

# Clinical and theoretical contrast of common non-septic causes of bone degeneration

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## Abstract

There is an abundance of diseases that cause dysfunctional bone remodeling. Some of these disorders that are commonly seen are porosis, thyrotoxicosis, Multiple Myeloma, and various cancers/neoplasms. They are all capable of causing the degeneration of bone and adversely affecting its structural integrity and stability.

There are numerous etiologies that can be implicated in the degeneration of bone, spanning across many disciplines. Unless one is a specialist in all areas, discerning the correct diagnosis can be an arduous task. Usually, when there are a number of different pathologies causing a similar defect, e.g. bone degeneration, they can exhibit similar semblances. Under such circumstances an incorrect diagnosis is often made which results in practitioners administering a battery of unnecessary tests and medications. Aside from the added expense, it is also detrimental to the patient's morbidity and mortality, as this is when the majority of unwarranted complications arise; all of which contribute to the rising costs of patient healthcare. It is the objective of the presented paper to provide the most salient information to improve the ability of general practitioners to recognize and manage these scenarios, specifically those involving the degeneration of bone. It is to be hoped that it will minimize mistakes and the financial burdens they levy.

Generally, the diseases mentioned above have already been extensively researched within their individual spheres in the medical community. Although, publications specifically scrutinizing their similarities and differences within clinical constructs are sparse.

In dealing with issues such as bone degeneration where it can be attributed to a multitude of causes it is often most useful to focus on those that are the most prevalent. Understanding their differences on a theoretical level can compound the benefits yielded in a clinical setting, especially with regard to diagnosis, management, and treatment.

## Key words

bone diseases, bone neoplasms, Graves' disease, multiple myeloma, osteitis fibrosa cystica, osteoporosis

There are numerous etiologies responsible for the degeneration of bone that subsequently adversely affect the architecture of skeletal bone. Determining the serum levels of certain markers indicative of bone turnover can assist in discovering the prevalence of these diseases in patients. Some examples of these markers are bone specific alkaline phosphatase (ALP), calcium, phosphate, osteocalcin, transforming growth factor beta (TGF- $\beta$ ), insulin-like growth factors I and II (IGF-1, IGF-2), fibroblast growth factors (FGF), and platelet-derived growth factors (PDGF). Unfortunately, these markers are not very specific and when used alone the information will be equivocal. Therefore, it is recommended that this information should be used in an ancillary capacity and in conjunction with other findings [1, 2].

Osteoporosis (OP) is characterized as a systemic skeletal disease where there is a diminution in bone mineral density (BMD). The pathophysiologic mechanisms may vary in male OP, postmenopausal OP, and glucocorticoid-induced OP, but the underlying principal remains the same: the rarefaction of bone. The rarefaction is due to an imbalance in bone remodeling, a physiologic process of bone resorption followed

by new bone formation (also known as 'coupling' when occurring at the same locus/bone remodeling unit). This ultimately leads to the deterioration of the microarchitecture of bone [3], a process controlled/regulated by hormones and cytokines that act on bone-forming osteoblastic cells as well as osteoclasts (giant cells that resorb bone). Gonadal steroids/hormones such as estrogen (and possibly testosterone) exert their effects on the bone resorption aspect of bone remodeling, as it is normally responsible for inhibiting the production of several cytokines; particularly Tumor Necrosis Factor- $\alpha$ , interleukin-1 and interleukin-6, all of which stimulate bone resorption. Circulating gonadal hormones, together with parathyroid hormone and calcitriol (1,25-OH Cholecalciferol), are also responsible for the regulation in osteoclast formation. Thus, the estrogen deficiency commonly seen in post-menopausal women (and possibly elderly men) has been inculcated for inducing the acceleration in the loss of bone. Osteoporosis may also occur secondarily due to long-term usage of glucocorticoid drugs. This has galvanized the medical and pharmaceutical community to develop numerous treatment options. Commonly, varying regimens of estrogens, selective estrogen receptor modulators (i.e. Raloxifene), bisphosphonates (i.e. Alendronate, Etidronate), fluoride, and calcitonin have been used effectively. The World Health Organization has devised guidelines to establish the presence of this disease which has been determined to be present in an individual when their BMD is measured using

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dual-emission X-ray absorptiometry (DXA), and found to be at least 2.5 standard deviations below the mean peak bone mass (the average in healthy adults) [4, 5]. However, when there is a lack of sufficient empirical evidence this may be superfluous and expensive, and it may be more prudent to attempt to rule out OP first through the aid of biochemical markers (rather than try to rule in). In OP serum levels of calcium, phosphate, PTH, and ALP are all unaffected, meaning elevation of any of these markers would be suggestive of an etiology other than OP [6].

Thyrotoxicosis is a hypermetabolic clinical syndrome resulting from elevations in serum levels of thyroid hormones, specifically triiodothyronine ( $T_3$ ) and/or free thyroxine ( $T_4$ ). This may be the result of excessive hormone production, as is the case in hyperthyroidism (i.e. Graves' disease). Degenerative effects on bone may occur in long-standing and untreated hyperthyroidism. Clinically, hyperthyroidism may present with a goiter, exophthalmos, heat intolerance, pretibial myxedema, seizures, tremor, tachycardia, dyspnea, weakness, fatigue, osteoporosis, fractures, increased appetite, as well as weight loss. The effects of thyroid hormones on bone are predominantly mediated by  $T_3$ -receptor ( $T_3$ -r) and  $T_3$  (which acts permissively). During childhood the effects of  $T_3$ -r and  $T_3$  are anabolic. They are crucial in the normal endochondral and intramembranous ossification of bone, and thus normal skeletal development and linear bone growth. In adulthood, they have an overall catabolic effect and are involved in the maintenance of bone mass, and are also imperative in the healing process of fractures [7, 8]. In 1990, Mosekilde et al. found that in hyperthyroidism there is an acceleration of bone remodeling with a disproportion between the bone-forming processes conducted by osteoblasts and the bone-resorbing processes conducted by osteoclasts. This imbalance approximately yields a net loss of 10% of mineralized bone during each remodeling cycle [9]. It is therefore not surprising that thyrotoxicosis (especially Graves' disease) has been implicated in the development of osteoporosis and pathologic fractures, which is most pronounced in post-menopausal women. Determining free serum  $T_3/T_4$  hormone levels is paramount to the diagnosis of thyrotoxicosis and is generally the preferred approach. Laboratory results indicative of thyrotoxicosis would reveal elevated free  $T_3/T_4$  serum levels, along with suppressed thyrotropin levels. Treatment of thyrotoxicosis and restoration of euthyroidism is contingent on the underlying cause. For example, in Graves' disease primary treatment options may include radioiodine therapy, antithyroid drugs (i.e. propylthiouracil, methimazole, etc.), and/or surgery, while adjunctive treatment includes beta-blockers, corticosteroids, inorganic iodide and iopanoic acid [7, 8, 10].

The origins of neoplasms can vary greatly, but the mechanisms through which they exert their effects upon bone share many congruencies. The symptoms they present with may be just as diverse. There are, however, some symptoms common in most cases, such as unintentional weight loss, fever, fatigue, lymphadenopathy, etc. Those exerting direct effects are primary bone tumors (i.e. osteosarcoma, multiple myeloma) or by bone metastases [11]. Bone is among one of the most common locales for metastases, occurring predominantly where red bone marrow is found. Cancers of the lungs, breasts, and prostate gland are notorious for metastasizing to bone hematogenously. It is known to occur in approximately up to 70% of patients who died from these

cancers. They may cause osteoblastic lesions (prostate cancer) or osteolytic lesions (lung and breast cancer), or mixed lesions containing both elements [12, 13]. Multiple myeloma (MM) is a plasma cell dyscrasia that commonly presents as a tetrad of hypercalcemia, renal failure, anemia, and focal osteolytic bone lesions. Laboratory examinations characteristically reveal an increased erythrocyte sedimentation rate, as well as a monoclonal protein band spike (most commonly gamma protein, IgG) on protein electrophoresis.

The pathogenesis of this disease is mainly mediated through the induction of cytokine synthesis by plasma cells. For instance, interleukin-6 (similarly in OP) has been found to be the cardinal perpetrator in the formation of these osteolytic lesions. On x-ray they appear as numerous 'punched-out' (rounded, sharply circumscribed) osteolytic lesions, commonly present in the skull ('pepper-pot' skull), vertebrae, and ribs [11, 13, 14, 15]. Osteoblastic metastases cause an area of bone to appear denser/sclerotic, appearing on x-rays as spots that are whiter than the bone that circumscribes them. Osteolytic metastases by definition lyse areas of bone causing it to appear on x-rays as a darker hole (hypodense areas) in the gray-white bone image. These metastatic cancers, along with multiple myeloma, have similar clinical manifestations; both may show elevation of biochemical markers of bone turnover (i.e. TGF- $\beta$ , ALP, calcium etc.) and bone pain. Bone metastases are the most common cause of cancer-related pain [11, 13]. The onset and type of bone pain is probably one of the most important pieces of empirical information. Although the mechanisms are poorly understood, it is widely accepted that in bone metastases the bone pain is often the first sign of metastasis that appears prior to the onset of pathologic fractures. The pain often initially presents as an intermittent dull ache that worsens at night and is alleviated by movement. It then may progress to intermittent periods of sharp, jagged pain. In MM, the bone pain is similar, except that it worsens with activity. In both cases the development of persistent, severe pain is highly suggestive of the development of pathologic fractures [15, 16].

Tumors can also exert effects upon bone in an indirect manner, most notoriously known as paraneoplastic syndrome. This is a phenomenon where secretions by the tumor, such as hormones and humoral factors (peptides or cytokines), mediate the alteration in the architecture of bone. Most commonly, excessive levels of parathyroid hormone (PTH), e.g. in parathyroid adenoma/glandular hyperplasia, or parathyroid hormone-related protein (PTHrP), e.g. in breast cancer, lymphoma, and multiple myeloma, are implicated. Hypercalcemia is a prominent feature when this type of phenomenon is observed and may manifest clinically with symptoms such as nausea, vomiting, lethargy, renal failure, and coma [17]. The excessive PTH or PTHrP prompts the rarefaction of bone as a result of overstimulation of osteoclastic resorption of bone. The most remarkable changes are seen in the cortical areas of bone with its thickness decreasing and porosity increasing. The formation of 'brown tumors' may occur, which are accumulations of osteoclasts and blood pigment (which imparts the reddish-brown color) within cystic/fibrous nodules. Additionally, the bone marrow may be replaced by vascularized fibrous tissue and osteoclast-like giant cells. These changes can be seen prominently on x-rays. The skeletal manifestation in any type of hyperparathyroidism is technically referred to

as Osteitis Fibrosa Cystica [1, 3]. Clinically, it can present with ostealgia, bone fractures (most commonly at arms, legs, or the spine), kidney stones, constipation, and lethargy. Examinations of blood will characteristically reveal high serum levels of calcium, parathyroid hormone, and ALP, but low serum levels of phosphate [6, 11]. In these diseases the structural integrity of bone is so compromised that pathologic fractures may develop that are incommensurate with the amount of force applied. Effective treatment options for hyperparathyroidism include varying combinations of vitamin D, bisphosphonates, and estrogen hormone replacement therapy [18, 19]. Tumor markers such as CEA, CA 15-3, CA 125, ALP, and prostate-specific antigen (PSA) are all useful tools for monitoring the efficacy of treatment. They can also be used diagnostically as they are sensitive for many diseases, but their functional capacity is limited as they lack specificity. Ultrasonography and radiography (standard x-rays and computed tomography) are the preferred methods for visualizing changes in bone, while magnetic resonance imaging may prove most useful especially when determining the origin and degree of metastasis. Biopsy with subsequent histopathologic examination is used for staging, grading, and definitive diagnosis in tumors. Varying regimens of antineoplastic drugs and/or surgical tumor resection are indicated in the course of neoplasms, as well as supportive and palliative management [1, 17, 20].

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