

Metabolic Bone Disease and the Gastroenterologist

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Series Introduction:

This series of articles on metabolic bone disease (Osteoporosis and Osteopenia), will highlight the importance of this disorder for gastroenterologists in their everyday practice. We will define the disorder, review its pathophysiology among the aging American population and highlight the many hepatic and digestive disorders that are predisposed to this condition. Lastly, we will give a practical review of how to diagnosis and treat your patients with aging and diseased bones.

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Metabolic Bone Disease: Part I General Concepts Of Osteoporosis and Osteopenia.

The most common bone disease is osteoporosis.¹ It affects 10 million people (80% of which are women over the age of 50) in the U.S. alone, with an additional 34 million at risk for fracture due to low bone mass.² Population growth and aging are projected to cause these figures to increase.¹ The causes of bone disease may be primary (which women are at a greater risk for because they have less bone mass and lose it more quickly after menopause)² or a result of certain underlying conditions or the drugs used to treat them, **Table 1**. Regardless of the cause, the result is impaired bone strength and integrity.

Bones are formed on the basis of function. Those that are more weight bearing, such as long bones, contain a greater percentage of cortical bone, which is an outer dense layer that provides strength and attachment sites for muscles and tendons. Bones that are more flexible, such as the spine, contain a greater percentage of trabecular bone. Trabecular (also known as cancellous) bone resides in the inner core. It helps maintain skeletal integrity and promotes mineral exchange via a large surface area. It is particularly prevalent in the spine and at the ends of long bones. Trabecular bone (such as that found in the spine) is made up of an intricate network of dense, interconnected plates of bone, and is more frequently remodeled than cortical bone.^{1,3} When this structure is weakened by osteoporosis, the bone becomes fragile and susceptible to fracture (**Figure 1**).⁴

Table 1: Conditions and Medications Associated with Osteoporosis

Drugs	Cyclosporin Glucocorticoid Heparin Lithium Phenobarbital Phenytoin Tacrolimus Thyroid excess
Endocrine	Cushing's Hypogonadism Hyperthyroidism Hyperparathyroidism
Malignancy	Multiple Myeloma
Miscellaneous	Alcohol Abuse COPD HIV Malnutrition Multiple Sclerosis Prolonged Bed Rest Vitamin D Deficiency
Renal Insufficiency	
Rheumatologic	Ankylosing Spondylitis Juvenile Rheumatoid Arthritis Rheumatoid Arthritis Systemic Lupus Erythematosus

Bone Remodeling: Breaking Down and Building Up

Bone is constantly being broken down (resorption) and rebuilt. Bone modeling, which occurs during childhood and adolescence, involves the creation of new bone without previous bone resorption. During adulthood, when bones are no longer growing, remodeling becomes the primary process. In remodeling, bone is resorbed and replaced at the same site. The process of remodeling begins with the resorption of weak or damaged bone via osteoclasts, which is followed by new bone formation at the resorption site via osteoblasts.³ This process removes bone damage and maintains bone strength. The overall structure remains the same, as the volume of bone removed is equal to the volume replaced.^{1,5} Remodeling is a normal and necessary physiologic event, and is not, in and of itself, harmful. In fact, almost one-tenth of the skeleton is renewed each year.³ However, unbalanced remodeling, where there is more old bone resorption than there is new bone formation, leads to osteoporosis. In rare cases, an unbalance occurs where there is more new bone formation than old bone resorption, which is called osteopetrosis.³ The remodeling process for healthy bone is illustrated in *Figure 2*.

Bone remodeling is regulated by a variety of factors, including hormones, local signals, and mechanical loads.¹ Alterations in any of these factors can have a negative impact on bone health. Estrogen deficiency plays a predominant role in postmenopausal osteoporosis, which is characterized by increased resorption relative to formation. Reduced levels of estrogen are associated with increased numbers of osteoclasts and increased activation of bone multicellular units, leading to greater resorption and an overall decrease in bone tissue.^{3,6} For glucocorticoid-induced osteoporosis, bone health is weakened by both a profound reduction in the formation of new bone, and to a lesser extent, to an increase in bone resorption.¹

Osteoporosis and Osteopenia

Osteoporosis and osteopenia (low bone mass) have traditionally been defined on the basis of bone mineral density (BMD) levels measured at the spine and hip by dual-energy x-ray absorptiometry (DXA).² BMDs are often expressed as standard deviations (SD) above or below mean normal scores. T scores are normalized to young healthy adults of the same sex.² The World Health Organization (WHO) utilizes the following T score cutoffs to define normal, osteopenia, and osteoporosis:⁷

Normal:	BMD within 1 SD of the young adult mean
Osteopenia:	BMD between 1 and 2.5 SD below the young adult mean
Osteoporosis:	BMD \geq 2.5 SD below the young adult mean

The diagnosis of osteoporosis should not be made solely on BMD score. Studies have shown that age is as important a risk factor as BMD, and most osteoporotic fractures occur in patients who do not meet the BMD definition for osteoporosis.⁷ In one recent study of osteoporotic fractures (defined as nontraumatic fractures of the hip, spine, forearm, and proximal humerus), 22% occurred in women with normal BMD, 38% occurred in women with osteopenia, and 40% occurred in women with osteoporosis according to WHO categories.² For these reasons, the WHO has shifted its emphasis from the use of BMD alone to determine osteoporosis to a more comprehensive approach of assessing 10-year fracture risk. Data analyses identified risk factors that predict fracture risk (*Figure 3*) and these were included in an assessment algorithm that calculates the estimated 10-year fracture risk. This algorithm (FRAX™) is available at www.shef.ac.uk/FRAX.⁷ Assessment tools are

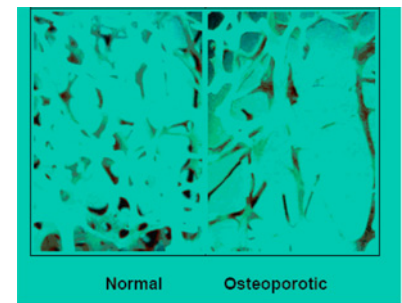


Figure 1: Histomorphometry of normal and abnormal trabecular bone obtained from iliac crest biopsies. (Adapted from J Bone Miner Res 1986;1:15-21 with permission of the American Society for Bone and Mineral Research)

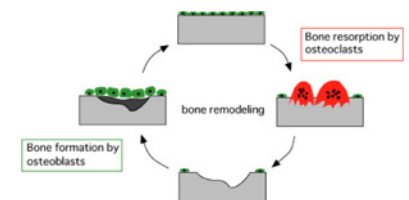


Figure 2: Healthy bone remodeling involves resorption of bone by osteoclasts and formation of new bone by osteoblasts. [http://www.coe-stemcell.keio.ac.jp/member/img/member_img/zu_matsuo2.jpg]

offered for several different countries and for different ethnicities in the US. The fracture risk at which therapeutic intervention is appropriate is left to the determination of individual countries. In the US, the National Osteoporosis Foundation recommends that postmenopausal women and men over 50 years of age with a 10-year probability of osteoporosis-related fracture $\geq 20\%$ or a $\geq 3\%$ risk of hip fracture should receive pharmacologic therapy for osteoporosis.²

Although primary (age-related) osteoporosis is the most prevalent form of osteoporosis, secondary osteoporosis, bone loss caused by specific diseases or medications, is also of significant clinical concern.¹ There are a number of disorders that contribute to osteoporosis, some have their origin among hepatic and digestive diseases, others overlap or simply coexist with them and are among the list of problems that gastroenterologists and hepatologists must take into consideration in managing their patients, **Tables 1 & 2**.

Table 2: Gastrointestinal and Hepatic Conditions Associated with Osteoporosis⁸

Alcoholic pancreatitis Anorexia Nervosa/Bulimia Celiac Disease Cirrhosis Alcoholic Cirrhosis Primary Biliary Cirrhosis Primary Sclerosing Cholangitis Liver Transplant Crohn's Disease Gastric Bypass Hypogonadism (↑↑Association with IBD, Hemochromatosis) Low Body Weight <127 lbs. Pancreatic Malabsorption GI/Hepatic Disorders Treated with Glucocorticoids Crohn's Disease (risk accelerated by glucocorticoid treatment) Ulcerative colitis and Autoimmune hepatitis after >3 months of glucocorticoid treatment

Approximately 1 in 2 women over the age of 50 and 1 in 5 men will suffer an osteoporotic fracture during their lifetimes.^{1,2}

Osteoporotic fractures are associated with increased mortality, significant disability, and high costs. Compared to an age- and sex-matched general population, hip and vertebral fractures result in a more than 10-fold increase in mortality rates in the first year after fracture in men or women 60 years of age, and an approximately 3-fold increase in mortality rates in men or women 80 years of age.¹⁰ Overall, an estimated 5.8 million Disability Adjusted Life Years (DALYs) are lost each year due to osteoporosis.¹¹ The estimated cost of osteoporotic fractures is \$17 billion in the US, with hip fractures accounting for the largest proportion of these costs. Costs of treating osteoporotic fractures are expected to increase by approximately 50% by 2025.^{9,12}

On the personal level, osteoporotic fractures can have a devastating impact on patient lifestyles. Hip fractures

The image shows a screenshot of the FRAX (Fracture Risk Assessment) questionnaire. At the top, it indicates the user is from the US (Caucasian) and is Patient 1. The questionnaire includes fields for age (68), sex (Male), weight (78.7 kg), and height (177 cm). It also asks about previous fractures, current smoking, glucocorticoid use, and rheumatoid arthritis. A summary box on the right shows a T-score of -2.1 and a 10-year probability of fracture of 29%. A red box highlights that this is a 'Major osteoporotic' risk with a 10% probability of a hip fracture.

Figure 3: Sample of the FRAX Questionnaire With Risk Factors for Fracture.

**Secondary osteoporosis includes rheumatoid arthritis, type I diabetes, osteogenesis imperfecta, malabsorption, chronic liver disease, and any other disorder strongly associated with osteoporosis.*

Diseases that can cause or contribute to osteoporosis include cystic fibrosis, type 1 diabetes, inflammatory bowel disease, and rheumatoid arthritis. In some cases this association may be at least partly due to the medications used to treat the disease, particularly glucocorticoids for inflammatory or autoimmune disorders. Glucocorticoid-induced osteoporosis is the most common form of drug-related osteoporosis, but other medications may also cause bone loss, including heparin, lithium, anticonvulsants, cyclosporine, and methotrexate.¹

Consequences of Poor Bone Health

Fractures are the most significant clinical consequence associated with bone disease, and osteoporosis is the major cause of fracture, particularly in older individuals.¹ In the US, an estimated 2 million new osteoporotic fractures occur each year, including approximately 300,000 hip fractures, 550,000 vertebral fractures, and 400,000 wrist fractures (**Figure 4**).⁸

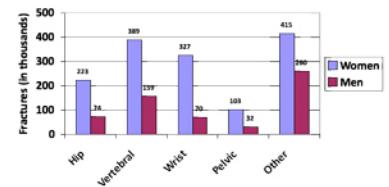


Figure 4: Estimated number of fractures (in thousands) in the US* by site of fracture and gender.⁹

**In 2005*

are the most disabling osteoporotic fracture and are associated with high rates of nursing home admissions and disability.^{13,14} Vertebral fractures can lead to spinal deformity (**Figure 5**).^{1,15} Patients with vertebral fractures report severe impairments in health-related quality of life that are maintained for at least 2 years.¹⁶

Conclusion

Osteoporosis is a highly prevalent condition which can lead to significant disability. It can be primary or occur secondary to other disorders or the drugs used to treat them, particularly glucocorticoids. Bone loss in postmenopausal osteoporosis is due to increased resorption, and in glucocorticoid-induced osteoporosis is due to reduced bone formation. Fractures are the major clinical consequence of osteoporosis. Hip and vertebral fractures are associated with increased mortality and disability and can have a substantial impact on quality of life.

Future topics to be covered in “Metabolic Bone Disease and the Gastroenterologist,”

II. Osteoporosis and Inflammatory Bowel Disease.

III. Osteoporosis Associated with Chronic Liver Disease.

IV. An Endocrinologist’s Recommendation on Treatment and Prevention of Osteoporosis.

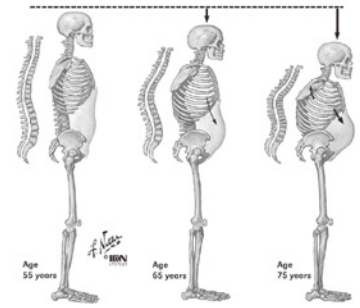


Figure 5: Progressive spinal deformity in osteoporosis. Compression fractures of thoracic vertebrae lead to loss of height and progressive thoracic kyphosis (dowager’s hump). Lower ribs eventually rest on iliac crests, and downward pressure on viscera causes abdominal distention.¹

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