61] formations, pre-existing osteopenia before pregnancy, decreased oestrogen after pregnancy leading to increased activity of osteoclasts, and stimulate bone resorption through OPG-RANK-RANKL pathway [62,63], the lordotic posture of pregnancy and the increased weight-bearing might induce thoracic or lumbar fractures [64] and inactivity during pregnancy from bed rest or hospitalisation would increase bone loss [65], however the exact aetiopathogenesis still eludes us [21].

Hyperprolactinemia

Hypogonadism is believed to be the major mechanism by which these patients develop low BMD, due to abnormalities in the normal pulsatile secretion of GnRH [67]. A study showed there is an presence of prolactin receptors on osteoblasts, and prolactin treated osteoblasts had a reduced proliferation with an overall elevated rate of apoptosis. There was also reduced mineralization as suggested by decreased calcium content in these cells [68].

EVALUATION

History and physical examination

To elucidate the risk factors for fractures, the underlying disease, and potential drugs, a detailed history alongwith physical examination should be performed with special attention to the following factors.

The medical history should include information on:

- Adult and childhood fractures
- Adult and childhood illnesses and medication exposures
- Menstrual history
- Timing of recent pregnancy or lactation
- Dieting and exercise behaviour
- Gastrointestinal symptoms
- Nephrolithiasis
- Family history of osteoporosis and/or nephrolithiasis
- Evaluation of nutritional status, calcium and vitamin D intake
- An exhaustive review of all medications partaken is necessary, as is assement of the smoking and alcohol habits, and the hereditary disposition of osteoporosis or fractures.

Physical examination should be performed to looks for signs of: [Table/Fig-3]:

- Nutritional deficiency or eating disorder
- Cushing syndrome
- Thyroid hormone excess
- Connective tissue disorders and structural collagen disorders (e.g. Osteogenesis imperfecta, Ehlers Danlos syndrome, Marfan syndrome),
- Inflammatory and Rheumatological conditions conditions (e.g. rheumatoid arthritis, SLE)

Endocrine disorder	Clinical features
Cushing's syndrome	Weight gain, moon facies, buffalo hump, Pink or purple broad striae on the skin of the abdomen, thighs, breasts, and arms, proximal muscle weakness, thin fragile skin that bruises with minor trauma
Primary hyperparathyroidism	weakness, polydipsia, polyuria, nocturia, joint pain, bone pain, nephrolithiasis, nausea, vomiting, pancreatitis
Hyperthyroidism	Unintentional weight loss, tachycardia, palpitations, nervousness, anxiety, irritability, tremors, excessive sweating, sensitivity to heat, goiter
Hypogonadism	Underdeveloped secondary sexual characters and genitals, Disproportionate growth of the limbs in relation to the trunk of the body (eunochoidal habitus), hot flashes, and vasomotor symptoms in females, fatigue, and lethargy.
Diabetes	Polydipsia, polyuria unexplained weight loss, fatigue, delayed wound healing, frequent infections, Type 2 diabetes mellitus individuals can be obese and have signs of insulin resistance
Growth hormone deficiency	Decreased muscle mass and strength, Difficulty to concentration, Fatigue and/or tiredness, history of pituitary surgery or irradiation
Acromegaly	Enlarged hands and feet, Coarse enlarged facial features, Coarse oily thickened skin, Excessive sweating

[Table/Fig-3]: Clinical clues to endocrine causes of adult secondary osteoporosis.

Once detailed history and examination have been performed the next step is to perform the relevant laboratory evaluation.

Laboratory and radiological evaluation: Initial and specific laboratory and radiological evaluations are summarised in [Table/Fig-4].

DIAGNOSIS

Diagnosis of secondary osteoporosis requires a high index of suspicion in the younger population and is usually made in the setting of a low trauma fracture i.e., trauma equivalent to a fall from a standing height or less. DXA is used to make a diagnosis of osteoporosis. The International Society for Clinical Densitometry (ISCD) recommendation is to use BMD Z scores rather than T scores at the lumbar spine, hip, and forearm. A Z score ≤ –2.0 indicates "below the expected range for age" and a Z score > –2.0 indicates "within the expected range for age [69]. For postmenopausal t score of < –2.5 is considered as osteoporosis [70].

Investigations	Diagnostic implication
Complete blood count, peripheral blood film	May show anaemia
Renal and liver function test	Deranged function may be a feature of primary disease (diabetic nephropathy, Hyperparathyroidism) or may contribute to osteoporosis itself
Serum calcium and phosphate levels	Levels reflect underlying disease states (severe hypercalcemiacaemia and low phosphorus may reflect hyperparathyroidism)
Serum bone-specific or total ALP activity	Elevated levels in hyperparathyroidism
Serum 25-hydroxyvitamin D	Inadequate vitamin D levels predispose to osteoporosis
24-h urinary calcium excretion, protein, phosphorus (with creatinine control)	Assesses for hypercalciuria (e.g., hyperparathyroidism, cushings disease, hyperthyroidism)
Bone turnover markers	Formation markers indicate high turnover states (Elevated in patients with hyperparathyroidism, acromegaly, cushings and reduced in hypothyroidism, GHD)
X-ray lumbar and thoracic spine with a skeletal survey	To assess overall skeletal integrity, diagnosis of fractures, specific signs such as sub-periosteal bone resorption, acro-osteolysis, brown tumours etc.,
DEXA (Bone mineral density measurement)	Gold standard for diagnosing osteoporosis
Quantitative Computed Tomography (QCT)	It estimates BMD as a true volume density in g/cm^3, which is not affected by bone size. Most sensitive method of diagnosing osteoporosis, not widely available
Quantitative Ultrasound (QUS)	Heel is the only validated skeletal site for the clinical use of QUS, advantage of not using radiation, low cost portable, lacks precision
Diagnostic conditions	Specific investigations
Cushing's disease	Serum (8 am), ACTH, Morning fasting serum cortisol after dexamethasone suppression, CT abdomen, MRI brain
Hyperparathyroidism	Intact parathyroid hormone, USG and CECT neck, Tc99 Sestamibi Scan
Hyperthyroidism	T3, T4, TSH, USG neck
Hypogonadism	Serum testosterone levels in men, LH, FSH
Diabetes	Fasting glucose levels, HbA1c
Growth hormone deficiency	IGF-1, GH stimulation test, MRI sella
Acromegaly	IGF-1, GH suppression test, MRI sella
Hyperprolactinemia	Prolactin

[Table/Fig-4]: Laboratory and radiological evaluation of secondary osteoporosis.
ALP: Alanine phosphatase; h: hour, GHD: Growth hormone deficiency; DEXA: Dual energy x-ray absorptiometry; BMD: Bone mineral density; ACTH: AdrenoCortical thyrotropin hormone; CT: Computed tomography; MRI: Magnetic resonance imaging; USG: Ultrasonography; CECT: Contrast-enhanced computed tomography; Tc99: Technetium 99; T3: Triiodothyronin, T4: Tetraiodothyronin, TSH: Thyroid stimulating hormone; LH: Leutinizing hormone; FSH: Follicle stimulating hormone; IGF: Insulin-like growth factor

MANAGEMENT

Once identified, the essential concept of treatment of secondary osteoporosis is to manage the underlying cause wherever possible including surgery drug discontinuation, and switching over to other therapy. If drug discontinuation is not possible, then the lowest possible dose should be used and the patient should be assessed for osteoporotic therapy.

Treatment of the predisposing disease is the best course of action with the increase in BMD over time and a reduction in the possibility of fracture. Intervention in the form of medical therapy would include vitamin D treatment in deficient patientss, change of medication, testosterone treatment in hypogonadal men, decreasing the dose of corticosteroids, if possible, in GIO, and correction of metabolic disorders or malabsorption [71,72].

Ensuring ample consumption of calcium (800-1200 mg/day) via

dietary uptake or supplements is recommended in all patients with risk of osteoporosis or on treatment with drugs that can cause osteoporosis. Vitamin D replacement (at least 800 IU/day) is recommended as vitamin D deficiency has a high prevalence and may contribute to reduced bone mass and increase the propensity to falls, in addition to various adverse extraskeletal effects [73]. Use of bisphosphonates, teriparatide, Denosumab, and Selective Estrogen Receptor Modulators (SERM) is advised in high-risk patients irrespectively of the cause and especially cause of secondary osteoporosis cannot be treated. The guideline is available for the management of GIO and is discussed below.

Glucocorticoid induced osteoporosis: Removal of ACTH secreting pituitary tumor or cortisol secreting adrenal tumour forms the primary basis for the management of Glucorticoid induced osteoporosis. In the case of exogenous causes of Cushing's disease stopping glucocorticoid therapy should be considered and if not possible then medical management of osteoporosis should be considered [Table/Fig-5].

Cause of osteoporosis	Management
Hyperparathyroidism	Parathyroidectomy results in improvement in BMD. If not a candidate for surgery give bisphosphonates
Hyperthyroidism	Maintain TSH in the median range of normal using anti-thyroid medication such as carbimazole and methimazole, surgery and radioiodine ablation may be considered
Hypogonadism	Testosterone replacement in males, Oestrogen replacement in females, Selective Oestrogen Receptor Modulators such as Raloxifene. Resumption of normal menstrual function and weight gain appears necessary for skeletal recovery in patients with functional hypothalamic amenorrhea due to anorexia nervosa
Acromegaly	Resection of tumours, somatostatin receptor ligands
Hyperprolactinemia	Cabergoline, Resection of tumours
Growth hormone deficiency	Replacement with recombinant growth hormone

[Table/Fig-5]: Specific management of secondary causes of osteoporosis.
BMD: Bone mineral density; TSH: Thyroid stimulating hormone

Therapies investigated include bisphosphonates, teriparatide, Selective Estrogen Receptor Modulators (SERMs), and Denosumab of which bisphosphonates (Oral alendronate, and risedronate, and intravenous zoledronic acid) and teriparatide were FDA approved but recently Denosumab has also been approved [Table/Fig-5]. Recent American college of rheumatology guidelines [74] recommends that risk stratification based on BMD, history of fracture, and the use of FRAX (for adults ≥40 years) should be assessed in individuals taking glucocorticoid treatment for a long term, within six months of initiation and repeated with 1-3 yrs; the use of the smallest possible dose of glucocorticoids is recommended to reduce fracture risk. Optimisation of calcium supplementation (1,000-1,200 mg/day) and vitamin D supplementation (600-800 IU/day) and lifestyle adjustments such as a balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake (1-2 alcoholic beverages/day) is also needed. Various studies have shown the beneficial effects of bisphosphonates on the lumbar spine and hip BMD in people treated with glucocorticoids [74,75] with some showing evidence of a reduction in the rate of vertebral fractures. In a trial comparing the effects of teriparatide and bisphosphonates in GIO, teriparatide showed larger improvements in spinal BMD and TBS. Treatment is indicated in all patients at moderate to high risk and oral bisphosphonate are preferred over IV bisphosphonates, teriparatide, and Denosumab with Raloxifene for post-menopausal women when other therapies cannot be given in the same order of preference. Consideration for changing treatment includes a fracture after >18 months of therapy or > 10 % BMD loss in a year [Table/Fig-4] [74,75].

Denosumab with its action on RANKL provides a novel therapy for GIO, given six monthly ensures better compliance than oral bisphosphonates and a recent randomised double-blind, double-dummy, active-controlled study on the treatment with Denosumab versus risedronate in GIOP showed higher BMD at lumbar spine on comparison to risedronate in both glucocorticoid-continuing (4.4% vs 2.3%) and glucocorticoid-initiating (3.8% vs 0.8%) groups, however rebound increase in bone loss following discontinuation of therapy remains a concern [10].

Osteoporosis Management in diabetes: Glycemic control and lifestyle measures should be adopted to improve general heath in patients with diabetes. Drugs associated with increased risk of fractures i.e., thiazolidinediones and SGLT-2 inhibitors should be avoided in patient at high risk of fractures. Maintainance of a healthy lifestyle with calcium and vitamin D supplementation as needed and exercise to improve muscle strength and reduce the risk of falls also decrease the chances of fractures. In a recent systematic review of nine studies (predominantly trials evaluating alendronate, risedronate, raloxifene, and teriparatide for the treatment of osteoporosis), there were indistinguishable increases in bone density and reductions in vertebral (alendronate, raloxifene) or nonvertebral (teriparatide) fracture risk in patients with and without diabetes [Table/Fig-5] [16].

CONCLUSION(S)

The strength of this review is that Authors have summated and brought together what is known regarding secondary osteoporosis and identify the gaps in this knowledge providing an avenue for both readers who are new to the topic and well versed with it, to understand and make an informed decision on the topic. The limitations of a literature review of this nature are the excessive dependency on previously available and published studies and while a detailed discussion of management would have been preferable, only an overview could be provided. As the understanding of bone biology and mechanisms of osteoporosis increases, newer pathways and cell signaling systems are discovered and more therapeutic options become available for successful management strategies. In any individual presenting with a recent diagnosis of osteoporosis, screening for the most common secondary causes must be done especially in men and pre-menopausal women. A team consisting of orthopaedicians, rheumatologists, physicians, nurses, physical and occupational therapists can help by early identification of patients, and making appropriate referrals which can improve the number of individuals who receive treatment with medications and thus, improve the osteoporosis and fracture outcomes. A significant number of patients who do not receive such treatment because of affordability and are lost to follow-up, suffer the burden of fractures which can be prevented by understanding the risk factors and providing appropriate management at initial diagnosis.

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