

## Review Article

# Approach to Pathological Fracture-Physician's Perspective

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## Abstract

A pathological fracture occurs without adequate trauma and is caused by pre-existent pathological bone lesion. Excluding the senile osteoporosis which is the commonest cause of fracture in elderly population, 5% of all fractures are pathological fractures due to local or systemic diseases. Metastatic bone diseases from breast, lung, kidney, prostate, thyroid and haematological malignancies including multiple myeloma are common causes of pathological fracture. Other causes include endocrinopathies (Cushing's syndrome, thyrotoxicosis, hyperparathyroidism, diabetes mellitus, male hypogonadism and growth hormone deficiency), osteomalacia of varied etiology (vitamin D deficiency and resistance, hypophosphataemia, chronic kidney disease, renal tubular acidosis, mineralization inhibitors, hypophosphatasia, inadequate calcium intake) and drugs (glucocorticoids, thiazolidinediones, antiepileptic drugs, proton pump inhibitors, antidepressants, antipsychotics, long term heparin, L-thyroxin overdose and androgen deprivation therapy). Less common causes are gastrointestinal disorders (celiac disease, inflammatory bowel disease, gastrointestinal surgery), HIV infection, non-malignant haematological diseases (thalassemia, systemic mastocytosis) and rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis and systemic lupus erythromatosus). Uncommon bone diseases like osteogenesis imperfecta, Paget's disease of bone and polyostotic fibrous dysplasia are also important causes of pathological fracture. A definite diagnostic algorithm is needed to reach an etiological diagnosis. Thorough history and clinical examination is mandatory to find out the underlying cause. Baseline haematological and biochemical tests are the initial step of evaluation. Depending on the clinical clue, other biochemical, endocrine and radiological investigations are sought for to reach the final diagnosis. Proper etiological diagnosis and appropriate treatment of underlying disorder is the key to the successful management of pathological fracture.

**Keywords:** Pathological fracture; Metastatic bone disease; Hematological malignancies; Endocrinopathies; Drugs

## Introduction

A bone fracture is a complete or incomplete discontinuity of bone caused by a direct or indirect force. A pathological fracture is the fracture which occurs without adequate trauma and is caused by pre-existent pathological bone lesion. Apart from osteoporosis which is the commonest cause of fracture in elderly men and postmenopausal women worldwide, many other local or systemic diseases may lead to fracture due to trivial trauma. If senile and postmenopausal osteoporosis are excluded, its frequency amounts to 5% of all fractures. The pathologic mechanisms which contribute include resorption of bone mass (osteoporosis), reduction of bone quality (osteomalacia, osteonecrosis), insufficient bone production (osteogenesis imperfecta, fibrous dysplasia), augmented bone resorption (giant cell granuloma, aneurysmal bone cyst), pathological bone remodelling (Paget's disease) and local bone destruction by primary or secondary bone tumors [1]. A definite diagnostic algorithm is needed to reach an etiological diagnosis which is essential for comprehensive management of the fracture. Various diseases that may lead to pathological fracture are discussed here and an approach to diagnosis is outlined. Primary bone tumors are beyond the scope of

discussion here as they are primarily managed by orthopedic surgeon and usually not physician's concern. Causes of pathological fracture are enumerated (Table 1).

## Case 1

A 54 year old man, clerk by occupation, presented with low back pain for last 6 months followed by pain over ribs for last 3 months. The pain was dull aching in type, predominantly nocturnal and gradually progressive. The patient gave history of recurrent urinary tract infection- 3 times in last 4 months. There was no history of trauma or preceding viral illness. There was no history of bleeding per rectum, haematuria, haemoptysis or lump anywhere in the body. He was normotensive, non-diabetic, non-smoker with history of occasional alcohol intake. He was a non-vegetarian with history of intake of 200 milliliter milk daily and had adequate sun exposure. He had no history of steroid intake in past. On examination, he had moderate anaemia and tenderness over L4 vertebra without any focal neurological deficit.

Investigation revealed: Hb-8.8 g/dl, ESR- 110 mm/hr with normal total and differential leucocyte count. Blood urea was 110 mg/dl and

**Table 1:** Etiology of pathological fractures.

<b>Malignancies:</b>
Metastatic bone disease
Haematological malignancies
<b>Endocrinopathies:</b>
Cushing's syndrome
Thyrotoxicosis
Primary hyperparathyroidism
Diabetes mellitus
Male hypogonadism
Growth Hormone deficiency
<b>Osteomalacia:</b>
Vitamin D deficiency and resistance
Hypophosphatemic osteomalacia
Chronic kidney disease
Renal tubular acidosis
Mineralization inhibitors
Hypophosphatasia
Inadequate calcium intake
<b>Drugs:</b>
See Table 2
<b>Gastrointestinal disorders and fragility fractures:</b>
Coeliac disease
Inflammatory bowel diseases
Gasdrointestinal surgery
<b>Rheumatological diseases:</b>
Rheumatoid arthritis
Ankylosing spondylitis
Systemic lupus erythematosus
<b>Infection:</b>
Human Immunodeficiency Virus (HIV) infection
Spinal tuberculosis
<b>Non-malignant haematological diseases:</b>
Thalassemia
Systemic mastocytosis
<b>Uncommon diseases of bone and connective tissue:</b>
Paget's disease of bone
Fibrous dysplasia
Osteogenesis imperfect
Marfan's syndrome
Homocysteuria
Ehlers los syndrome

serum creatinine was 3.8 mg/dl, serum bilirubin and liver enzymes were normal with altered albumin: globulin ratio (serum albumin-3.8 g/dl, serum globulin- 5.0 g/dl), serum corrected calcium was 13.7 mg/dl, serum phosphate was 3.8 mg/dl and serum uric acid was 8.3 mg/dl. Serum 25 hydroxy vitamin D3 level was 38ng/ml (normal). Skull x-ray showed multiple osteolytic lesions. X- Ray of lumbosacral spine revealed wedge compression fracture of L4 vertebra (Figure 1). Serum protein electrophoresis showed M spike ( $\alpha$ -1 globulin- 0.48g/l) and serum immune fixation electrophoresis confirmed M spike in gamma globulin region which was IgA kappa type. Bone marrow aspiration revealed more than 50% plasma cells. Urine Bence Jones protein was absent. Serum  $\beta$ 2 microglobulin level was 9517ng/ml. The patient was diagnosed as a case of multiple myeloma, stage III ISS and was treated with thalidomide, bortezomib and dexamethasone.

### Malignancies and Bone disorders

**Metastatic bone disease:** Apart from primary bone tumors, the vast majority of tumor-related bone disorders leading to pathological fractures are due to skeletal metastasis from distant sites. The most common primary malignancies that metastasize to bone are breast, lung, kidney, prostate and thyroid carcinomas accounting for 80% of skeletal metastasis. Many other primary bone tumors may spread to bone which include uterine leiomyosarcoma, hepatocellular and uterine carcinomas. Prognosis largely depends on aggressiveness of

**Figure1:** L4 vertebral pathological fracture in a patient of multiple myeloma.

primary tumor, severity and extent of bone involvement and early diagnosis and intervention [2].

Skeletal metastasis is mostly multifocal, although few primary tumors like renal and thyroid carcinoma may produce solitary osseous lesions. The most common site of bone metastasis is axial skeleton followed by proximal femur and proximal humerus. Metastatic bone tumors are 40 times more frequent than all primary bone tumors combined [3]. In an autopsy series, one-third of patients who died of cancer had vertebral body metastasis, more frequently in anterior elements of spine than posterior [4]. 90% of metastatic prostate cancer, 75% of metastatic breast cancer and 45% of metastatic lung cancer involve spine.

The patients with metastatic bone disease and pathological fracture have varied presentation. The most common symptom is pain in local site, often severe, mechanical in nature, mostly nocturnal and unresponsive to non-narcotic and narcotic analgesics. Next common presenting complaint is neurological symptoms especially radicular pain in spinal metastasis. Fractures may recur in different sites in cases of malignancy.

### Haematological malignancies

**Multiple myeloma:** It is the second most common haematological malignancy after non-Hodgkin's lymphoma. Multiple myeloma is a clonal B-cell disorder characterized by proliferation and accumulation of B-lymphocytes and plasma cells in bone marrow, and less commonly extramedullary sites. Approximately 80% of patients with newly diagnosed multiple myeloma have bone disease and 70% of them present with bone pain. 60% of these lesions involve spine as because of the fact that vertebral bodies contain a high amount of haematopoietic bone marrow. Vertebral involvement may occur in the form of generalized osteoporosis or localized osteolysis mostly in vertebral bodies, but rarely in transverse processes, spinous processes or pedicles. 80% of vertebral fractures occur in D6 to L4 region. Spine is also the commonest site for bone solitary plasmacytoma, the average incidence being 50% compared to 12% in pelvis and 9% in ribs. A retrospective cohort study showed 16 times more than expected fracture in the year before myeloma was diagnosed of which two-third was spine or rib fractures [5]. Monoclonal Gammopathy of Unknown Significance (MGUS) also carries an increased risk of



**Figure 2A and B:** Osteitis fibrosa cystica at left lower end of humerus in a patient of hyperparathyroidism and pathological fracture at the same site.

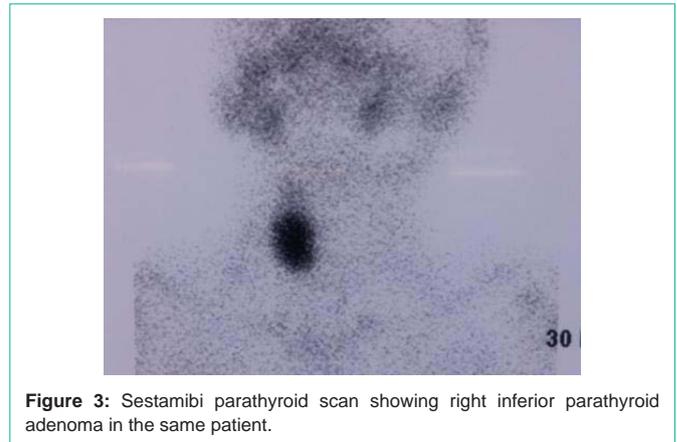
osteoporotic fractures.

**Non Hodgkin’s Lymphoma (NHL):** It may rarely cause pathological fracture. A review of world literature shows that incidence of skeletal manifestation in NHL is less than 5% and in all cases bony involvement was reported many years after the primary disease was diagnosed. Pathological fracture is either due to tumour itself, radiotherapy and disuse atrophy. Fracture of proximal femur or humerus secondary to soft tissue tumour is more common than primary lymphoma of bone [6].

**Leukaemias:** Various types of leukaemias, both acute and chronic may involve skeletal system. Musculoskeletal involvement is commonly seen in growing children with Acute Lymphatic Leukemia (ALL) which may range from mild pain to debilitating osteonecrosis causing fracture. Bone involvement is well recognized at diagnosis, during therapy and as long term sequelae after therapy. At the onset of diagnosis there is radiological evidence of periosteal reaction (2-19%), osteolytic lesions (19-38%) and fractures (2-10%). There is six-fold higher risk of fracture in maintenance phase of treatment of ALL. Incidence of non-traumatic vertebral fractures in children after 1 year of therapy is as high as 16% and 85% of them occurring in previously normal vertebral body. Osteotoxic chemotherapy, steroid exposure, poor nutrition, reduced muscle mass and low vitamin D may be responsible for increased fracture rate. Hypo- and hypermagnesemia associated with aminoglycosides and glucocorticoids during treatment for ALL may affect hydroxylation reaction hampering production of 1,25 dihydroxy vitamin D contributing to mineralization defect [7].

**Case 2**

A 52 year old apparently well lady admitted in hospital with unexplained pain in left lower arm. An x-ray left lower arm showed cystic bony lesion at lower end of left humerus (Figure 2A). Her pain became intolerable while she was turning in bed at night. Next day, another x-ray of left lower arm showed fracture at the site of cystic bony lesion (Figure 2B). Later asymptomatic lytic lesions were also seen in left femur radiograph. The patient was further evaluated and hypercalcaemia was detected with corrected serum calcium level of 11.8 mg/dl (normal: 8.5-10.5mg/dl). Serum creatinine level was within



**Figure 3:** Sestamibi parathyroid scan showing right inferior parathyroid adenoma in the same patient.

normal limit. Serum iPTH level was 730 pg/ml. High resolution USG of neck and Tc99 sestamibi scan suggested right inferior parathyroid gland adenoma (Figure 3). DEXA scan revealed gross osteoporosis with a T score of -3.0 SD at 2 sites. Parathyroidectomy was done which was found to be benign parathyroid adenoma on histopathological examination. Despite a transient hypocalcaemia the patient was discharged 2 weeks later with normal serum iPTH level (52 pg/ml).

**Endocrinopathies and secondary osteoporosis**

Secondary osteoporosis is defined as bone loss, micro-architectural alterations and fragility fractures due to an underlying disease or concurrent medication. Adequate response to osteoporosis does not occur unless primary disorder is treated.

Among various diseases causing secondary osteoporosis, endocrine disorders top the list. Common endocrine diseases causing fragility fracture are Cushing’s syndrome, hypogonadism, hyperparathyroidism, thyrotoxicosis and type 1 diabetes mellitus.

**Cushing’s syndrome:** This is a disease caused by excessive cortisol secretion clinically characterized by central obesity, fatigability, weakness, amenorrhoea, hirsutism, edema, hypertension, impaired glucose tolerance and secondary osteoporosis. There is 50% prevalence of osteoporosis in these patients. At least 30-50% patients with Cushing’s syndrome experience fractures particularly vertebral fracture. Excess glucocorticoids may inhibit osteoblast maturation and promote apoptosis. There is accelerated degradation of existing collagen and inhibition of new collagen formation. Moreover intestinal calcium absorption is reduced and renal calcium excretion is increased. All these mechanisms may lead to reversible and irreversible bone mineral loss and weakening of bone architecture.

**Thyrotoxicosis:** Thyrotoxicosis, both overt and subclinical, is established risk factors for osteoporotic fractures. A large study of 686 postmenopausal women demonstrated that a TSH < 0.1 mIU/ L was associated with a four and five- fold risk of vertebral and hip fracture respectively [9]. Increased bone resorption is mainly attributed to activation of thyroid hormone receptor  $\alpha$  on osteoclasts. Moreover high bone turnover results in increased mobilization of calcium from bone leading to hypercalcaemia in up to 20% of hyperthyroid patients. This relative hypercalcaemia inhibits PTH secretion and reduces 1- $\alpha$ -hydroxylation of 25-OH vitamin D. Increased metabolic clearance due to thyrotoxicosis further reduces circulating 1,25 ((OH)<sub>2</sub> vitamin D which leads to decreased intestinal calcium and

phosphate absorption together with increased faecal calcium loss. Reduced PTH level also leads to increased urinary calcium loss and phosphate reabsorption. Thus increased skeletal calcium mobilization along with reduced PTH and 1,25 (OH)<sub>2</sub> vitamin D levels result in a significant negative calcium balance in thyrotoxicosis.

**Primary hyperparathyroidism:** It is the most common cause of hypercalcaemia affecting 1 in 1000 persons, more with increased age. The disease results from excessive secretion of parathyroid hormone either due to solitary (50-85%) or multiple (10%) adenomas, hyperplasia (10-40%), or rarely due to carcinoma of a single parathyroid gland. Most patients are asymptomatic at diagnosis and diagnosed on incidental biochemical assays. Fracture due to hyperparathyroidism is relatively uncommon. Crude fracture rate is 15/1000 person years in comparison to 8/1000 person years in controls [10]. The fractures are due to brown tumors which is a rare complication of hyperparathyroidism. These are benign focal bone lesions caused by increased osteoclastic activity and fibroblast proliferation usually seen in primary, but rarely in secondary hyperparathyroidism. They can be found in any bone, but most commonly found in facial bones and jaws, sternum, ribs, pelvis, femur and rarely vertebrae. Histological findings are similar to giant cell tumour or aneurysmal bone cyst.

**Diabetes mellitus:** Both type 1 and type 2 diabetic patients are more prone to fractures. There is 12 fold increased risk of osteoporotic fractures in type 1 diabetes mellitus [11]. Low bone mineral density in type 1 diabetes is probably due to lack of bone anabolic action of insulin and other β-cell derived proteins like amylin. On the other hand, type 2 diabetes mellitus patients often show increased bone mineral density (4-5% increased in hip), but still has increased fracture risk [12]. One of the reasons behind this is increased tendency to fall in patients with retinopathy and peripheral and autonomic neuropathy. Moreover, the patients with advanced nephropathy may have renal osteodystrophy. The patients on thiazolidinediones are also more prone to osteoporosis and fragility fracture.

**Male hypogonadism:** It is a major risk factor for rapid bone loss and osteoporotic fracture in males. Androgens are important hormones for developing peak bone mass. Androgen action is mediated through local aromatization of androgen to estrogens [13].

**Growth Hormone (GH) deficiency:** GH deficient patients have a two to three fold higher risk of osteoporotic fractures mainly due to lack of insulin like growth factor 1 (IGF-1) which is a potent stimulator of osteoblastic activity [14].

### Case 3

A 58 year old male patient office clerk by occupation, presented with history of aches and pains all over the body, dull aching in nature for last 2 years which started as low backache but gradually involved shoulder, chest wall and hips. He also complained of difficulty in standing up from squatting position, climbing upstairs and taking over-head office files for last 18 months. The pain was not associated with any arthritis or arthralgia, prolonged fever or any other neurological symptoms. He was a non-vegetarian with daily intake of milk and adequate sun exposure. He was a non-smoker, non-alcoholic without any history of substance abuse. There was no past history of steroid intake and he was not on any regular drug including



Figure 4: X-ray pelvis showing looser zone in right femur (white arrow).



Figure 5: Multiple pathological fracture in the same patient.

any hypolipidaemic drug. He was born of a non-consanguineous marriage without any history of similar disease in the family and without any significant past history of hepatic dysfunction, renal dysfunction, known rheumatological disease or malignancy. The only positive clinical findings were tenderness over bony points and proximal myopathy over all 4 limbs (grade 4-/5) with preserved deep reflexes and intact sensory system. His routine haemogram, ESR, CRP, fasting plasma glucose, renal hepatic and thyroid function test were normal. Serum protein electrophoresis showed no M band. ANA and ENA profile were negative. Serum calcium- 9.8 mg/dl, serum phosphate- 1.1 mg/dl, serum alkaline phosphatase- 518 iu/l, 25 hydroxy vitamin D3- 40 ng/dl (N> 30 ng/dl), 1,25 dihydroxy vitamin D3- 11.2 pg/ml (N= 13-46 pg/ml) and iPTH -36.1 ng/l (N= 10-72 ng/l). 24 hours urinary phosphate was 1.1 g/day (N= 0.465-0.95 g/day) and TmP-GFR was 0.627mmol/l (N=0.65-0.85 mmol/l) with normal 24 hours excretion of calcium, uric acid, glucose and protein. X-ray pelvis showed multiple Looser's zones (Figure 4). He was diagnosed as a case of hypophosphataemic osteomalacia. He was suspected as a case of tumour induced osteomalacia but 18F FDG PET-CT scan was normal at that time. He was prescribed with high dose active vitamin D and oral phosphate salt but he left treatment and discontinued follow up. 2 years later he came in bed-bound state with multiple fractures in pelvis (Figure 5) with almost similar

**Table 2:** Drugs causing osteoporosis and/or fragility fractures.

Drug class	Examples	Mechanism
Glucocorticoids*	Prednisolone	Inhibit osteoblast maturation and promote apoptosis, renal calcium loss ↓mRNA osteoprotegerin, ↓sex hormones, ↓ calcium absorption, ↓ creatinine clearance Shifting of pluripotent mesenchymal stem cells to adipocyte differentiation Lowering sex hormones Lowering sex hormones ↓ calcium absorption due to high gastric pH Inhibits osteoblastic and promote osteoclastic activity Promotes osteoclastic activity, mobilization of calcium from bone Induce hepatic enzymes and accelerates vitamin D metabolism. Modulate skeletal response to PTH Lowering estrogen Increasing prolactin Hypovitaminosis D due to fat malabsorption
Calcineurine inhibitors*	Cyclosporin A	
Thiazolidinediones*	Pioglitazone	
GnRH agonists*	Goserelin, buserelin, flutamide	
Aromatase inhibitors*	Anastrozole, letrozole	
Proton pump inhibitors*	Pantoprazole, rabeprazole	
Unfractionated heparins*		
Thyroid hormones*	L-thyroxin (supraphysiological)	
Anticonvulsants	Phenytoin, carbamazepine	
Antidepressants (SSRI)*	Fluoxetine, escitalopam	
Progesterone	Depot medroxyprogesterone acetate	
Antipsychotics	Amisulpiride, risperidone	
Lipase inhibitors	Orlistat	

\*Drug associated with increased fracture.

biochemical reports. The patient was re-advised for FDG PET-CT scan. This time it spotted a localised increased uptake in second metatarsal of left foot. Subsequent investigation including biopsy proved it to be a mesenchymal tumour. Sometimes it takes years to localize mesenchymal tumour of bone which can produce tumour induced osteomalacia at an early date.

### Osteomalacia- a metabolic cause of fracture

Osteomalacia is a disorder due to decreased mineralization of newly formed osteoid at sites of bone turnover. It may occur as a consequence of inadequate calcium, phosphate and/or alkaline phosphatase, or in the presence of abnormal bone matrix or direct inhibition of mineralization process. It is a spectrum disorder from asymptomatic to multiple fractures. Common clinical manifestations are diffuse bone and joint pain, bone tenderness, muscle weakness particularly proximal myopathy, waddling gait, muscle cramps, spasms, tingling and numbness and in severe cases single or multiple fractures.

Different disorders that may cause osteomalacia are as follows:

**Vitamin D deficiency and resistance:** They produce osteomalacia by following mechanisms: [15] impaired availability of vitamin D (lack of sun exposure, dietary deficiency, fat malabsorptive disorders), impaired 25- hydroxylation of vitamin D in liver (chronic liver disease, phenytoin, carbamazepine, oxcarbamazepine, phenobarbitone, theophylline, INH, rifampicin), impaired  $\alpha$ -hydroxylation of 25-hydroxyvitamin D in kidney (chronic kidney disease, vitamin D resistant rickets type 1) and end organ insensitivity to vitamin D metabolites (hereditary vitamin D resistant rickets).

**Hypophosphatemic osteomalacia:** Probable mechanisms are: phosphaturia due to secondary hyperparathyroidism (e.g hypovitaminosis D), phosphaturia due to phosphaturic hormone fibroblast growth hormone3 (FGF23) (e.g hereditary PHEX gene related X-linked dominant disorder, mesenchymal tumour induced osteomalacia) [16] and phosphaturia due to proximal tubular transport defect (e.g Fanconi syndrome) [17].

**Chronic Kidney Disease (CKD):** Factors responsible are: reduced formation of 1,25 dihydroxy vitamin D, metabolic acidosis, aluminium toxicity [18] and secondary hyperparathyroidism.

**Renal Tubular Acidosis (RTA):** Osteomalacia is commonly seen in proximal RTA (type2). Causes of proximal RTA include: multiple myeloma and other monoclonal gammopathy, drugs like acetazolamide, topiramate, iphosphamide and mutation in gene for sodium carbonate transporter (SCL4A4 gene) [19-21].

Mechanisms of osteomalacia in proximal RTA are: proximal phosphate wasting, increased calcium loss due to metabolic acidosis and secondary hyperparathyroidism.

Although the association is controversial, distal RTA may also cause osteomalacia on rare occasions. In one study, two of seven patients with Sjogren's syndrome and distal RTA had findings consistent with osteomalacia [22].

**Mineralization inhibitors:** Older bisphosphonates, aluminium, fluoride.

**Hypophosphatasia:** This is a rare autosomal disease associated with low alkaline phosphatase in serum and bone leading to osteomalacia and severe periodontal disease. Perinatal form is lethal whereas infantile form may spontaneously improve and recur later in adulthood. Adult hypophosphatasia is characterized by poorly healing recurrent metatarsal stress fracture and bone pain and also increased incidence of chondrocalcinosis [23].

**Inadequate calcium intake:** It may also produce osteomalacia apart from hypovitaminosis D.

### Case 4

A 32 year old woman, known case of bronchial asthma presented with sudden severe pain in left hip. She could not remember any significant trauma over the site. An x-ray of left hip showed trochanteric fracture. Careful history revealed intermittent use of oral prednisolone, sometimes without medical advice. No calcium supplementation was taken along with steroid.

### Drugs and osteoporotic fractures

Various drugs affect bone metabolism in different ways. Some of them impair absorption of vitamin D, calcium and phosphate, some affect vitamin D metabolism and action; others have direct effects on osteoblasts, osteoclasts and osteocytes or interfere with the amount or quality of bone matrix protein. (Table 2) shows the drugs responsible

for secondary osteoporosis.

**Glucocorticoids:** These are the most important drugs causing fragility fracture. Even minimum dose of prednisolone (2.5-7.5 mg/day) is associated with 2.6 fold higher risk of vertebral fracture and it carries five-fold higher risk when the dose is more than 7.5 mg/day [24]. Mechanism of action is same as mentioned in endogenous glucocorticoid excess or Cushing's syndrome.

**Thiazolidinedione:** This commonly used antidiabetic is associated with three- to five-fold increased risk of fracture of femur, humerus and hip in postmenopausal women. This is because glitazones lead to shunting of pluripotent mesenchymal stem cells to adipocyte differentiation at the cost of osteoblastic lineage [25].

**Antiepileptic drugs:** Phenytoin, phenobarbitone and carbamazepine induce hepatic enzymes and accelerates vitamin D metabolism.

**Proton pump inhibitors:** These drugs when used in high dose for prolonged period, carries a 3.5 fold increased risk of vertebral fracture in postmenopausal women. Decreased calcium absorption due to loss of gastric acidification is the probable cause [26].

**Antidepressants:** Selective serotonin reuptake inhibitors (SSRIs) causes higher rate of annual bone loss and 4-5% lower bone mineral density. Serotonin appears to modulate skeletal response to parathyroid hormone (PTH) possibly through receptors and transporters on osteoblasts and osteocytes [27].

**Antipsychotics:** Antipsychotics also have well-established relation between falls and fracture. Conventional antipsychotics are known to raise prolactin which eventually lowers estrogen and testosterone concentration and causes bone loss.

**Heparin:** Long term use of heparin in pregnancy may produce symptomatic vertebral fracture in 3 out of 100 patients due to significant reduction of bone mineral density [28].

**L-thyroxine:** Supraphysiological doses of L- thyroxin maybe responsible for increased incidence of fragility fracture. A meta-analysis of 21 studies showed that L-thyroxine suppressive therapy in management of differential thyroid carcinoma resulting in subclinical hyperthyroidism was associated with osteoporosis in postmenopausal women [29].

**Androgen deprivation therapy:** These include Gonadotrophin Releasing Hormone (GnRH) agonists (goserelin, buserelin, triptorelin) which cause hypogonadotropic hypogonadism or antiandrogens (bicalutamide, cyproterone acetate). These drugs are commonly used in prostate cancer. They may cause rapid turnover of bone and fracture. Similarly, aromatase inhibitors (letrozole, anastrozole) used in treatment of breast carcinoma reduces conversion of adrenal androgen to estrogen and have the same effects on bone [30].

### Gastrointestinal disorders and fragility fractures

**Coeliac disease:** Malabsorption leads to hypovitaminosis D leading to secondary hyperparathyroidism. Associated autoimmune disorders like type A gastritis, Graves' disease and type 1 diabetes mellitus may further affect skeletal health causing increased chance of pathological fracture. It has been reported that there is 17-fold higher

prevalence of coeliac disease in osteoporotic individuals compared to non-osteoporotic individuals supporting screening for coeliac disease in pathological fracture [31].

**Inflammatory Bowel Diseases (IBD):** Multiple factors are responsible for osteoporosis and increased probability of fracture in IBD. Chronic inflammation, diarrhoea and malabsorption, low Body Mass Index (BMI), intermittent or chronic use of steroids, functional loss of terminal ileum and prolonged immobilization are the possible risk factors for osteoporosis [32].

**Gastrointestinal surgery:** One-third post-gastrectomy patients develop osteoporosis as a result of decreased calcium absorption due to increased gastrointestinal pH [33]. Bone loss is a common accompaniment after bariatric surgery. Different forms of bariatric surgery are associated with decreased fractional calcium absorption and vitamin D malabsorption. Bone loss is often directly proportional to the degree of weight loss. A study shows doubling of fracture rate after bariatric surgery [34].

### Rheumatological diseases as a cause of weak bone

Rheumatological diseases like Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS) and Systemic Lupus Erythematosus (SLE) may have periarticular and generalized bone loss, with an increased incidence of fractures compared with the general population [35]. In RA, T lymphocytes, tissue macrophages, and synovial-like fibroblasts release inflammatory cytokines (IL-1, TNF, IL-6) and inhibitory wnt signaling proteins such as dkk-1 and RANKL, which stimulate preosteoclasts in the bone marrow and synovium to actively resorb bone; in addition, osteoblast maturation is altered [36,37]. AS is also associated with fractures and reduced bone density in the spine and proximal femur, even early in the disease [38]. SLE patients also have a high rate of osteoporotic fractures in the presence of low to normal bone mass which suggest systemic inflammation alters bone turnover. Increased serum levels of tumor necrosis factor can reduce osteoblast maturation and increase osteoclast maturation and activity. In addition, other inflammatory factors such as oxidized low-density lipoproteins and inflammatory high-density lipoproteins can direct mesenchymal stem cells to differentiate into adipocytes instead of osteoblasts and impair bone mass [39].

### Infective causes

**Human Immunodeficiency Virus (HIV) infection:** Osteoporosis and osteoporotic fractures are more prevalent in HIV disease. The risk of osteoporosis is 3.7 fold higher in HIV infected patients as compared to non-HIV patients [40]. In older individuals with HIV disease, the fracture rate is three to four folds higher in comparison to controls. Various factors including antiretroviral drugs, low BMI, hypogonadism, vitamin D deficiency, GH deficiency, prolonged immobilization, smoking and alcohol abuse are responsible.

**Spinal tuberculosis:** Spinal tuberculosis is a commonly encountered destructive form of extrapulmonary tuberculosis in developing countries. In developed countries the disease is mostly associated with immigrants from endemic countries. Epidemic of HIV infection caused resurgence of all forms of tuberculosis necessitating increased awareness about spinal tuberculosis. Spinal tuberculosis accounts for 50% cases of skeletal tuberculosis, 15% cases of extrapulmonary tuberculosis and 2% of all cases of tuberculosis

[41]. Dorsal vertebra is the most commonly affected part of spine. Characteristically there is destruction of the intervertebral disc space and adjacent bodies, collapse of the spinal elements and anterior wedging leading to gibbus formation. Concave collapse (compression fracture without involvement of intervertebral disc) may occur due to extensive vertebral destruction [42]. Concave collapse may bulge into the parenchyma of spinal cord developing neurological complication.

### Non-malignant haematological diseases

Apart from plasma cell disorders, lymphoma and leukemia, several non-malignant haematological disorders may lead to pathological fracture.

**Thalassemia:**  $\beta$ -thalassemia major is known to have several skeletal manifestations among all haemolytic anaemias. Most of the skeletal problems are due to close proximity of bones and joints to active centre of haemopoiesis. One-third to half of  $\beta$ -thalassemia major patients used to sustain long bone fractures earlier due to minor direct or indirect trauma which was either solitary or multiple or recurrent [43,44]. Improvement of transfusion therapy not only increased the life span of thalassemia patients but also decreased the frequency and changed the character of fractures. An Indian series shows 13.3% fracture rate. Maintenance of haemoglobin at 8 to 9 g/dl markedly brings down the fracture rate [45].

**Systemic mastocytosis:** It is a rare disease, may cause rapid bone loss affecting both long bones and spine. Osteoporosis results from excessive degranulation of mast cell products including interleukins (IL-1, IL-3 and IL-6) and histamine which promotes osteoclast differentiation from precursor cells. Activating mutation of c-kit is present in over 90% of adult patients [46].

Uncommon diseases of bone and connective tissue causing pathological fractures.

Few less common diseases are sometimes responsible for pathological fractures are:

**Paget's disease of bone:** It is a metabolic disorder characterized by high rates of bone remodelling which cause bone expansion, trabecular disorganization followed by reduced bone strength and quality with subsequent pathological fracture. It is commonly a disease of white Europeans above 55 years. Its etiology is controversial having both genetic and environmental origin. Bone pain is the commonest symptom followed by bony deformity. Pathological fracture is a rare complication, sometimes a manifestation of malignant transformation of Paget's disease.

**Fibrous dysplasia:** It is a congenital non-inheritable developmental anomaly of bone in which normal bone marrow is replaced by fibrous tissue and may lead to pathological fracture. It may be localized to a single bone (monostotic fibrous dysplasia) or involve multiple bones (polyostotic fibrous dysplasia). Polyostotic fibrous dysplasia can occur as a part of McCune Albright syndrome (combination of polyostotic fibrous dysplasia, cafe-au-lait spots, precocious puberty and other endocrinopathies) caused by activating mutation of gene encoding alpha subunit of stimulatory G-protein in bone marrow cells. The bones commonly involved are femur, tibia, ribs, skull, humerus and pelvis. Bony deformity, bone pain and

fracture are the common skeletal manifestations. Diagnosis is made by classical radiologic findings substantiated by bone scans and typical histopathological findings.

**Osteogenesis imperfecta:** It is a heterogeneous group of disorder characterized by susceptibility to bone fractures with varying severity in most cases with presumed or proven deficit of collagen biosynthesis. Other manifestations include short stature, blue sclerae, dentinogenesis imperfecta and hearing loss.

**Marfan's syndrome, homocystinuria and Ehlers Danlos syndrome** are few other genetically determined connective tissue disorders which may lead to increased incidence of fragility fractures since childhood.

## Diagnostic Approach

Thorough clinical history and examination is needed to reach at an aetiological diagnosis.

### History

**Age-** Young - genetic disorder

Middle age- endocrinopathies and drug induced

Old age- metastatic bone disease, multiple myeloma

### History of previous fracture

### History of known medical disorder including malignancy

### Dietary history

### Drug history

### History of addiction-smoking/alcoholism

### Family history

### Examination

### Built and nutritional status

**Pallor-** malignancy, chronic disease, haematological disorder

**Bony tenderness-**osteomalacia, haematological disorders

**Goitre/ tachycardia, tremor with or without exophthalmos-**thyrotoxicosis

**Palpation for breast lump-** breast carcinoma with bone metastasis

**Systemic examination including search for abdominal lump-** ovarian or colonic carcinoma with bone metastasis

**Proximal myopathy-**endocrine disorders, hypovitaminosis D, malignancy

### Investigations

### Haematological, biochemical and hormones

**Complete haemogram- Low haemoglobin** - malignancy, chronic disease, haematological disorder

**High ESR-** multiple myeloma

**Fasting plasma glucose-raised-** type 2 diabetes, secondary diabetes

**Renal function test**- raised creatinine - chronic kidney disease, multiple myeloma

**Liver function test**-- raised aminotransferase, altered albumin-globulin ratio- chronic liver disease

**Calcium**- raised calcium- hyperparathyroidism, multiple myeloma

Low calcium- hypovitaminosis D, osteomalacia

**Phosphate**-low phosphate- mild to moderate- calcipenic osteomalacia, severe- hypophosphatemic osteomalacia

**Alkaline phosphatase**- raised alkaline phosphatase-osteomalacia, hypovitaminosisD, recent fracture low alkaline phosphatase-hypophosphatasia

**25 hydroxy vitamin D3**- low- hypovitaminosis D

**1,25 dihydroxy vitamin D**- low- vitamin D resistant rickets type 1 (VDDR 1), CKD high- vitamin D resistant rickets type 2 (VDDR 2)

**Thyroid function test** - raised TSH, low free T3 and free T4- thyrotoxicosis

**Serum protein electrophoresis/ urine protein electrophoresis** - Monoclonal band- multiple myeloma (may be absent in solitary plasmacytoma)

**Intact Parathormone (iPTH)** - high- primary and secondary hyperparathyroidism

**24 hours urinary calcium**- high- hyperparathyroidism, hyperthyroidism, multiple myeloma

**Prostate Specific Antigen (PSA)** - raised-prostatic carcinom

**Serological tests for hepatitis B, C and HIV**

**Urine pH**- low- untreated proximal RTA, High- treated proximal RTA, distal RTA

**Tissue Transglutaminase (TTG)**- gluten enteropathy

**Other tests**: according to clinical clue:

**Morning cortisol**- low- exogenous Cushing's syndrome

**Overnight low dose dexamethasone suppression test**- Non-suppression- endogenous Cushing's syndrome

**IGF-1**-low-growth hormone deficiency

**Testosterone**- low- hypogonadism

## Radiological

**Chest X-ray/ CT scan thorax**- lung carcinoma

**Abdominal sonography**- Abdominal malignancy - Bilateral shrunken kidney- Chronic kidney disease

**Skeletal survey**- fracture, bone cyst, osteolytic or osteosclerotic lesions

**Dual energy X-ray absorptiometry scan (3 sites)** - Low bone mineral density- Osteopenia, osteoporosis

**PET CT scan- occult malignancy**

## Histopathological

**CT guided fine needle aspiration cytology (FNAC)**

**Bone biopsy**

## Conclusion

Etiological diagnosis of pathological fracture is a real clinical challenge to physicians. It has varied clinical presentation, etiology and prognosis. Thorough history and clinical examination are needed for judicious choice of investigations. Sometimes extensive investigations are required to arrive at a diagnosis. Proper etiological diagnosis and treatment of underlying disorder is the key to the successful management of pathological fracture.

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