

AGA Technical Review on Osteoporosis in Gastrointestinal Diseases

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Osteoporosis is increasingly recognized as a source of significant disability, an awareness that has prompted clinicians to actively pursue the diagnosis among high-risk patients. Fractures have an obvious associated morbidity, negative impact on quality of life, and both direct and indirect costs. Hip fractures have long been associated with an increased mortality rate, but only recently has excessive mortality also been shown to accompany non-hip fractures and low bone mass.¹⁻³ The excessive mortality associated with fractures is largely confined to elderly males and postmenopausal females. Many patients with gastrointestinal (GI) disorders at risk for osteoporosis are young, and these data may not apply to them. Much of the available clinical information regarding osteoporosis screening, outcomes, and therapeutic interventions is derived from the postmenopausal osteoporosis literature. It is recognized, however, that osteoporosis may accompany many other medical conditions, occurring as a sequela to disease or even to its treatment.

Disorders of the GI tract and liver may be associated with osteoporosis. The digestive tract obviously is associated with intake and absorption of critical bone nutrients, including calcium and vitamin D. Some digestive disorders may be associated with local and/or systemic inflammation that may have a negative impact on bone homeostasis. We have undertaken a systematic review of 5 main digestive disorders and associated osteoporosis. The present review presents our findings related to inflammatory bowel disease (IBD), celiac disease, and postgastrectomy states. Issues specific to osteoporosis and chronic liver disease or liver transplantation are discussed separately.⁴

Methods

We conducted a systematic literature review and critically appraised the studies found using published methods.⁵ We graded evidence using guidelines adapted from the Practice Guidelines Committee of the American Association of the Study of Liver Diseases,⁶ as summarized in Table 1. The results formed the basis for evidence-based conclusions and recommendations for each of the GI disorders covered in this review.

We searched MEDLINE and the ISI Web of Science using general terms related to osteoporosis and metabolic bone disease ("osteopor-" OR "osteopen-" or "bone density" or "fractures" or "bone loss" or "bone mineral" or "bone metabolism" or DXA [TITLE] or DEXA [TITLE] or "bone densitometry") and combined these with specific terms for the relevant GI disorders ("inflammatory bowel disease" or "Crohn" or "Crohn's" or "ulcerative colitis;" "celiac disease" or "coeliac disease;" "postgastrectomy syndromes"[MESH] or "gastrectomy"[MESH] or "gastrectom-" or "postgastrectom-;" "liver/transplantation"[MAJR] or "liver diseases"[MAJR] or "liver transplantation"[MAJR]). We manually searched recently published reviews, references from retrieved articles, and expert committee reports for additional studies. Information related to the specific GI or hepatic disease was supplemented with background data on osteoporosis in the general population and non-GI disorders.

Point estimates of osteoporosis prevalence and mean bone density were extracted and combined (weighted for patient numbers) to give pooled estimates. Combining data from studies with different designs does not take study heterogeneity into account, but can be taken to reflect general trends in the published data and is useful for approximating the overall magnitude of the impact of various GI disorders on bone metabolism. Pooling of data was site-specific but did combine related technologies, different vendors, reference ranges, and genders.

Abbreviations used in this paper: 25-OHD, 25-hydroxy-vitamin D; BMC, bone mineral content; BMD, bone mineral density; BUA, broadband ultrasound attenuation; CI, confidence interval; CT, computed tomography; %CV, percent coefficient of variation; DPA, dual photon absorptiometry; DXA, dual-energy X-ray absorptiometry; GI, gastrointestinal; IAPP, ileoanal pouch procedure; IGF, insulin-like growth factor; IL, interleukin; OPG, osteoprotegerin; pDXA, peripheral DXA; PGE₂, prostaglandin E₂; pQCT, peripheral QCT; PTH, parathyroid hormone; QCT, quantitative computed tomography; QUS, quantitative ultrasonography; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; RR, relative risk; SAP, serum alkaline phosphatase; SD, standard deviation; SOS, speed of sound; SPA, single-photon absorptiometry; TNF, tumor necrosis factor.

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Table 1. Quality of Evidence on Which a Recommendation Is Based

Grade	Definition
A	Homogeneous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power
B	Evidence from at least 1 large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis
C	Evidence based on clinical experience, descriptive studies, or reports of expert committees
D	Not rated

NOTE. Adapted from Standardized Guidelines of the Practice Guideline Committee of the American Association for The Study of Liver Diseases.⁶

Our analysis did not demonstrate any difference in results restricted to a technology or vendor. When considered in light of the many other assumptions inherent to bone densitometry, this simplification does not appear unreasonable.

This review excludes skeletal disorders unrelated to osteoporosis, such as avascular necrosis, hepatitis C–associated osteosclerosis, and hypertrophic osteoarthropathy. Cystic fibrosis, although associated with significant bone demineralization and imbalance between bone formation and degradation, is not a primary GI disorder, and thus is not discussed further. Hepatobiliary rickets and liver disorders of infancy and early childhood (e.g., extrahepatic biliary atresia) are quite different from skeletal disorders that present in adults and older children and thus have also been excluded.

Overview of Osteoporosis

Biology of Bone Metabolism

Bone is a dynamic tissue comprising cellular, organic, and inorganic components with a complex internal structure. Bone is constantly remodeled throughout life as the result of the opposing activities of 2 major cellular elements, osteoblasts and osteoclasts.

Bone tissue reacts to stress and injury through a well-orchestrated sequence for removing old bone and building new tissue. Bone remodeling is carried out by the *basic multicellular unit*, which consists of both osteoclasts and osteoblasts.^{7,8} The basic multicellular unit typically takes 3 to 6 months to complete a cycle. Bone remodeling affects 3%–5% of cortical bone per year but up to 25% of trabecular bone, due in part to the latter's greater surface area. *Osteoclasts*, multinucleated cells of monocyte origin, resorb bone through the release of acid and enzymes, such as cathepsin K, from their ruffled

borders. *Osteoblasts*, derived from mesenchymal cells, enter the resorption pit and lay down organic matrix (osteoid). The osteoblasts then die or enter a dormant stage. Osteoid is subsequently mineralized over a period of several months. The activities of osteoclasts and osteoblasts are closely coupled; processes that stimulate (or suppress) one cell type result in stimulation (or suppression) of the other. For example, after menopause, osteoblast activity increases in an attempt to compensate for increased osteoclastic resorption. On the other side of the equation, anti-resorptive treatments targeted at suppressing osteoclast activity are able to achieve only a modest gain in bone mass, because there is a parallel reduction in osteoblast activity. The bone remodeling cycle is regulated by a myriad of factors, including growth factors and cytokines.

Apoptosis of bone cells is a normal component of bone remodeling that leads to termination of osteoclast bone resorption and allows osteoblasts to begin the process of bone restoration.⁹ Some antiresorptive agents, such as the aminobisphosphonates, appear to act predominately through induction of osteoclast apoptosis by inhibiting the mevalonate pathway, resulting in loss of protein prenylation. Conversely, premature osteoblast apoptosis appears to be a major mechanism involved in corticosteroid-induced osteoporosis.

Skeletal mass accumulates rapidly during childhood, especially during the years of most rapid growth in early adolescence. Peak bone mass is achieved by age 20–30. In healthy individuals, genetics, physical activity, body weight, diet, and ethnicity are factors known to influence peak bone mass.¹⁰ The specific genes involved have yet to be elucidated, but twin studies suggest that up to 85% of the variation in peak bone mass is determined by genetic factors.¹¹ On average, blacks have higher bone mass than Caucasians, who in turn have higher bone mass than Asians.

After early adulthood, both men and women experience a slow decline in bone mass that continues until death. Bone turnover accelerates in women at menopause, particularly in trabecular bone, and usually results in the loss of 5%–15% of bone mass over the first 5 years after menopause. After early menopause, age-related bone loss continues at a rate of 0.5%–1% per year. The pathogenesis of age-related bone loss is unclear, but it may be related in part to changes in calcium absorption and vitamin D availability. Other factors that can increase bone loss are listed in Table 2.

Pathophysiology of Osteoporosis

The World Health Organization has defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of

Table 2. Secondary Causes of Bone Loss

Genetic factors
Defects in collagen synthesis or structure
Idiopathic hypercalciuria
Nutritional
Low calcium intake
Vitamin D deficiency
Malabsorption
Drugs
Excess glucocorticosteroids
Anticonvulsants
Heparin
Lifestyle
Immobility
Smoking
Alcohol
Endocrine/Metabolic
Hypogonadism
Early menopause or prolonged hypoestrogenism
Corticosteroid excess
Hyperparathyroidism
Hyperthyroidism
Diabetes mellitus
Renal insufficiency
Other
Myeloma
Malignancy

bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.¹² Bone mass is the primary determinant of bone strength; studies of excised bone have demonstrated that approximately 80% of bone strength is determined by the amount of bone.¹³ Measures of bone mass from different skeletal sites correlate moderately well ($r = 0.5-0.7$), but site-to-site differences are not uncommon and may reflect genetic factors, hormonal influences, and the individual's level and pattern of activity.

For bone loss to take place, a negative remodeling balance must occur, with the amount of bone resorbed exceeding the amount formed. In "low-turnover" osteoporosis, a normal degree of bone resorption is accompanied by a reduced synthesis of bone matrix that is normally mineralized. Biochemical indices of bone metabolism are typically normal. In "high-turnover" osteoporosis, the activity of osteoclasts is enhanced, resulting in accelerated bone resorption with elevated excretion of collagen breakdown products. This usually leads to a coupled increase in bone formation, albeit often insufficient to compensate fully for the degree of bone resorption, resulting in net bone loss. Postmenopausal osteoporosis usually follows the high turnover pattern, whereas corticosteroid-induced osteoporosis is usually of the low-turnover form.¹⁴ As discussed later, both patterns are seen in GI disorders.

Microarchitectural deterioration also has an important effect on bone strength, but this is difficult to assess

noninvasively. Typical changes in trabecular bone include reduced trabecular thickness and number and perforation of trabeculae by deep resorption pits, resulting in a loss of trabecular connectivity that is currently believed to be irreversible. These microarchitectural changes may not be reflected by reductions in bone density, but they nonetheless contribute to fracture susceptibility.

Of particular relevance in inflammatory GI disorders and liver transplantation, corticosteroids have multiple adverse effects on bone metabolism. They have been shown to impair osteoblast function, reduce intestinal calcium absorption (by interfering with the action of vitamin $1,25(\text{OH})_2$ -vitamin D) while increasing renal calcium excretion, induce secondary hyperparathyroidism, enhance osteoclast bone resorption via the production of interleukin (IL)-1, and possibly precipitate hypogonadism.¹⁵ Together, these mechanisms result in a pattern of low turnover with reduced bone formation rate and trabecular thickness that correlates with current corticosteroid dose and dose duration. Patients treated with corticosteroids have an increased risk of osteoporotic fractures, resulting in marked morbidity, particularly in elderly individuals. Some medications produce clinically significant reductions in vertebral fracture rates, an effect established most clearly in postmenopausal women.¹⁶ The greatest effect of corticosteroids is seen in the initial months of treatment, especially in areas of trabecular bone (such as vertebrae), which are the predominant sites of fracture. Some data indicate that low-dose corticosteroid treatment (i.e., prednisone <10 mg/day) has only a small effect on bone density and vertebral fracture rates,¹⁷ possibly through simultaneous suppression of the inflammatory state.

Vitamin D Metabolism and Osteomalacia

Prevention of vitamin D deficiency plays an important role in bone hygiene by promoting calcium absorption. Although dietary intake was once believed to be the major source of vitamin D in humans, endogenous skin synthesis has been shown to be quantitatively the most important source.^{19,20}

Osteoporosis is distinguished from osteomalacia, a disorder involving defective mineralization of newly formed osteoid. Histologically, osteomalacia appears as an increase in both the surface extent and width of the osteoid front, accompanied by defective bone mineralization. Specific radiographic findings of osteomalacia include radiolucent bands (pseudofractures or Looser's lines) perpendicular to the surface of the bone, usually occurring at sites of nutrient arterial perforation and frequently bilateral. These are not seen in osteoporosis,

which radiographically demonstrates only a decrease in density and thinning of the cortex. Serum concentrations of calcium, 25-hydroxy-vitamin D (25-OHD), phosphate, and alkaline phosphatase are usually normal in osteoporosis. When vitamin D deficiency causes osteomalacia, serum levels of vitamin D (and particularly 25-OHD) are usually low, calcium levels are normal or low, phosphate levels are usually low, and alkaline phosphatase levels are normal to elevated. Osteoporosis and osteomalacia are indistinguishable on bone mineral density (BMD) measurements and frequently coexist. Clinical, radiologic, and biochemical findings do not reliably differentiate among these conditions, and bone biopsy after a tetracycline label may be required. Early studies tended to overestimate the prevalence of osteomalacia in GI disease due to inadequate diagnostic methods (see below). A simple measurement of osteoid seam width was widely used as a determinant of osteomalacia. This alone is not sufficient to determine whether osteomalacia is present, and its use for this purpose probably explains why early studies overestimated the prevalence. A lack of histomorphometric data has fueled the opposite view, that osteomalacia is rare. Because of this view, clinicians may fail to suspect osteomalacia, which remains a real and very treatable complication of GI disease.²¹

Association With Inflammation

Osteoclasts are known to be activated by various inflammatory cytokines, which are probably pathological mediators in systemic and regional bone loss.^{8,22} This activity, formerly called *osteoclast-activating factor*, is now known to be contributed to by IL-1 α , IL-1 β , IL-6, IL-11, IL-17, tumor necrosis factor (TNF)- α and - β , transforming growth factor- α , epidermal growth factor, and prostaglandin E₂ (PGE₂).²³ In healthy postmenopausal women, epidemiologic data show that serum IL-6 concentration is a predictor of bone loss.²⁴ Many of these same soluble mediators—most notably IL-1, IL-6, and TNF- α —drive inflammation in rheumatoid arthritis and probably contribute to the localized periarticular osteopenia seen in this disorder.²⁵ Local or generalized bone loss has been reported in chronic infection, leukemia, autoimmune and allergic diseases, and inflammatory joint diseases, suggesting that an activated immune system can affect bone physiology.

The signaling system that normally maintains coupled bone remodeling has not been well defined, although it is clear that excessive osteoclastic bone resorption or defective osteoblast synthesis creates a dysequilibrium, with a net loss in bone mass. The initial step in the remodeling process involves osteoclastogenesis through a process of sequential proliferation, differentiation, and

activation of mononuclear precursors. The recent discovery of an elegant receptor-based interaction between osteoblast and osteoclast precursors appears to provide this “missing link” and simultaneously integrates this system with the immune response. Osteoblasts express a surface ligand (receptor activator of NF- κ B ligand [RANKL]) that can bind to osteoclast precursors (the receptor activator of NF- κ B [RANK]) or an osteoblast-derived soluble decoy receptor known as osteoprotegerin (OPG).²⁶ The binding of RANK to RANKL induces a signaling and gene expression cascade that results in differentiation and maturation of osteoclasts. OPG blocks this interaction, thereby inhibiting osteoclast formation. RANKL is also a regulator of T cell-dendritic cell interaction in the immune system and is a crucial factor in early lymphocyte development and lymph node organogenesis.²⁷ The central importance of this system is seen in RANKL gene-deficient mice that are unable to support osteoclast differentiation, display severe osteopetrosis (even in the presence of bone-resorbing factors, such as vitamin D₃, dexamethasone, and PGE₂), show no evidence of bone remodeling, and simultaneously lack all lymph nodes.²³ There is emerging evidence that the RANKL-OPG system may be the final common pathway for many of the classical bone-active agents. For example, 17 β -estradiol simultaneously increases OPG and inhibits RANKL, thereby shifting the system toward reduced osteoclast recruitment, whereas dexamethasone, parathyroid hormone [PTH], PGE₂, and 1 α ,25-(OH)₂D₃ stimulate RANKL expression but inhibit OPG production, with a corresponding increase in osteoclast function. New insights provided by these findings may lead to the development of novel approaches to osteoporosis management. Activated T cells can directly trigger osteoclastogenesis through RANKL, leading to bone loss, an effect that is blocked by OPG.^{23,28} In summary, compounds that increase RANKL appear to enhance osteoclastogenesis, whereas compounds that increase OPG inhibit osteoclastogenesis. Furthermore, this system may be critical in linking systemic or mucosal inflammation with altered bone metabolism and, ultimately, osteoporosis.

Measurement Tools in Osteoporosis

Technical review of bone densitometry. The development of bone densitometry has made it possible to measure bone mass and assess its contribution to fracture risk. It is generally accepted that bone mass is the single best predictor of in vitro skeletal strength^{13,29–31} and fracture risk.³² All bone measurement techniques rely on the ability of bone to block transmission of energy. The physical forms of energy used in clinical bone densitom-

Table 3. Characteristics of Different Techniques for Osteoporosis Diagnosis

Technique	Site	Relative sensitivity to change	Reproducibility error (%)	Accuracy error (%)	Duration of exam (min)	Absorbed dose (mrem)
Older techniques						
SPA	Radius	1X	2-3	3-5	15	<1
DPA	Spine, hip, total body	2X	2-4	4-10	20-40	5
QCT	Spine	3-4X	2-5	5-20	10-20	100-200
Newer techniques						
DXA	Spine, hip, total body	2X	1-2.5	5-6	5	1-3
QUS	Calcaneus, tibia, phalanges, patella	1X	2-5	Uncertain	5-10	0
PDXA	Radius, calcaneus	2X	1-2	5	1	<1
PQCT	Radius	3-4X	1-2	5-10	10	<10

NOTE. Modified from Isaia.²⁹⁴

etry are X-rays (generated from an X-ray tube), gamma rays (released from decaying radionuclides), and sound (emitted from an ultrasonic transducer). Ideally, a bone density method should have high accuracy and reproducibility and be rapid, inexpensive, painless, and safe (with little or no ionizing radiation). The most widely available bone density technologies are listed in Table 3.

Dual-energy X-ray absorptiometry. Dual-energy X-ray absorptiometry (DXA) grew out of dual-photon absorptiometry, which used gadolinium-153 as the photon source. This latter method had the drawbacks of needing radionuclide source changes and providing poor image resolution and reproducibility, and so has been largely replaced by DXA. DXA uses an X-ray tube to generate 2 different X-ray energies. Bone attenuates X-rays to a greater degree than soft tissue, and lower X-ray energies are attenuated more than higher energies. An X-ray detector records the amount of attenuation for the 2 energies and can calculate both the amount of soft tissue and the amount of bone calcium in the path of the beam. The X-ray tube and detector scan over the area of interest and generate an image of bone mineral content expressed in grams of calcium. Software identifies the projected bone area using an edge-detection algorithm. Dividing bone mineral content (grams of calcium) by the bone area (cm²) yields bone mineral density (as g/cm²). DXA has the advantage of being rapid (particularly with newer scanners that use higher-output X-ray tubes and a fan-beam configuration) and is able to scan the structures of greatest clinical interest, such as spine, hip, forearm, and even total body. DXA can also be used to assess body composition according to a 3-compartment model (fat, soft tissue, and bone mineral) and has been shown to be reliable in both normal subjects and patients with malabsorption and cirrhosis for estimating whole body and regional body composition.^{33,34} The radiation dose from a DXA scan is of negligible risk—a fraction of the annual normal background radiation. DXA is currently the gold standard for bone mass measurement.

Peripheral X-ray absorptiometry. Conventional DXA (also known as central DXA) is able to measure all skeletal structures, including those in the thicker body regions, such as the lumbar spine and hip. Conventional DXA equipment is expensive and not portable, however. Thus, a variety of compact, portable devices have been developed for measuring bone density in the extremities, such as the forearm and calcaneus. Single-photon absorptiometry (SPA) uses a radionuclide source (iodine-125) but requires periodic source replacements and, in some instances, immersion of the body part in water. Peripheral DXA devices avoid these limitations and impart an exceedingly small radiation dose. Peripheral measurements may not be as useful for monitoring the clinical response to many therapies for osteoporosis, however.

Quantitative ultrasonography. Ultrasonography has recently emerged as another tool for characterizing bone strength. It has the advantages of being radiation-free and using relatively inexpensive, portable devices.³⁵ Ultrasound penetrates bone poorly, and higher frequencies are attenuated more than lower frequencies. Two measures are typically derived from quantitative ultrasonography (QUS): (1) the speed of sound (SOS), a measure of the speed at which sound travels from 1 transducer to the other through the bone (m/sec), and (2) broad-beam ultrasound attenuation (BUA), the slope of the relationship between attenuation and frequency (dB/kHz). Because of the difficulty ultrasound has in penetrating deep structures, most devices measure the more accessible bones, such as the calcaneus, phalanges, and tibia. Whereas X-ray-based techniques are calibrated against calcium content, there is uncertainty over the physical properties measured by bone ultrasonography. Whether QUS measures bone quality independent of bone density is currently an area of controversy.

Other X-ray-based techniques. Computed tomography (CT) scanners are capable of measuring vertebral trabecular density by using a calibrated phantom and

specialized software. Such measurements, known as *quantitative CT* (QCT), reflect bone density in terms of volume (mg/cm^3). QCT is expensive and has a relatively high radiation dose, limiting its clinical utility. However, it does have the advantage of providing a true volumetric measure of bone density (in contrast with DXA, which gives an areal or 2-dimensional measure). This can be advantageous when skeletal size deviates markedly from average or when there are dense artifacts (such as a heavily calcified aorta or osteophytosis of the lumbar spine) that preclude accurate DXA measurements. Smaller CT devices (i.e., peripheral QCT) have been developed to study the distal radius.

Although conventional diagnostic radiographs are not quantitative, they are still an important component in the assessment of osteoporosis, because the presence of fragility fractures (such as vertebral compression fractures) indicates osteoporosis and high fracture risk independent of BMD. The presence of an incident spine fracture is reportedly associated with a 20% risk of sustaining a new vertebral fracture over the subsequent year.³⁶ Plain radiographs of the hand can also be used to measure cortical width in the fingers (radiogrammetry), but this is a relatively insensitive technique. With the introduction of aluminum calibration wedges, however, there is renewed interest in plain radiographs of the hands as an accessible and low-cost alternative to the methods discussed previously.

Performance evaluation of bone densitometry.

Accuracy, how closely a measured result approximates the "true" value, is of critical importance when comparing an individual patient with a reference population. The accuracy of bone mineral measurements is determined by comparison with dry weight or ash weight of bone samples. DXA, the predominant technology used to evaluate bone density, has a measurement error of 5%–6%.³⁷ This error is small relative to the range of values in the population, enabling its use as a tool to diagnose osteoporosis and assess fracture risk. Bone density may be overestimated in anteroposterior measurements of the lumbar spine due to the presence of degenerative sclerosis or osteophytes, compression fractures, superimposed vascular calcification, or other dense materials (e.g., barium, iodinated contrast medium, undissolved calcium tablets). Lateral spine DXA measurements are less susceptible to these artifacts, but these approaches are limited by poorer reproducibility and overlying ribs or iliac crest that reduce the number of evaluable vertebrae. Discrepancies between spine measurements and other skeletal sites are often seen in older subjects (>age 60 years) and those with known spine

disease. Hip or peripheral bone assessment can be of great value in these cases. Hip measurements are affected by patient positioning and the degree of hip rotation, making it critical that technologists standardize their technique. Hip measurements are less susceptible to degenerative changes, but thickening of the medial cortex of the femoral neck (called "buttressing") will be reflected in bone density measurements. The trochanteric region appears to be relatively unaffected by these changes. Previous fracture, surgery, or Paget's disease can affect hip results; the contralateral hip should be measured in such circumstances.^{38,39}

Reproducibility (i.e., test–retest reliability) refers to the ability of a system to obtain the same result in repeated measurements of the same individual. A technique must have good reproducibility if serial measurements are to be used in following an individual and greater reproducibility makes it possible to detect smaller changes. Current methodologies typically demonstrate measurement errors that are larger than the average annual change in bone density. Thus, in an individual patient it may be difficult to determine whether a small change in bone mass reflects a measurement error or a true change.

DXA reproducibility is influenced by instrument-, operator-, and subject-dependent factors. These last 2 tend to be much more important than the instrument itself, and patient positioning is the single most important determinant. Reproducibility is optimized through a systematic process that includes careful quality control of the instrument, scanning technique, and analysis. Measurements of the hip are less reproducible than those of the spine, caused in large part by the difficulty in obtaining consistent positioning. Reproducibility is much better with the total hip than with its subregions (femoral neck, trochanter, or Ward's area), and thus this has become the preferred site for clinical reporting. Ward's area has been largely abandoned due to its very poor reproducibility. This review therefore reports BMD for the total hip (or femoral neck from older studies when the total hip is not available).

Reproducibility can be stated as either standard deviation (SD) or percent coefficient of variation (%CV, defined as $100 \times \text{SD}/\text{mean}$). The smallest change that must be present before it can be concluded (with 95% confidence) that the change is not related to measurement error is $2.77 \times \text{SD}$ (or $2.77 \times \%CV$). Vendors frequently cite in vivo measurement as $\pm 1.0\%$ for modern DXA instruments. This significantly underestimates the error seen in nonresearch clinical populations, in which a change of at least 3%–5% at the lumbar spine and

Table 4. Diagnostic Categories Relating to Normal or Low Bone Density Values¹²

Normal	A value of BMD or BMC <1 SD below the average value of young adults (T score >−1)
Osteopenia (low bone mass)	A value of BMD or BMC more than 1 SD below the average value of young adults, but not more than 2.5 SD below (T score −1 to −2.5)
Osteoporosis	A value of BMD or BMC more than 2.5 SD below the average value of young adults (T score <−2.5)
Severe osteoporosis	Fragility fractures and a value of BMD or BMC more than 2.5 SD below the average value of young adults (T score <−2.5)

4%–6% at the total hip must be present to have 95% confidence that a real change has occurred.^{40,41}

Although DXA instruments are ultimately calibrated against excised bone samples, methodologic differences in how this is performed have led to large discrepancies in patient measurements when performed on instruments from different vendors.⁴² Measurements from different machines are very difficult to compare, and whenever possible, follow-up examinations should be performed on the same machine.

Clinical use of bone densitometry. Absolute measurements of bone density are of little value, because they are determined by the site of measurement, the calibration used by the equipment manufacturer, and even the particular instrument. Because bone density measurements follow a bell-shaped (Gaussian) distribution, they are described as the number of SDs by which the value deviates from the mean for normal controls. Age-related changes in bone density must be taken into account. The *Z score* refers to the number of SDs above or below the mean for an age-matched population. The *T score* refers to the number of SDs above or below the mean for a young adult population (corresponding to peak bone mass).

A World Health Organization report formulated diagnostic ranges for osteoporosis based on T score.¹² These ranges were originally intended to be used epidemiologically, but subsequently have been applied to the diagnosis of individuals (Table 4). The data reviewed for these recommendations were derived almost exclusively from postmenopausal Caucasian females. Therefore, caution must be exercised when extrapolating these data to other groups. There is no consensus on the diagnosis of osteoporosis in men or even on the appropriate reference population for generating the T score. All of the studies in GI disorders considered in this review used a gender-matched reference population for calculating the T score and Z score, although some authors propose a single (female-based) reference range, arguing that absolute fracture risk is more closely related to absolute BMD.⁴³ This can significantly affect interpretation of results, as indicated in the cross-sectional study of Floreani et al.,⁴⁴ in which absolute BMD was found to be significantly lower in 21 women than in 33 men with end-stage liver

disease, whereas the gender-based Z score was significantly lower in the men.

It is not enough for a bone density instrument to provide accurate and reproducible measurements. Beyond the technical performance of the test, it is important to ensure that there is an appropriate comparison group. BMD is strongly affected by age, gender, and ethnicity, and without the inclusion of appropriate healthy controls, it is possible to overestimate or underestimate the apparent prevalence of osteoporosis. Use of the Z score can conceal normal age-related loss, thereby underestimating fracture risk. The Z score is very useful in the assessment of whether bone loss is accelerated compared with age- and gender-matched controls. For example, it is possible for mean absolute BMD of the lumbar spine to be lower in postmenopausal females than premenopausal females (0.778 g/cm² vs. 0.804 g/cm²), whereas the average Z score is simultaneously greater (−1.74 vs. −0.88).⁴⁵ An important caveat exists when interpreting cross-sectional studies of bone density in relation to disease duration, because age and disease duration are positively correlated. Analysis that does not take into account the normal age-related bone loss can lead to the incorrect interpretation that greater disease duration causes decreased bone mass. Overreliance on vendor-supplied reference data can also produce misleading findings. In the past, systematic differences in reference population selection between DXA vendors were responsible for discrepancies in T score calculations, resulting in a twofold difference in the apparent prevalence of osteoporosis. Recognition of such problems has spurred efforts to establish common, vendor-independent reference data, such as that available from the Third National Health and Nutrition Evaluation Survey.⁴⁶

Different technologies and skeletal sites show markedly different age-related changes in the T score. Lumbar spine quantitative CT shows the earliest and most rapid change, with the average female crossing the osteoporotic threshold (T score, −2.5) by age 61. In contrast, peripheral measurements are less age responsive, and ultrasonography of the calcaneus will not reach the same threshold until after age 100.⁴⁷ It is clear that T scores cannot be used interchangeably between different sites and techniques, and the hip has been proposed as the

preferred site for diagnosis of osteoporosis (although other sites continue to be useful for fracture risk assessment).⁴⁸

Serum and urine markers. Bone cell activity can be evaluated through the measurement of biochemical markers.⁴⁹ Osteoblasts produce type I collagen (the primary collagen of bone tissue), noncollagenous proteins (e.g., osteocalcin or bone Gla protein) and enzymes (e.g., serum alkaline phosphatase [SAP]). Type I collagen is a triple-helical molecule containing 2 identical α -1 chains and a single α -2 chain. These undergo posttranslational modification including hydroxylation of prolyl and lysyl residues, glycosylation of lysyl or hydroxylysyl residues, and formation of intramolecular and intermolecular covalent cross-links. Extension peptides are cleaved from the carboxy or amino terminus of the procollagen molecule during its maturation, releasing carboxy-terminal propeptide of type I collagen and amino-terminal propeptide of type I collagen as indices of type I collagen synthesis measurable in the serum. These have not been found to be as specific for bone formation as bone Gla protein or bone-specific alkaline phosphatase. In contrast, covalent cross-links (i.e., pyridinoline, deoxypyridinoline, N-telopeptide, and C-telopeptide) are released during osteoclast-mediated digestion of bone matrix and excreted in the urine as measurable markers of bone resorption. One difficulty with urinary markers is their dependence on glomerular filtration. Although generally normalized to creatinine excretion, this may not be valid when significant alterations in muscle mass have occurred. There is also considerable diurnal variation in levels of urinary markers, which peak between 4 AM and 8 AM. For this reason, the time of sample collection should be standardized (usually the second morning void). Bone-specific alkaline phosphatase has a sufficiently long half-life that shows little circadian variability. The major limitation of biochemical markers has been their relatively poor reproducibility because of considerable technical and biologic variability.

Biochemical markers reflect bone turnover, but are not useful in predicting BMD. Higher levels of bone markers are associated with more rapid bone loss, although the correlation is relatively poor and limits the use of these markers in individual patients.⁵⁰ Higher rates of bone markers have been shown to predict greater fracture risk independent of BMD.^{49,51,52} Markers can show a dramatic and early reduction within weeks of starting anti-resorptive drug therapy, suggesting that they may be helpful in confirming therapeutic effect, because a nadir is usually reached between 2 and 3 months after initiation of treatment.^{53,54} This change is much more rapid

than can be seen with serial BMD measurements. Although the clinical role of biochemical markers is still unclear, eventually these markers may help characterize patients in terms of low- and high-turnover states—a decision that may be relevant in terms of understanding basic pathophysiology, predicting rates of bone loss and fracture risk, and perhaps guiding the choice of therapy.⁵⁵

Bone biopsy and histomorphometry. Transiliac bone biopsy has been a useful research tool for characterizing bone metabolism in normal and disease states. But this technique's high invasiveness, cost, and complexity markedly limit its widespread clinical application. The technique and its standardization have been well established and reviewed elsewhere.^{56,57} Its most important clinical role in GI disorders is in diagnosing osteomalacia. The use of dual labeling with tetracycline is critical in defining dynamic parameters, such as mineralization lag time. The diagnosis of osteomalacia is based on increased mineralization lag time and increased osteoid seam thickness. Both criteria must be present; a simple measurement of osteoid seam width alone is not sufficient to determine whether osteomalacia is present, probably explaining why early studies overestimated the prevalence of osteomalacia. Increased osteoid surface alone can occur in low-turnover and high-turnover bone disease without any sign of a mineralization defect. Strict adherence to standard nomenclature is required.⁵⁷ The iliac crest may not always be representative of the rest of the skeleton, and technical factors (e.g., compression of the core during the biopsy procedure) can limit the accuracy of this method for diagnosing osteoporosis.⁵⁸

Bone measurements in GI disease. DXA makes assumptions about body composition, most notably the distribution of fat and lean soft tissue. Large deviations in body composition can greatly affect the accuracy of BMD measurement, with errors up to 30% described.⁵⁹ Significant changes in body composition and/or mass (either weight gain or weight loss) have also been reported to artifactually influence BMD measurements with DXA. Measurement of total body and lumbar spine BMD with DXA does not appear to be affected by ascites or large-volume paracentesis,⁶⁰ but the changes in total body fat commonly seen with many GI disorders and liver transplantation may affect BMD measurements.⁴⁵

Biochemical markers may be less accurate in patients with chronic liver disease and/or malabsorption of fat-soluble vitamin K. Breakdown products of type III collagen associated with hepatic fibrosis have been reported to cross-react in urinary assays of bone collagen catabolism.^{61–64} Assays for total specific alkaline phosphatase

and bone-specific alkaline phosphatase are affected by liver disease, which limits their use as skeletal markers in these disorders.⁶⁵ Finally, serum immunoreactive bone Gla protein may vary with vitamin K status—a factor that must be considered if it is used as a marker for osteoblast activity.⁶⁶

Bone measurements in children. The use of any of these techniques in children requires particular attention. First, reference data tend to be much less abundant and are generally age-dependent. The inclusion of gender and age-matched controls is preferable whenever possible. Histomorphometric studies show that children's bones are more active by adult standards, and thus all well-established biochemical markers of bone formation or resorption are increased in childhood and adolescence. Values closely parallel the growth-velocity curve and peak around the time of puberty. Very high levels of markers can be quite normal in children. Even serum 1,25(OH)₂-vitamin D shows a pubertal increase in males and females, presumably contributing to the intense calcium accretion that occurs at this time of life.⁶⁷ Because most bone density techniques give an areal measurement based on a 2-dimensional projection of bone (g/cm²), larger bones will have a higher apparent bone density than smaller bones due to the increased depth. Although some techniques have been developed in an attempt to address this (e.g., calculations of skeletal volume based on modeling of the spine and femoral neck), only QCT provides a true volumetric measurement. Because delayed growth is a common feature of chronic disease in children, aggravated by the use of medication such as corticosteroids, analysis of BMD in children must address these issues. For example, growth failure is a common and serious sequela of childhood IBD, affecting 19%–35% of patients and resulting in permanent deficits in adult height.^{68,69} Longitudinal studies are also confounded, because 80% of the change in measured bone mass actually relates to nonspecific skeletal growth⁷⁰; therefore, increasing bone mass does not necessarily reflect treatment response. Skeletal size has not been reported to affect BMD results in adults with GI disorders, although bone size is known to explain much of the apparent differences in DXA measurements between men and women and between Caucasians and Asians. Much of the reduction in bone density seen with some clinical disorders, such as anorexia nervosa and delayed puberty, is actually a function of this volumetric artifact.^{71,72}

Fracture prediction. Many prospective studies have now shown that BMD and calcaneal ultrasound measurements predict clinical fractures in older men and

women.^{73–75} Although bone density is on average significantly lower in fracture patients than in nonfracture patients, there is considerable overlap between the 2 groups. Risk of fracture shows a continuous gradient relationship with bone density; there is no true “fracture threshold.” Results are usually stated in terms of relative risk (RR) of fracture per SD change in bone density. It appears that any measured site provides fracture risk information about other sites. The best site for characterizing hip fracture risk is the proximal femur (with a RR of 2.6 per SD change in bone density).⁷³ In general, hip fracture prediction is similar whether one uses the total proximal femur (total hip) or subregions (femoral neck, trochanter, or Ward's).

Recall that a unit change in SD is the same as a unit change in the Z score (or T score). The increase in fracture likelihood with decreasing bone density is exponential (not simply additive) and is proportional to $RR^{-Z \text{ score}}$. The influence of age on fracture risk is considerable and occurs independent of the age-related decline in bone density. This age-related fracture risk is in part secondary to an increased likelihood of falls as well as to microarchitectural changes in bone (such as increased bone turnover) that cannot be evaluated based on bone density.

Many other important factors in the pathophysiology of postmenopausal fracture cannot be measured by bone densitometry. Large cohort studies have identified clinical markers for hip fracture that operate independent of bone density measurement. Data from the Study of Osteoporotic Fractures indicate that when there are few clinical risk factors, hip fracture rates are very low (1.1–2.6 hip fractures per 1000 women-years).⁷⁶ In this study, women in the lowest bone density tertile with fewer than 3 clinical risk factors had a substantially lower fracture rate than those in the highest bone density tertile with at least 5 clinical risk factors (2.6 hip fractures per 1000 women-years vs. 9.4 hip fractures per 1000 women-years). The single most powerful predictor of a future osteoporotic fracture is the presence of previous such fractures. A single vertebral fracture puts the individual at greater risk of fracture than does low bone density alone. The combination of low bone density and previous fracture increases risk 25-fold, and the presence of 2 vertebral fractures increases that risk 75-fold. To date, the effect of GI diseases on non-BMD risk factors has been largely ignored.

Following osteoporosis with bone densitometry. Follow-up bone mass measurements in patients not receiving active treatment can aid the identification of individuals with rapid bone loss (“fast losers”). Repeat

testing may also be useful in confirming a positive treatment response, although some evidence suggests that much of the antifracture effect of current antiresorptive therapies is mediated through mechanisms other than increasing bone mass. The optimal time interval for follow-up measurements is a function of machine reproducibility and the expected rate of bone loss. For example, if a subject loses bone mass at a rate of 1% per year, then it would take 3 years for this to exceed (with 95% confidence) the reproducibility limits of a machine with "optimal" performance (%CV, 1%) and 6 years for a "typical" machine (%CV, 2%).

The timing of repeat testing needs to take into account patient-related factors, including the average rate of expected bone loss and the maximum rate of loss that likely will be encountered. The latter is critical, because follow-up bone mass measurements should ideally identify patients who are failing treatment before substantial bone loss develops or fractures occur. Average rates of bone loss are greater in untreated early postmenopausal women (approximately 2% per year) than in older women (<1% per year). The site of most rapid bone loss also changes with age. Loss of trabecular bone from the spine exceeds that of the hip in early postmenopausal women. Similarly, an increase in skeletal mass from antiresorptive treatment is usually most evident in the spine, due to the relatively faster turnover of trabecular bone. For untreated older subjects, the decline in mass of the hip bone generally exceeds that of the spine, because of the development of age-related degenerative artifacts in the spine.

Inflammatory Bowel Disease

Introduction

Bone demineralization and osteoporosis in patients with IBD was first reported 25 years ago.⁷⁷ Over the past 10 years, the widespread availability of DXA has brought a dramatic increase in the number of publications relating to bone density in IBD. These data, summarized in several review articles, generally report a high prevalence of osteopenia. This has generated some alarm over the potential for fracture morbidity in IBD patients and a call to systematically search for osteopenia.

Several important caveats need to be appreciated when evaluating this literature. There is a paucity of data in IBD patients correlating BMD with fractures, and the use of DXA measures to predict fracture risk is derived largely from work in postmenopausal osteoporosis. The pathophysiology of diminished bone mass in IBD and the postmenopausal state are undoubtedly distinct and cannot be distinguished with simple 2-dimensional

(areal) measures of bone. Corticosteroid use is clearly an important variable, but investigators define and quantify use in widely differing ways. For example, for some it means corticosteroid use even just once, whereas others attempt to reconstruct the total lifetime dose. Thus, each statement referring to the presence or absence of an impact of corticosteroid use on bone density should be interpreted in accordance with the definition used in the particular study.

One variable often cited as important in Crohn's disease is the relationship between osteomalacia and reduced vitamin D intake and/or absorption. Much of this comes from literature in the early 1980s that specifically addressed BMD in a selected group of Crohn's disease patients with decreased serum 25-OHD. A recent study showed that vitamin D absorption in Crohn's disease patients is normal, contrary to long-held dogma.⁷⁸ Some studies have shown no relationship between BMD and measured serum 25-OHD.^{79–81} Two studies have found that serum 25-OHD levels are actually lower in ulcerative colitis than in Crohn's disease.^{82,83} On the other hand, relative malnutrition and low body weight may not have received sufficient attention as risk factors. Past fractures are an important risk factor in postmenopausal osteoporosis for future fractures⁸⁴ and, intuitively, past fractures in IBD patients (particularly those of a low-impact nature) should be a warning signal for future fracture. Unfortunately, fracture history is rarely a routine aspect of an initial gastroenterology history of an IBD patient.

Pathogenesis

The underlying inflammatory process in IBD may play an important role in the induction of osteopenia in these patients. A rat model of colitis was associated with a dramatic 33% loss in trabecular bone and an even greater suppression in bone formation rate.⁸⁵ Healing of colitis was associated with an increased bone formation rate and a return of bone measurements to normal levels. Serum from children with Crohn's disease affects bone mineralization in an organ culture model without altering bone resorption.⁸⁶ These observations suggest that mediators produced during intestinal inflammation may alter osteoblast function and bone formation, and they are consistent with the observation that osteoporotic patients with IBD have higher serum IL-6 levels than nonosteoporotic patients.⁸⁷ Factors such as RANKL may link an intestinal or systemic inflammatory process and osteoclastogenesis, as discussed previously.

Factors that contribute to osteoporosis in the general population may be important in IBD as well. These include a sedentary lifestyle, underweight, hypogonad-

ism, dietary intake of calcium and vitamin D, smoking (most commonly in Crohn's disease), and corticosteroid use. To date, it has been difficult to separate the relative contributions of active inflammation and corticosteroid therapy in IBD-related osteopenia, because corticosteroids are most often prescribed during periods of active inflammation.

Bone histomorphometry. In one of the earliest studies to examine bone histomorphometry in Crohn's disease, 9 of 25 (36%) were claimed to have osteomalacia.⁸⁸ But because tetracycline labeling was not used, the diagnosis of osteomalacia is questionable. Nonetheless, these and similar early data likely biased the next generation of researchers. Modern clinicians caring for Crohn's disease patients rarely see elevations in bone-derived alkaline phosphatase. Furthermore, Crohn's disease patients are less likely to have long small bowel resections than they were 25 years ago, and more often receive vitamin D supplementation.

In a study of 31 patients with Crohn's disease and low serum 25-OHD levels, there was a correlation between serum 25-OHD level and BMD measured by cortical area and SPA of the distal radius.⁸⁹ However, it was difficult to determine whether or not there may have been a selection bias. In a study of 36 Crohn's disease patients after small bowel resection, bone histomorphometry using in vivo tetracycline double-labeling revealed a lower mean trabecular bone volume compared with age- and gender-matched controls ($P < 0.01$).⁹⁰ An increased surface extent of osteoid was seen in 5 of 36 (14%), and an increased osteoid seam width was seen in only 3 of 36 (8%). The bone formation rate was normal in all patients. The mean mineralization lag time was normal in all but 6 patients. Only 2 of 36 (6%) had both increased mineralization lag time and increased osteoid seam width suggestive of osteomalacia. Measures of serum vitamin D metabolites were unhelpful in predicting osteomalacia. This study suggested that osteomalacia after small bowel resection for Crohn's disease is uncommon.

In a more recent study of bone histomorphometry in 18 patients with IBD (and 1 patient with carcinoid syndrome) compared with bone biopsies from 57 controls, the IBD patients revealed significantly diminished bone formation but no evidence of osteomalacia.⁹¹ Maximal cavity depth was inversely correlated with cumulative corticosteroid dose ($r = -0.661$, $P < 0.05$). There was no correlation between biopsy findings and disease duration.

Prevalence of Bone Disease in Inflammatory Bowel Disease

Pediatric inflammatory bowel disease. IBD can impact on growth, nutrition, and puberty, all of which

are important factors in facilitating the growth and development of bones. There have been case reports of low-impact fractures in children with Crohn's disease,⁹² so osteoporosis in pediatric IBD may include significant morbidity. When assessing pediatric bone density, performing bone age adjustment is important.⁹³ One report of children with Crohn's disease and a chronological BMD Z score < -2 found a poor correlation with the Z score after adjustment for bone age ($r^2 = 0.34$, $P = 0.15$).⁹⁴ Among 19 children who had a chronological BMD Z score < -2 , the Z score increased to between -1 and -2 in 5 and to above -1 in 3 with bone age adjustment. Overall, using bone age in the analysis increased the average Z score from -1.75 ± 0.9 to -1.52 ± 0.9 ($P = 0.03$). In another study, a severely decreased bone mass with Z score of < -2 was found in 44%; however, this rate was reduced to 26% when accounting for bone age or to 30% when reanalysis of BMD accounted for height.⁹⁵

In a study that adjusted for bone age, females with Crohn's disease—but not females with ulcerative colitis—had significantly lower BMD than controls.⁹⁶ No difference among males by disease type was seen. An overview of these data is provided in Table 5. DXA—dual-photon absorptiometry data were pooled to give mean Z scores of -0.86 for the spine and -0.45 for the hip.

No relationship was found between BMD and disease duration,^{93,96} serum or urine measures of bone metabolism,^{96,97} or disease activity. Lifetime corticosteroid dose was found to be inversely correlated with BMD in 3 studies,^{93,96,97} whereas no correlation was found in 1 study.⁹⁵ A correlation between weight⁹⁸ or lean tissue mass and BMD was seen.⁹³ Thus corticosteroid use and body mass are important predictors of BMD in children with IBD; however, the most critical aspect of assessing BMD is to correct for bone age or make a volumetric assessment of BMD.

Longitudinal follow-up at 1 and 2 years in 17 males with Crohn's disease showed no change in BMD compared with controls despite corticosteroid use by all children.⁹⁹ Another longitudinal study conducted in 21 of 54 subjects with IBD who underwent an initial DXA⁹³ found no change in BMD at 1 year and a significant increase in the BMD Z score at the lumbar spine and total body calcium level at 2 years.⁹³ Details regarding disease activity, patient age, and pubertal status were not given. Although definitive conclusions cannot be drawn from these 2 small studies, they tend to suggest that children with IBD, like adults, generally have longitudinal changes in bone mass that are similar to those in controls.

Table 5. Cross-Sectional Studies of Bone Density in Children With IBD

Reference	BMD instrument	Subjects	Prevalence of reduced bone density and definition used	Mean bone density
Boot ⁹³	DXA	CD, <i>n</i> = 22 UC, <i>n</i> = 33	Spine Z < -2: CD + UC 7% Total body Z < -2: CD + UC 15%	Spine Z: CD + UC -0.75 Total body Z: CD + UC -0.95
Cowan ^{295a}	DXA	CD, <i>n</i> = 21 UC, <i>n</i> = 11 Control, <i>n</i> = 58	Spine T < -1: 34% Femoral neck T < -1: 47% Whole body T < -1: 41%	Spine CD 96% controls UC 97% controls Femoral neck CD 92% controls ^a UC 96% controls Total body CD 96% controls ^a UC 99% controls
Gokhale ⁹⁶	DXA	CD, <i>n</i> = 51 UC, <i>n</i> = 37 Control, <i>n</i> = 63	Spine Z < -2: CD: 18% UC: 3% Femoral neck Z < -2: CD: 11% UC: 6%	Spine Z: CD Males -0.55 ^a Females -0.88 ^a UC Males +0.06 Females -0.43 Femoral neck Z: CD Males -0.26 Females -0.94 ^a UC males -0.15 Females -0.16
Herzog ⁹⁵	DXA	CD, <i>n</i> = 43 (remission)	Spine Z < -2: 44% (26% bone age adjusted)	Spine Z:
Semeao ^{94,98}	DXA	CD, <i>n</i> = 119	Spine Z < -2: Males: 39% Females: 21%	Males: -1.48 Females: -1.08

^a*P* < 0.05 vs. controls.

Adult inflammatory bowel disease. For patients with established IBD, uncontrolled studies (Table 6) give a prevalence of severe demineralization by DXA (Z score of < -2 or a T score of < -2.5) that ranges from 18% to 42%.^{83,87,100-102} In studies limited to Crohn's disease and containing at least 100 subjects, the prevalence is much lower, at approximately 12%.^{103,104} A number of studies have examined the prevalence of osteoporosis by BMD measurement comparing an IBD group with healthy controls (Table 7). The larger studies, with group sizes of at least 60 subjects and in some cases well over 100 subjects, revealed prevalence rates of severely reduced BMD of 2%-16%.¹⁰⁵⁻¹⁰⁸ These data are similar to the uncontrolled data.

DXA-dual-photon absorptiometry data for the spine and hip from combined Crohn's disease and ulcerative colitis patients were pooled to give a mean lumbar T score of -1.45, mean lumbar Z score of -0.48, mean hip T score of -1.94, and mean hip Z score of -0.58. This analysis also revealed that 14% of IBD patients had a lumbar T score of < -2.5, 6% had a lumbar Z score of < -2, 16% had a hip T score of < -2.5, and 13% had a hip Z score of < -2.

Where data are presented to distinguish the site of BMD measured, BMD is lower at the hip than at the spine in 3 studies,^{83,102,109} the same in the hip and the

spine in 3 studies,¹⁰⁴⁻¹⁰⁶ and somewhat better in the hip than in the spine in 2 studies.^{108,110} Therefore, in contradistinction to postmenopausal and corticosteroid-induced osteoporosis, IBD-associated osteoporosis may be at least as common at the hip.

Two small studies performed in newly diagnosed patients revealed low prevalence (3%-5%) of severe demineralization.^{111,112} One controlled study evaluated subjects within 6 months of diagnosis of IBD and found no difference between Crohn's disease, ulcerative colitis, and control subjects, with rates of Z scores of < -2 at the spine, hip and total body ranging from 0% to 2%.¹¹³

When studies reported on important covariates affecting osteoporosis rates, several consistent patterns emerged. Males and females generally had similar BMD Z and T scores.^{79,83,100-102,108-112,114-117} When gender differences were evident, males were seen to have lower Z and T scores than females.^{103,104,106,118,119} Disease diagnosis (Crohn's disease vs. ulcerative colitis) was generally not a factor; however, 2 small studies showed trends toward lower BMD in Crohn's disease.^{83,108} Disease duration had no effect on BMD in most series.^{105,109,118,120} Two studies showed a correlation between longer disease duration and lower BMD; however, the effects of aging and obligatory bone loss must be considered when evaluating data showing a negative effect of disease duration

Table 6. Uncontrolled Cross-Sectional Studies of Bone Density in Adults With IBD

Reference	BMD instrument	Subjects	Prevalence of reduced bone density and definition used	Mean bone density
Abitbol ⁸²	DXA	CD, n = 34 UC, n = 50	Z < -1 (spine) CD + UC 43%	Mean Z Spine CD + UC -0.73 Femoral neck CD + UC -0.69
Bernstein ⁸³	DXA	CD, n = 26 UC, n = 23	Z < -2 Spine all IBD; 18%, total hip all IBD; 24% spine CD 32% UC 4% Total hip CD 36% UC 13%	Mean Z Spine CD -1.1 UC -1.0 total hip CD -1.5 UC -1.1
Bischoff ¹¹⁵	QCT	CD, n = 61 UC, n = 22 Indeterminate, n = 7	T < -1 (spine) (no data for T < -2.5) CD, 40% UC, 39%	Mean Z CD -0.76 UC -0.5
Bjarnason ¹⁰²	DXA	CD, n = 44 UC, n = 35	Z < -2.5 CD + UC spine; 18% femoral neck; 29%	Mean T Spine CD + UC -0.93 Femoral neck CD + UC -1.92
Clement ¹¹⁴	SPA	CD, n = 33 UC, n = 17	Radius Z < -2: CD 12% UC 6%	Mean Z: M -0.11 F -0.37 ^b
Compston ⁷⁹	SPA	CD, n = 51 UC, n = 17 Other, n = 7	Z < -2 (radius or spine): CD + UC 31%	
Dressner-Pollak ⁸⁷	DXA	CD, n = 33 UC, n = 26	T < -2.5 Spine + femoral neck CD 58% UC 50% CD + UC Spine; 42% Femoral neck; 41%	Mean T Spine CD -2.26 UC -1.6 Femoral neck CD -2.49 UC -2.09
Ghosh ^{111a}	DXA	CD, n = 15 UC, n = 15	Z < -2 (spine) CD 3% UC 0 forearm CD 3% UC 0	Mean Z Spine CD -1.06 UC -0.03 ^b Forearm CD -1.04 UC +0.11 ^c
Lee ^{112a}	DXA	CD, n = 14 UC, n = 25	T < -2.5 (spine) CD 0 UC 8% Femoral neck:	Mean Z Spine CD -0.61 UC -0.58 Femoral neck CD +0.03 UC +0.14
Pigot ¹⁰⁰	DXA	CD, n = 27 UC, n = 21 IAPP, n = 13	Z < -2 (spine or femoral neck) CD 30% UC 29% IAPP 23%	Mean Z Spine CD -1.11 UC -0.93 IAPP -1.53 Femoral neck CD -0.83 UC -0.70 IAPP -1.17
Roux ¹⁰¹	DXA	CD, n = 14 UC, n = 9 IAPP, n = 12	Z < -2 (spine or fn) CD 29% UC 22% IAPP 8%	Mean Z Spine CD -1.12 UC -0.37 IAPP -0.96 Femoral neck CD -1.01 UC -0.28 IAPP -0.57
Schoon ¹⁰⁴	DXA	CD, n = 119	T < -2.5 Spine; 7% Femoral neck; 11% Total body; 6% spine or femoral neck 13%	Mean T Spine -0.42 Femoral neck -0.96 Total body -0.5
Staun ¹⁰⁹	DPA	CD, n = 108 With colon, n = 40 Without colon, n = 68	Z < -2 10% (spine) 24% (femoral neck)	Mean Z Spine P vs. control With colon -0.51 ^b No colon -0.80 ^c Femoral neck With colon -1.24 ^b No colon -1.23 ^c

^aNewly diagnosed cases enrolled only.

^bP < 0.05 vs. controls.

^cP < 0.001 vs. controls.

CD, Crohn's disease; UC, ulcerative colitis; M, males; F, females.

Table 7. Controlled Cross-Sectional Studies of Bone Density in Adults With IBD

Reference	BMD instrument	Subjects	Prevalence of reduced bone density and definition used	Mean bone density
Andreasson ¹¹⁶	DXA	CD, <i>n</i> = 113 Control, <i>n</i> = 113	T < -2.5 (trochanter) CD 3% Control 2%	Mean Z, T, or % control not stated
Ardrizzone ¹¹⁹	DXA	CD, <i>n</i> = 51 UC, <i>n</i> = 40 Control, <i>n</i> = 30	T < -2.5 (femoral neck) CD + UC: 29% CD: 37% UC: 18%	Mean T Spine CD -1.49 UC -1.67 Femoral neck CD -1.8 UC -1.6
Dinca ¹¹⁸	DXA	CD, <i>n</i> = 54 UC, <i>n</i> = 49 Control, <i>n</i> = 18	T < -2.5 (spine) CD, 6% UC, 6%	Mean Z (spine) CD -0.9 ^a UC -0.63 ^a Control +0.25
Jahnsen ¹⁰⁶	DXA	CD, <i>n</i> = 60 UC, <i>n</i> = 60 Control, <i>n</i> = 60	Z < -2 Spine CD 5% UC 2% Cont 0% Femoral neck CD 12% UC 2% Cont 2% Total body CD 15% UC 8% Cont 2%	Mean BMD % of controls Spine CD 93% ^a UC 99% Femoral neck CD 93% ^a UC 100% Total body CD 95% ^a UC 100%
Robinson ^{107,122}	DXA	CD, <i>n</i> = 117 Control, <i>n</i> = 50	T < -2.5 (spine or femoral neck) 12%	Mean Z Spine -0.09 Femoral neck -0.2
Scharla ²⁹⁶	DPA	CD, <i>n</i> = 15 UC, <i>n</i> = 4 Control, <i>n</i> = 19	Z < -2 (spine) CD + UC 0%	Mean Z (spine) CD + UC -0.6 ^a Control -0.1
Schoon ^{113b}	DXA	CD, <i>n</i> = 24 UC, <i>n</i> = 44 Control, <i>n</i> = 68	Z < -2 Spine CD 0% UC 0% Femoral neck CD 0% UC 2% Total body CD 0% UC 0%	Mean BMD % of controls Spine CD 98% UC 100% Femoral neck CD 100% UC 99% Total body CD 100% UC 97%
Schulte ¹⁰⁸	DXA	CD, <i>n</i> = 104 UC, <i>n</i> = 45 Control, <i>n</i> = 55	T < -2.5 Spine CD 15% UC 9% Femoral neck CD 12% UC 4%	
Silveinonnen ¹⁰⁵	DXA	CD, <i>n</i> = 78 UC, <i>n</i> = 76 Indeterminate, <i>n</i> = 7 Control, <i>n</i> = 73	Z < -2 (spine or fn) IBD, 2% Control, 0%	Mean Z Spine All IBD -0.028 Control +0.4 ^a Femoral neck All IBD -0.364 ^a control +0.122
Ulivieri ¹¹⁷	DXA	UC, <i>n</i> = 43 Control, <i>n</i> = 121	No data given	Mean Z Spine Males -0.59 Females -0.05 Total body Males -0.93 Females -1.23

^a*P* < 0.05 vs. controls.^bNewly diagnosed cases enrolled only.

CD, Crohn's disease; UC, ulcerative colitis.

on BMD.^{108,121} One study of newly diagnosed patients revealed an inverse relationship between symptom duration and BMD; in this study, disease onset before age 18 years was associated with lower BMD.¹¹³ Disease activity was found to have no effect on BMD.^{111,119} Disease site had no effect in 2 controlled studies,^{105,116} whereas 1 study reported lower BMD in Crohn's disease patients with jejunal disease.¹⁰³

In most studies, no correlation was found between BMD and previous surgery, whether defined as any intestinal surgery or analyzed by length of resection,^{100,106,116,119} although 1 study reported a lower BMD in patients who underwent ileal resection compared with those who had no intestinal surgery.¹¹⁰ Regarding estrogen status, 2 studies found no difference in spine and femur T scores¹¹⁹ or Z scores¹⁰⁴ between postmenopausal and premenopausal females. The latter study reported that postmenopausal females with Crohn's disease had a higher prevalence of more severe osteopenia than premenopausal females.¹⁰⁴ In a study of males with Crohn's disease, serum testosterone levels did not predict BMD measures.¹²² No relationship between smoking status and BMD was found in 3 studies,^{106,111,123} but such a relationship was reported in 1 study.¹⁰⁵ Serum and urine bone markers did not correlate with any BMD measures in 7 adult studies.^{83,105,111,112,115,117,119} One study suggested an inverse relationship with urinary N-telopeptide cross-links at the hip.

Grip strength,¹⁰⁸ body weight,^{79,82,103} skin-fold thickness,¹²⁴ and body mass index (BMI) correlated with BMD in 4 controlled studies and 3 uncontrolled studies.^{82,108,110,113,118,119,125} Measurement of hand skin-fold thickness might become a simple office test for identifying patients at risk for low BMD. A skin-fold thickness of <2.5 mm had a sensitivity for a DXA T score of <-2.5 of 93% with a specificity of 54%.¹⁰⁷ A cutoff of <1.9 mm would increase specificity to 93% but at the expense of reduced sensitivity.

In 5 studies total corticosteroid dose was inversely associated with BMD,^{79,82,105,108,123} but 2 studies reported no effect on BMD.^{102,109} Bjarnasson et al.¹⁰² showed no effect of current corticosteroid use on BMD, but 2 other studies reported an association between current corticosteroid use and diminished BMD.^{83,103} One study showed that current corticosteroid use was associated with lower BMD in Crohn's disease, but not in ulcerative colitis.¹⁰⁶ Another report stated that current corticosteroid use negatively impacted on BMD only in females, whereas total corticosteroid dose negatively impacted on BMD only in males.¹¹⁹ It is uncertain whether

an apparent corticosteroid effect results from the medication itself or is simply a marker for more severe IBD. In a small study of 59 patients with Crohn's disease, of whom 18 were receiving corticosteroids, 20 were receiving corticosteroids plus azathioprine, and 21 were not using any corticosteroids, the main determinant of BMD was corticosteroid dose irrespective of concurrent azathioprine.¹²⁶ If azathioprine is corticosteroid-sparing, then an added benefit may be an attenuation in bone loss. In a study of 53 females with Crohn's disease and sacroiliitis matched to 53 females with Crohn's disease without sacroiliitis, the sacroiliitis group had significantly reduced bone mass ($P < 0.05$).¹²¹ Thus, yet another variable to consider in terms of stratifying fracture risk might be concurrent musculoskeletal conditions such as sacroiliitis.

Calcaneal quantitative ultrasonography. Three studies have assessed calcaneal QUS in IBD patients.^{123,127,128} In a small study (Crohn's disease, $n = 22$; ulcerative colitis, $n = 11$) with DXA as the gold standard, both BUA and SOS correlated significantly with BMD ($r = 0.67$ and $r = 0.61$, respectively; $P < 0.0001$).¹²³ In a larger study¹²⁷ of patients with Crohn's disease ($n = 53$) and ulcerative colitis ($n = 57$), calcaneal QUS correlated poorly with DXA in individual patients. In Crohn's disease, a Z score of <-1 for either BUA or SOS had a sensitivity for DXA Z score of <-1 of 60% with a specificity of 92%. For ulcerative colitis, sensitivity was 71%, but specificity was only 77%. The SOS Z score for patients with Crohn's disease and a past fracture was -1.08, compared with -0.39 for those without a history of fracture ($P = 0.027$), and the mean SOS Z score for those with ulcerative colitis with a past fracture was -0.75, compared with +0.06 for those without a past fracture ($P = 0.009$). In the largest study to date, 100 patients with Crohn's disease were compared with 52 controls using calcaneal QUS and DXA as gold standard.¹²⁸ Crohn's disease subjects had significantly lower BUA ($P = 0.0004$) and lower SOS ($P = 0.02$) than controls. For a DXA T score of <-2.5 at the lumbar spine and femoral neck, BUA had a sensitivity of 75% and 67%, respectively, and a specificity of 86% and 89%, respectively. The odds ratio for having a previous fracture by a T score of <-2.5 versus BUA was 3.63 (95% CI, 1.4-9.3). It was concluded that although calcaneal BUA was significantly associated with BMD at the hip and spine, the correlation was insufficient to recommend ultrasonography as a screening tool for DXA.

Table 8. Bone Density Results in Adults With IBD Followed Longitudinally

Reference	BMD instrument	Subjects	Mean follow-up (years)	Percent change
Clements ¹¹⁴	SPA radius	IBD, <i>n</i> = 39	7.2	M = -0.07%/yr F = -0.74%, <i>P</i> = 0.02
Dinca ¹¹⁸	DXA	CD, <i>n</i> = 30 UC, <i>n</i> = 14	1.75	CD -0.31%/yr UC -2.47%/yr
Ghosh ¹¹¹	DXA	CD, <i>n</i> = 11 UC, <i>n</i> = 12	1	spine CD change in Z = -0.31/yr UC change in Z = +0.07/yr
Motley ¹²⁹	SPA radius QCT spine	CD, <i>n</i> = 51 UC, <i>n</i> = 22	4	Z -0.13/yr SPA Z -0.18/yr qCT
Roux ¹⁰¹	DXA	CD, <i>n</i> = 14 UC, <i>n</i> = 9 IAPP	1.6	NS CD -6.42%/y (spine), -6.91%/y (femoral neck) UC -3.08%/y (spine) -5.59%/y (femoral neck) IAPP +1.96%/y (spine) +1.01%/y (femoral neck)
Schulte ¹³¹	DXA	CD, <i>n</i> = 61 UC, <i>n</i> = 19	1.5	CD, +0.8%/y (spine) +0.12%/y (hip) -0.46%/y (total body) UC, -0.48%/y (spine) +0.26%/y (hip) -0.46%/y (total body)
Staun ¹⁰⁹	DPA	CD, <i>n</i> = 108	4.8–5.9	-2.2%/yr for those with colon (femoral neck) ^a -1.4%/yr for those without colon (femoral neck) ^a

^a*P* < 0.05 vs. controls.

CD, Crohn's disease; UC, ulcerative colitis; M, males; F, females.

Longitudinal Changes in Bone Density in Inflammatory Bowel Disease

In general, longitudinal changes in BMD for IBD patients are similar to those in the general population (Table 8). In a study using radial SPA in 39 patients with an average of 7.2 years' follow-up, the change in BMD for males (-0.07% per year) was insignificant.¹¹⁴ For females, the change of -0.74% per year (*P* = 0.02) was similar to expected age-related loss. Another report from the same group using both radial SPA and QCT with a mean follow-up of 4 years in 73 patients showed no meaningful difference in the rate of change in IBD patients compared with expected losses in a healthy population.¹²⁹ Several other small studies have reported minimal short-term bone loss.^{101,111,118,130,131} However, a study of 35 patients (14 patients with Crohn's disease, 9 with ulcerative colitis, and 12 after an ileoanal pouch procedure [IAPP]) reported rapid bone loss.¹⁰¹ In Crohn's disease, the mean annual decrease was 6.42% at the spine and 6.91% at the femoral neck. In ulcerative colitis, the mean annual decrease was 3.08% at the spine and 5.59% at the femoral neck—rates of bone loss that exceed those seen during the early accelerated phase of bone loss in menopausal women. However, patients with IAPP actually exhibited an increase in bone mass in the

spine and proximal femur (annual change of +1.96% and +1.01%, respectively).

In a study with a 1.5-year mean follow-up, no significant change in BMD was seen at the lumbar spine, femoral neck, or total body for patients with either ulcerative colitis (*n* = 19) or Crohn's disease (*n* = 61).¹³¹ No correlation was found between rate of BMD loss and Crohn's disease activity. Overall, the rate of change was similar in Crohn's disease and ulcerative colitis. Interestingly, however, a substantial number (16 of 81; 20%) had a baseline lumbar Z score of < -2, and these patients showed the greatest average increase in spine BMD (+2.08 ± 2.9% per year versus +0.147 ± 3.0% per year for all others; *P* = 0.04).

Bone loss may be affected by the surgical status of the colon. In a group of 108 patients with Crohn's disease, the BMD of those with an intact colon (*n* = 40) was compared with that of those who had a colectomy (with ileostomy or ileorectal anastomosis) (*n* = 68).¹⁰⁹ At a mean follow-up of 4.8–5.9 years, a significant decrease in femoral neck BMD was seen in both groups (-2.2%/year for those with a colon [*P* < 0.001] and -1.2%/year for those without [*P* < 0.05]), although the difference between groups was not statistically significant. No significant change occurred at the lumbar spine. No correla-

tion was seen between small bowel resection and rate of bone loss. BMD is less responsive to surgery in Crohn's disease than ulcerative colitis (in which BMD often improves after an IAPP).^{100,101,132} For example, in 20 patients who underwent IAPP followed for a mean of 28 months postoperatively, the mean annual increase was $+2.3 \pm 3.8\%$ at the spine and $+2.1 \pm 5.6\%$ at the femoral neck.¹³² An increase in spinal BMD of $>5\%$ over the course of the follow-up was seen in 5 of 15 patients (33%), an increase of $<5\%$ was seen in 7 patients (47%), and a decrease of $<5\%$ was seen in 3 patients (20%). A positive correlation was seen between time since colectomy and BMD at the spine ($r = 0.71$, $P = 0.05$) and femoral neck ($r = 0.63$, $P = 0.003$). Whether pouchitis also affects BMD is uncertain. These data suggest that an additional benefit of colectomy in patients with ulcerative colitis may be bone density enhancement.

Corticosteroid use was correlated with bone loss in 3 studies,^{118,129,131} but another study reported no correlation with bone loss.¹⁰⁹ In the first study, the prescribed dosage of corticosteroid was correlated with spinal bone loss in males ($r = -0.58$, $P < 0.05$), but no such correlation for females or other clinical parameters was reported.¹²⁹ The second of these 3 studies found a correlation with bone loss from the hip but not from the spine or total body.¹³¹ The third study reported an effect of corticosteroids in bone loss in ulcerative colitis, but not in Crohn's disease.¹¹⁸

The lack of correlation between longitudinal BMD measures and biochemical bone markers has been corroborated in multiple studies.^{83,96,97,105,111,112,115,117,119} Measurement of these factors does not appear to predict bone loss in patients with IBD.

Fracture Prevalence and Incidence in Inflammatory Bowel Disease

Case series have reported considerable ranges in fracture rates in IBD patients. One group found no new spinal fractures during follow-up,¹²⁹ whereas another reported vertebral fractures in 6 of 23 (26%) patients with Z scores of < -2 .⁷⁹ Larger series have reported vertebral fractures in 7% of IBD patients ($n = 84$)⁸² and other fractures in 24%–27% ($n = 119$ and $n = 120$).^{104,106} In the latter, fracture history correlated with lower total body BMD and also with greater total corticosteroid use.¹⁰⁶ Other studies confirm that past history of fracture correlates with lower BMD and QUS^{106,127,128}; however, fractures, including vertebral fractures, can occur despite a normal BMD measurement.¹¹² The assessment of spinal fractures without vertebral X-rays may underestimate the true incidence of these fractures, because $\frac{2}{3}$ of spinal fractures are not clinically evident. This

underscores the fact that BMD cannot replace the use of population-based fracture data and systematic spinal X-rays in measuring the clinical burden of osteoporosis.

A survey was mailed to members of the Danish Crohn's/Colitis Association regarding fractures.¹³⁴ The RRs for fracture in patients with Crohn's disease and ulcerative colitis patients were calculated; however, the controls were not well matched and were significantly more likely to be male and older and less likely to be a current smoker or using hormone-replacement therapy (HRT). Furthermore, the nature of that study was prone to bias, because subjects who are at greater risk for fracture are more likely to respond. Patients with ulcerative colitis had an overall fracture rate similar to controls; however, patients with Crohn's disease had a RR of 1.7 (95% CI, 1.7–2.3) for all fractures, 2.5 (95% CI, 1.7–3.6) for fractures in females, and 2.9 (95% CI, 1.8–4.8) for fractures in premenopausal females. The RR was 1.8 (95% CI, 1.0–3.3) in postmenopausal females and 0.6 (95% CI, 0.3–1.3) in males. Patients with Crohn's disease were more likely than controls to fracture vertebrae (RR, 6.7; 95% CI, 2.1–21.7), and there was a similar trend for those with ulcerative colitis (RR, 2.4; 95% CI, 0.5–11.9). No significant increased risk of femur fractures was seen in either Crohn's disease or ulcerative colitis. A family history of fracture increased the RR for fracture in Crohn's disease (2.4; 95% CI, 1.4–4.1), particularly for paternal fracture history (3.6; 95% CI, 1.9–6.8). Conversely, maternal fracture history led to an increased fracture risk for ulcerative colitis patients (RR, 2.4; 95% CI, 1.2–4.7). Current smoking increased the fracture risk in patients with ulcerative colitis (RR, 3.8; 95% CI, 1.9–7.8) as in other patient groups, although it did not impact on fracture risk in patients with Crohn's disease. There was no correlation for either disease group and fracture risk based on corticosteroid use.

A recently reported population-based study of IBD and fractures from hospital discharge abstracts¹³⁵ compared IBD subjects and age- and gender-matched controls randomly selected from the population (matching ratio 1:3). The study assumed that all patients with IBD were captured (i.e., that all IBD patients before 1994 were inpatients and all those since 1994 were seen in either the inpatient or the outpatient setting of a Danish hospital) and that all patients with fracture diagnoses were seen in a hospital setting. This is potentially a major flaw of the study, because several fractures (particularly those of the arms, ribs, and spine) do not usually lead to hospitalization. Furthermore, the authors identified 7072 Crohn's disease patients and 8323 ulcerative

colitis patients, but a random sample of case validation was done on only 19 Crohn's disease patients and 22 ulcerative colitis patients. The validity of ulcerative colitis diagnoses based on chart review was only 64%. The authors found that the RR of sustaining a fracture requiring hospitalization was 1.19 (95% CI, 1.06–1.33) in Crohn's disease patients, whereas it was not significantly increased at 1.08 (95% CI, 0.97–1.20) in ulcerative colitis patients. The small difference in observed fracture rates was not significant.

Only 2 North American population-based studies of fracture risk in IBD have been published.^{136,137} The largest of these reported on 6027 IBD patients and an age-, gender-, and geographic residence-matched control group of 60,270. Fractures were identified using the administrative databases for the Canadian province of Manitoba, which provides comprehensive health care coverage for all residents. The overall fracture rate for IBD patients was found to be approximately 1 per 100 patient-years, higher than that for controls (RR, 1.41; 95% CI, 1.27–1.56). Increased fracture risk at the spine and hip was mostly accounted for by fractures in patients over age 60. The incidence rate ratio was 2.06 (95% CI, 1.41–2.95) at the spine and 1.59 (95% CI, 1.27–2.00) at the hip for subjects over age 60. A trend toward an increased wrist fracture rate with aging was found. No differences were reported between males and females or between Crohn's disease and ulcerative colitis patients; however, in patients with ulcerative colitis, males had a significantly higher relative risk of fracture than females. Several important messages can be gleaned from this study. First, because the study is population based, it should not be affected by the referral bias seen in reports from specialized referral centers. Second, the study quantifies and puts into perspective the fracture risk, which is higher than that of controls but nonetheless is not a large increase. The observed fracture rate is consistent with the modest BMD reduction reported earlier. (A pooled Z score of -0.5 would translate into a RR of fracture of 1.4 assuming a doubling of fracture rate for each SD reduction in BMD.) It also should temper our approach in pursuing widespread DXA assessments in all patients, because the magnitude of the major osteopenic morbidity risk (fracture) does not mandate a widespread hunt for diminished BMD. The data also refute the notion that Crohn's disease patients have higher fracture rates than ulcerative colitis patients. Finally, although age-related osteoporosis is predominantly a female problem, it is gender-neutral among IBD patients.

The second North American population-based study used the Olmsted County, Minnesota database of 243

Crohn's disease patients.¹³⁷ Compared with controls, the overall risk ratio for any fracture was 0.9 (95% CI, 0.6–1.4), whereas the relative risk for an osteoporotic fracture was 1.4 (95% CI, 0.7–2.7). The risk ratio for thoracolumbar vertebral fracture was 2.2 (95% CI, 0.9–5.5). Cox proportional hazards regression identified only age as a significant clinical predictor of fracture risk (hazard ratio per 10-year increase in age, 1.3; 95% CI, 1.1–1.5). Thus the risk of fracture was not greater than in the general population, except in the elderly. Although this study is of a small sample size of a relatively homogenous population, the main message is similar to that from the Manitoba study: IBD patients may have an increased risk of fracture over matched control populations, but it is a small increased risk, and the greatest increased risk is evident in elderly patients with IBD.

Summary of Bone Disease in Inflammatory Bowel Disease

1. Osteomalacia and vitamin D deficiency are not common in IBD (including Crohn's disease) and are unlikely to be important causes of most cases of diminished BMD in IBD (level B evidence).
2. IBD has only a modest effect on BMD, with a pooled Z score of -0.5 (level A evidence).
3. The overall prevalence of osteoporosis (T score of <-2.5) using DXA is approximately 15%, but the rate is strongly affected by age, with osteoporosis more common in older subjects (level A evidence).
4. At diagnosis, the prevalence of diminished BMD is low (level B evidence) and when followed longitudinally, changes in BMD are similar to those expected (level B evidence).
5. DXA is a marker of diminished bone mass and fracture risk but is not the only marker of fracture risk. It should be used in concert with other clinical variables to predict fracture risk (level D evidence).
6. The risk of osteoporosis is similar in males and in females (level A evidence).
7. Crohn's disease and ulcerative colitis have comparable risks for osteoporosis (level B evidence).
8. Corticosteroid use is the variable most strongly associated with osteoporosis (level A evidence). However, distinguishing corticosteroid use from disease activity in terms of causal impact on bone density is difficult, because these 2 factors are closely linked.
9. Biochemical bone markers do not correlate suffi-

- ciently well with current BMD or rate of bone loss for routine use (level B evidence).
10. The IAPP after curative colectomy in ulcerative colitis may be associated with an improvement in DXA (level C evidence).
 11. Calcaneal ultrasonography has not been as well evaluated as DXA, but could potentially aid in selecting patients for DXA (level B evidence).
 12. Pediatric DXA should be adjusted for bone age, or else BMD typically will be underestimated (level B evidence).
 13. The overall incidence of fractures in a population-based study is 1 per 100 patient-years, but the rate is strongly affected by age, being higher in subjects over age 60 (level A evidence).
 14. The overall RR of fractures is 40% greater than that in the general population and increases with age (level A evidence).
 15. Crohn's disease and ulcerative colitis have comparable risks for fracture (level A evidence).
 16. Males and females share a comparable risk for fracture (level A evidence).
 17. DXA scans should be selectively ordered in IBD patients based on a thorough risk factor assessment (level D evidence).

Celiac Disease

Introduction

Celiac disease can present at any age. It can affect the developing bones of infants and children, compromise bone accretion during adolescence and young adulthood, and add to the effects of menopause and aging in the elderly. The female-to-male ratio of celiac disease is approximately 2:1,¹³⁸ and this female preponderance should be kept in mind when considering studies of osteoporosis prevalence rates that do not perform a gender-specific analysis. Prevalence rates of osteoporosis in celiac disease vary considerably. This may reflect the focus on adults in some studies and on children in others. As discussed later, children with celiac disease are more likely than adults with celiac disease to reach normal bone mass after gluten avoidance.

In contrast to IBD, in celiac disease there are no population-based data on associated fracture or osteoporosis rates. A Veteran's Administration database study found that 5% of celiac disease cases abstracted from hospital discharge records had a concurrent discharge diagnosis of osteoporosis or another bone disorder.¹³⁹ Comparing this with the 0.6% of controls gives an odds ratio of 4.24 (95% CI, 1.95–9.22). The actual prevalence of low bone mass, as determined by bone density mea-

surement, is much higher. Only 1 study has estimated incident fracture rates, and even this used a retrospective historical design.¹⁴⁰ In the absence of population-based or large-database data on fractures in known celiac disease patients, the true burden of osteoporosis in this disease will remain uncertain.

Pathogenesis

The association between systemic inflammation in celiac disease and BMD has been only minimally explored. Serum levels of IL-6 are inversely correlated with BMD, and serum levels of IL-1 receptor antagonist were directly correlated with BMD.¹⁴¹ Increases in serum insulin-like growth factor-1 (IGF-1) correlated with increased BMD during short-term follow-up, but this was true only in subjects with normal baseline serum PTH levels.¹⁴² Thus, 1 possible paradigm contributing to osteoporosis in celiac disease may be a PTH-IGF-1 interaction. Nutritional status is positively associated with IGF-1 levels and offers a possible mechanism to explain how celiac disease may lead to low bone mass. Conversely, high IGF-1 levels may be present in subjects who do not have severe malabsorption and whose disease does not lead to vitamin D deficiency and secondary elevations in PTH levels. IGF-1 exerts anabolic effects on bone, whereas PTH increases bone resorption; therefore, low IGF-1 levels resulting from, for example, low BMI or delayed puberty would lead to depressed bone formation. Zinc deficiency also impairs IGF-1 production and leads to decreasing IGF-1 levels with age.^{143,144} In summary, zinc deficiency, other nutritional factors, and aging may affect IGF-1 and IGF-binding proteins in patients with malabsorption and in postmenopausal women at risk for osteoporosis. The enterocyte defect of celiac disease impairs zinc absorption, and diets high in calcium may also reduce zinc absorption.¹⁴⁵ Thus administering calcium supplementation without correcting the mucosal lesion may exacerbate zinc depletion, a second mechanism reducing IGF-1, and indirectly lead to impaired bone metabolism.

Reduced calcium intake and impaired calcium absorption may trigger a sequence of events that leads to impaired bone mass. These events include hypersecretion of PTH, enhanced 1,25(OH)₂-vitamin D, and diminished 25-OHD.^{146–153} The 1- α hydroxylase enzyme is enhanced because the defective enterocytes cannot respond to 1,25(OH)₂-vitamin D, and ultimately the level of this hormone may increase. Calcium malabsorption and impaired activity of 1,25(OH)₂-vitamin D may be secondary to relative resistance of the vitamin D receptor to vitamin D action. The vitamin D-dependent transporter protein (calbindin-D9K) may be undetectable in

patients with active celiac disease, further reducing the level and, subsequently, biological activity of vitamin D.¹⁵³ Despite subnormal 25-OHD, it is unknown how many of these patients will have osteomalacia. Currently, vitamin D deficiency is defined as a serum 25-OHD level <15 ng/mL. Although osteomalacia has been reported in several cases of celiac disease,¹⁵⁴ there is a paucity of bone histomorphometric data. Nonetheless, the goal in treating patients with vitamin D should be to maintain serum 25-OHD levels above 25–30 ng/mL.¹⁵⁵

A genetic predisposition to osteoporosis in patients with celiac disease has yet to be adequately investigated. One study could not find any correlation between osteoporosis (as determined by calcaneal ultrasonography) with vitamin D receptor genotyping.¹⁵⁶ Finally, in some instances celiac disease is associated with amenorrhea or male hypogonadism, either of which would also negatively affect bone mass.^{157,158}

Prevalence of Bone Disease in Celiac Disease

Pediatric celiac disease. Children with celiac disease also present with osteopenia (Table 9). However, once a gluten-free diet is instituted, their bone density typically returns to normal.^{159–161} Adults with celiac disease diagnosed as children are likely to have normal bone density if they adhere to a gluten-free diet, whereas those diagnosed as adults do not necessarily share this property. Thus, a childhood diagnosis of celiac disease allows for full restitution of bone mass once nutrition is restored and calcium and vitamin D absorption are normalized. A pooled analysis of treated children with celiac disease yielded a mean lumbar Z score of -0.53 and a mean total body Z score of -0.57 . Long-standing celiac disease patients diagnosed during childhood tend to be shorter than age- and sex-matched controls despite bone mass recovery.¹⁶² Children diagnosed with celiac disease before age 2 years have greater absolute bone mass than those in whom the diagnosis is made at an older age, and those with at least 24 months of a gluten-free diet had significantly greater absolute bone mass than those with less than 12 months of this diet.¹⁶³

Untreated adult celiac disease. The studies assessing bone density in patients with untreated celiac disease generally showed diminished bone density regardless of the method of bone density analysis used (Table 10). Untreated celiac disease is generally (although not invariably) associated with lower BMD than treated celiac disease.^{146,164,165} By pooled analysis of DXA–dual-photon absorptiometry results, patients with untreated celiac disease have a mean lumbar T score of -1.91 , lumbar Z score of -1.42 , hip T score of -1.72 ,

and hip Z score of -1.14 . Osteoporosis was evident in 28% at the spine and 0% at the hip (by a T score <-2.5). Alternatively, very low bone masses compared with age and gender-adjusted controls (Z score <2) were seen in 40% at the spine and 15% at the hip. Bone density of the forearm typically showed a Z score between 0 and -1 .

In 2 studies, patients with symptomatic celiac disease had lower BMD than those patients diagnosed with subclinical disease,^{149,166} although 1 study could not find any difference.¹⁶⁴ Duration of symptoms before diagnosis of celiac disease did not correlate with BMD at time of diagnosis in 1 small study ($n = 14$),¹⁶⁷ whereas a larger study ($n = 41$) did find the expected negative correlation.¹⁶⁸ BMI correlated directly with BMD in all studies in which it was assessed.^{166,169,170} Among patients diagnosed as adults, age at diagnosis did not correlate with BMD.^{149,166,167} Postmenopausal females had lower BMD adjusted for age than premenopausal females in 1 study,¹⁷¹ but not in another.¹⁵¹ Otherwise, gender did not influence BMD in newly diagnosed patients.^{140,146,151,171} History of previous fracture did not correlate with lower BMD.¹⁴⁰

An important serological variable in newly diagnosed celiac disease is serum PTH. The higher the PTH, the lower the BMD.^{146,151,167,172} Patients with secondary hyperparathyroidism were more likely to have grade IV villous atrophy and lower BMI than patients with normal serum PTH levels.¹⁷² Serum osteocalcin¹⁷¹ and SAP^{151,171} were found to be negatively correlated with BMD, whereas serum 25-OHD levels were positively correlated with BMD.^{146,151}

Treated adult celiac disease. Studies that measured bone density in patients with celiac disease on a gluten-free diet reported heterogeneous results (Table 11). Three studies reported no difference between BMD in treated celiac patients and healthy controls,^{147,173,174} whereas 6 studies reported significantly reduced BMD in treated celiac disease.^{150,152,165,175–177} Pooled analysis of DXA–dual-photon absorptiometry results in treated celiac disease gives a mean lumbar T score of -1.58 , a mean lumbar Z score of -0.96 , a mean hip T score of -1.31 , and a mean hip Z score of -0.50 . Osteoporosis was evident at the spine in 29% and at the hip in 19% (T score <-2.5), with markedly decreased bone mass compared with age-adjusted controls (Z score <-2) in 21% at the spine and 7% at the hip. Thus, despite small bowel histology and even full villous restitution, BMD in adults may not fully normalize. Those with persistently abnormal small bowel morphology have the lowest BMD;¹⁷³ therefore, broader screening of family members

Table 9. Bone Density in Children With Treated Celiac Disease on a Gluten-Free Diet

Reference	BMD instrument	Subjects at diagnosis/ at F/U	Follow-up period	Prevalence of reduced bone density and definition used	Mean bone density	Increase/yr by Z-score or %
Barera ¹⁶²	DXA	29 20 23 (control)	At dx 1 year 10.6 years		Mean Z (Total body) At dx 81% At 1 yr f/u 96.1% treated 94.3%	
Mora ¹⁵⁹	DXA	44/25 (control)	1.4 years		Spine Z T body Z 94.1% ^a 88.6% ^b	Spine: +5.2% T body: +5.3 +22% ^a +15% yr ^a
Mora ¹⁶⁰	SPA	33/14	1.3 years			
Mora ²⁹⁷	DXA Cross-section on GFD for mean of 10.7 years	30 (control)	N/A	Z < -2.5 Spine; 3% Total body; 3%	Mean Z Spine; -0.42 Total body; +0.27	Cross-sectional study only
Rea ¹⁶¹	SPA	23/23	1 year	Z < -2 At baseline 39% At 1 yr 4%	Forearm Z at baseline -0.76 ^a at 1 yr -0.05	Change in Z score +0.71

GFD, gluten-free diet.

^aP < 0.05.

^bP < 0.01.

of patients with celiac disease and those with type 1 diabetes mellitus, Addison's disease, and other polyglandular diseases is needed, because low BMD does not appear to be fully reversible in adults. Thus, early diagnosis and treatment for asymptomatic celiac disease may optimize skeletal health and prevent fracture development. Severe osteopenia (Z score < -2) was found in 4 of 11 adults (36%) diagnosed with celiac disease during childhood who later became symptom-free and resumed a normal diet during adolescence.¹⁷⁸ Thus symptom-free does not imply disease-free in reference to bone mass.

Two studies specifically analyzed BMD on the basis of follow-up small bowel histology.^{146,179} Both studies reported an association between persistent villous atrophy and worse BMD than occurred in those subjects whose small bowel histology normalized.^{146,179} Even for patients with normalization of small bowel morphology, 11%–17% of subjects still had osteoporosis of the spine.¹⁴⁶ One large study showed no statistically significant differences between patients who maintained a strict gluten-free diet versus those with a partial gluten-free diet,¹⁴⁰ although small bowel histological correlates were not given.

The duration of prediagnosis symptoms, known diagnosis of celiac disease, or gluten-free diet does not correlate with BMD,^{175–177} although 1 study found a direct correlation between duration of diagnosis and lower BMD.¹⁷³ A history of previous fracture was correlated with lower BMD in 1 study,¹⁸⁰ but was not correlated in another.¹⁷⁵ BMI correlated with BMD in all studies in which it was analyzed.^{175–177,180}

Postmenopausal females had significantly lower BMDs than premenopausal females.^{173,180} In 1 study, postmenopausal females had significantly lower BMDs than controls, whereas premenopausal females had BMDs similar to those of controls.¹⁷⁷ Males had lower BMD T scores than premenopausal females in the 1 study of treated celiac disease in which they were compared.¹⁸⁰

One study reported no correlation with bone biomarkers or 25-OHD and BMD for patients treated with a gluten-free diet,¹⁷⁵ though another study reported that BMD correlated negatively with both serum PTH and 1,25-(OH)₂-vitamin D.¹⁴⁷ Patients who respond to a gluten-free diet have shown lower levels of bone-specific alkaline phosphatase and osteocalcin and higher levels of 25-OHD than those with refractory disease or ongoing villous atrophy.^{150,179}

Longitudinal Changes in Celiac Disease

Longitudinal studies of BMD in patients with untreated celiac disease have not been conducted, for obvious ethical reasons. Studies that measure follow-up BMD in celiac disease patients after initiation of a gluten-free diet (Table 12) reveal that BMD generally increases over time,^{141,148,167,168,170,175,181} although some studies still report a substantial number of patients with osteoporosis after 1–3 years of follow-up.^{151,154,182} Up to 50% of patients may not exhibit increased BMD at 1 year,¹⁶⁴ and even those who do show an increase may have a final BMD still below normal.¹⁸³ The average increase in BMD is approximately 5% in the first year, with a final mean Z score or T score similar to that

Table 10. Cross-Sectional Studies of Bone Density in Adults With Newly Diagnosed, Untreated Celiac Disease

Reference	BMD instrument	Subjects	Prevalence of reduced bone density and definition used	Mean bone density
Molteni ¹⁷⁴	SPA	29 (control)		BMD % of control 88.9% ^a
Bai ¹⁷⁰	DXA	25	Z < -2 Spine; 56% Total body; 56%	Mean Z Spine; -1.9 Total body; -2.2
Caraceni ¹⁵³	SPA	20		BMD % of control 85.1%
Corazza ¹⁴⁸	DXA	20		Median Z Spine; -2.0 Proximal femur; -2.0
Corazza ¹⁴⁹	DXA	24	Z < -2 Spine Symptoms 80% Subclinical 21%	Mean Z Spine Symptoms -2.6 Subclinical -1.3 Mean Z total body -2.1
Corazza ¹⁵²	DPA	17		Mean Z Spine ^a Symptoms -2.5 Subclinical -1.1 Femoral neck ^a Symptoms -2.5 Subclinical -1.1
Di Stefano ¹⁶⁶	DXA	39		
Di Stefano ¹⁶⁹	DXA	16	Z < -2 Spine; 44% Proximal femur; 31%	
Fornari ¹⁴¹	DXA	16	Z < -2 Spine; 44% Total body; 56%	Median Z Spine T body -1.6 -2.4
Gonzalez ¹⁶⁵	DXA	20	Z < -2 spine 70%	Mean Z Spine; -2.5 Total body; -2.9
Keaveny ¹⁵⁰	QCT	19	T < -2.5 36%	Mean T (spine) -1.67
Kemppainen ¹⁴⁶	DXA	28 (control)	T < -2.5 Spine Females 21% Males 63% Femoral neck Females 0% Males 0%	BMD % of control Spine Females 94.3% Males 91.6% Femoral neck Females 94.9% Males 91.7%
Mautalen ¹⁶⁷	DXA	14	Z < -2 Spine; 29% Total body; 36%	Mean Z Spine; -1.3 Total skeleton; -1.5
Mazure ²⁹⁸	DXA	20 (control)	Z < -2 Spine; 61% Total body; 56%	
McFarlane ¹⁸³	DXA	21 (control)	Z < -2 Spine; 43% Femoral neck; 19%	BMD % of control Spine; 80.5% Femoral neck; 84.2%
Meyer ¹⁸⁰	DXA	31	T < -2.5 35%	Mean T Spine; -1.91 Femoral neck; -1.72
Mustalahti ¹⁶⁴	DXA	49		Median T Spine Symptoms -1.1 Subclinical -1.9 Femoral neck Symptoms -0.8 Subclinical -0.9
Sategna-Guidetti ¹⁷¹	DXA	86	T < -2.5 Spine 26%	Mean T Spine; -1.7 Femoral neck; -1.4
Valdimarsson ¹⁴²	DXA	29		Mean Z Spine; -1.12 Total hip; -1.23
Valdimarsson ¹⁵¹	SPA DXA	63 (control)	Z < -2 Spine; 15% Femoral neck; 9% Forearm; 22%	
Valdimarsson ¹⁷²	SPA DXA	105 (control)		Mean Z Spine; -0.72 Total hip; -0.79 Forearm; -0.88
Walters ¹⁷³	DXA	10		Mean Z Spine Females -1.85 Males -0.95 Femoral neck Females -0.89 Males -0.95 Total body Females -1.79 Males -2.24

NOTE. Here "control" refers to studies where a control group was used as a comparison as opposed to DXA software database.

^aP < 0.05 vs. controls.^aP < 0.001 vs. controls.

Table 11. Cross-Sectional Studies of Bone Density in Adults With Celiac Disease on a Gluten-Free Diet

Reference	BMD Instrument	Subjects	Prevalence of reduced bone density and definition used	Mean bone density
Bode ¹⁷⁶	SPA DPA	22		BMD % of control Spine, 87% Forearm, 91%
Corraza ¹⁵²	DPA	14		Mean Z (total body) -1.5
Gonzalez ¹⁶⁵	DXA	12	Z < -2 (spine or total skeleton) 42%	Spine Z, -1.2 Total body Z, -1.2
Keaveny ¹⁵⁰	QCT	24 Remission, 16 Refractory, 8	T < -2.5 Remission, 50% Refractory, 36%	Spine T Remission, -1.83 Refractory, -2.03
Kemppainen ¹⁴⁶	DXA	49 (control)	T < -2.5 Females Spine No remission 57% Remission 17% Femoral neck No remission 29% ^a Remission 0 Males Spine No remission not stated Remission 11% Femoral neck No remission not stated Remission 0 Controls Spine 4% Femoral neck 1%	
Mazure ²⁹⁸	DXA	14 (control)	Z < -2 Spine; 21% Total skeleton; 14%	
McFarlane ¹⁷⁵	DXA	55 (control)	Z < -2 Spine + F neck: 7% Spine or F neck: 20%	
Meyer ¹⁸⁰	DXA	97	T < -2.5 Spine F neck 34% 27%	Mean T Spine, -1.58 Femoral neck, -1.31
Molteni ¹⁷⁴	SPA	22 (control)		BMD % of control 102%
Pistorius ¹⁷⁷	DXA	81 females (control)		BMD % of control Spine, 93.2% ^b Femoral neck, 91.9%
Selby ¹⁴⁷	SPA DXA QCT	35		Spine Z, -0.44 -0.35 by QCT Femoral neck Z, -0.27 Forearm Z, -1.4
Valdimarsson ¹⁷⁹	SPA DXA	13: persistent villous atrophy 17: villous restitution	Z < -2 Forearm Atrophy: 23% Restitution: 0 Femoral neck Atrophy: 15% Restitution: 0	Forearm Z Atrophy, -1.2 Restitution, -0.2 Femoral neck Z Atrophy, -1.1 Restitution, -0.1
Vasquez ¹⁴⁰	DXA	114 (control)		Spine Z Strict GFD -1.2 Partial GFD -1.6 Total body Z Strict GFD -1.0 Partial GFD -0.9
Walters ¹⁷³	DXA	34		Mean Z Spine M -1.5 F -0.18 Femoral neck M -1.83 F -0.05 Total body M -0.42 F +0.27

^aP < 0.05 vs. controls.

^bP < 0.001 vs. controls.

Table 12. Bone Density Results in Adults Followed Longitudinally With Treated Celiac Disease

Reference	BMD Instrument	Subjects	F/U period	Prevalence of reduced bone density and definition used	Mean bone density	Increase/yr by Z-score
Bai ¹⁷⁰	DXA	25	4 yr median		Spine Z; -0.9 Total body Z; -1.1	Median % change in BMD Spine; + 12% ^b Total body; + 7.3% ^b
Caraceni ¹⁵³	SPA	20	1 yr		85.1% controls	No change Change in BMD as % of baseline
Ciacchi ¹⁶⁸	DXA	41	1 yr			Spine; +14.0% Femoral neck; +10.4%
Corazza ¹⁴⁸	DXA	20 (control)	2 yr			Median Change in Z after Spine; +0.7 Proximal femur; +0.65
Fornari ¹⁴¹	DXA	16	3 yr	Z < -2 Spine; 31% Total body; 31%	Spine Z; -1.0 Total body Z; -1.1	
Kemppainen ¹⁸¹	DXA	22	5 yr			Change in BMD as % of baseline Spine Female +2%/yr Male +1%/yr Femoral neck Female +0.5%/yr Male +3.8%/yr Change in BMD as % of baseline
Mautalen ¹⁶⁷	DXA	14	1 yr	Z < -2 Spine; 21% Total body; 21%		Spine; +5% ^a Total body; +5% ^a Change in BMD as % of baseline
McFarlane ¹⁸³	DXA	21	1 yr		Spine; 85.1% controls Femoral neck; 86.7% controls	Change in BMD as % of baseline Spine; +6.6% ^a Femoral neck; + 5.5% ^a
McFarlane ¹⁷⁵	DXA	55 (control)	1 yr			Change in BMD as % of baseline Spine Males; +2.76% Females; +0.25% P < 0.025 Females only Femoral neck Males; +2.41% ^a Females; +0.66%
Sategna-Guidetti ¹⁷¹	DXA	72	1 yr		Spine T: -1.3 Femoral neck T: -1.2 P < 0.0002 for both sites	Change in Z-score Spine; +0.5 Femoral neck; +0.22 P < 0.004 at both sites
Valdimarsson ¹⁵¹	SPA DXA	63 (control)	1 yr	Z < -2 Spine; 8% Femoral; 2% Forearm; 17%	Spine Z; -0.32 Forearm Z; -0.92	Change in Z-score Spine; +0.43 ^a Femoral neck; Not stated Forearm; +0.1 ^a Change in BMD as % of baseline
Valdimarsson ¹⁴²	DXA	28 (control)	1 yr		Spine Z; -0.575 ^b Total hip Z; -0.81 ^b	Spine; +6.6% ^b Total hip; +5.8% ^b
Valdimarsson ¹⁷²	SPA DXA	54 (control)	3 yr		Spine Z; -0.15 Total hip Z; -0.57 Forearm Z; -0.60	Change in Z-score after Spine; -0.57 ^b Total hip; -0.22 ^b Forearm; -0.28 ^b

^aP < 0.05 vs. controls.^bP < 0.001 vs. controls.

specified in the cross-sectional data for treated patients summarized earlier. Two studies have reported a greater increase in axial BMD than appendicular BMD,^{167,168,170} whereas 1 cross-sectional study found the reverse.¹⁴⁷ Based on other skeletal disorders, axial sites would be expected to show greater responsiveness to interventions such as initiation of a gluten-free diet, and site of assessment should be considered when analyzing studies that longitudinally assess changes in bone mass. One study found that the increase in BMD at 1 year did not depend on whether or not a change in small bowel histology occurred,¹⁷¹ whereas another study found that less small bowel mucosal atrophy correlated with higher BMD.¹⁷² Symptoms of malabsorption (e.g., weight loss, diarrhea) do not appear to correlate with BMD response to a gluten-free diet.¹⁵¹

Several studies have addressed changes in BMD in relation to the implementation and duration of a gluten-free diet. Bone disease in celiac patients can be cured in many patients after several years of a gluten-free diet.¹⁸¹ Most of the BMD increase typically occurs within the first year after initiation of a gluten-free diet, with little change seen thereafter.^{181,183} One study reported that the annual increase in BMD correlated inversely with the duration of a gluten-free diet.¹⁷⁵ In fact, at 5 years after initiation of the diet, no correlation between adherence to diet and BMD was seen.¹⁸¹ Increases in fat mass,¹⁶⁷ weight,¹⁸¹ and BMI¹⁴² all correlate with greater increase in BMD. Normalization of calcium absorption may not always translate into normalization of BMD,¹⁸⁴ and calcium and vitamin D supplementation were not additive to a gluten-free diet for increasing BMD in 1 small pilot study.¹⁶⁷ Lower BMD at diagnosis was associated with a larger BMD increase, though some adults with prolonged duration of disease will still have reduced BMD despite a gluten-free diet.^{168,170,172}

Changes in BMD have been studied in relation to age and gender. Premenopausal females had significantly greater remineralization than postmenopausal females.^{141,168,170} Younger age at diagnosis^{151,168,170} correlated with a greater BMD response, and earlier age at menopause correlated with greater annual BMD loss.¹⁷⁵ In some other studies, neither age nor menopausal status affected BMD.^{167,181} Males had higher BMDs than females in 1 study,¹⁶⁸ but less than females in another.¹⁷⁵

Treatment for celiac disease decreases levels of serum PTH, 1,25(OH)₂-vitamin D, and markers of bone turnover. To date, only limited data have correlated serological measures with changes in BMD. Patients with secondary hyperparathyroidism at baseline did not increase their BMD to normal levels by 3 years, whereas those

whose serum PTH was normal at baseline achieved normal BMD.¹⁷² One study reported a correlation between bone-specific alkaline phosphatase and an increase in femoral neck BMD.¹⁸¹ Baseline levels of carboxy-terminal propeptide of type I collagen have been reported to show the best correlation with increases in BMD.¹⁴⁸

Prevalence and Incidence of Fracture in Celiac Disease

One set of population-based data derives from a random sample ($n = 1064$) of New Zealand adults selected from electoral rolls, of whom 13 (1.2%) proved to have celiac disease.¹⁸⁵ Five of 12 patients (42%) reported past fractures. Unfortunately, the fracture rate in the general nonceliac population of New Zealand was not stated. A more recent population-based report from Denmark that captured hospital discharge abstracts for patients previously hospitalized with celiac disease suggested no increased risk of sustaining a fracture.¹³⁵ This study's design has several flaws, however. First, we must accept, as reported, that all new subjects with celiac disease before 1995 were hospitalized for diagnosis. Second, in this study of 1071 celiac disease subjects, case validation was done on only a random sample of 9, and the validity rate was 78%. Finally, the study relied only on hospital-based fracture diagnoses, potentially missing fractures of the spine, forearm, or rib that did not require hospitalization. With these caveats in mind, these authors reported no increased risk of fracture requiring hospitalization in celiac disease patients.

In a study of newly diagnosed celiac patients ($n = 25$) followed for a median of 47 months after initiation of a gluten-free diet, no fractures were seen.¹⁷⁰ Another small study of 30 patients with treated celiac disease showed no difference in fracture prevalence from controls.¹⁷⁹ In a group of 75 celiac patients evaluated, 21% had a past fracture history that was significantly greater than that of age- and sex-matched controls ($P < 0.0004$).¹⁵⁴ Patients with a fracture history did not have a significantly different mean T score than those with no fracture history. Thus, bone density may not be a strong predictor of fractures in this disorder.

In the largest fracture study of 165 patients with well-established celiac disease, 41% of patients had a history of past fractures, compared with 8% of age- and sex-matched controls (odds ratio, 3.5; 95% CI, 1.8–7.2, $P < 0.0001$).¹⁴⁰ In this group, 80% of fractures occurred before diagnosis or in noncompliant patients, whereas only 7% of fractures occurred in patients compliant with a gluten-free diet. The most common fracture site was the wrist. Patients with celiac disease and fractures were diagnosed later in life ($P = 0.06$) and remained undiag-

nosed for longer ($P < 0.05$) compared with patients without fractures. Kaplan–Meier survival analysis estimated fracture rates by age 70 of 43% in celiac disease patients but of only 20% in controls ($P < 0.0001$). Gender, BMI, or BMD (as measured by DXA) did not correlate with fractures. These data underscore that BMD is only part of the story in explaining the increased fracture risk in celiac disease; other factors, including older age, longer symptom duration, and vitamin D deficiency, need to be considered.

Summary of Bone Disease in Celiac Disease

- Osteoporosis is more common in patients with untreated celiac disease than the general population (level A evidence).
- Vitamin D deficiency is common in celiac disease, but the actual prevalence of osteomalacia in celiac disease is unknown (level B evidence).
- Among newly diagnosed patients, the prevalence of osteoporosis using DXA is approximately 28% at the spine and 15% at the hip (level B evidence).
- Among adults with a known diagnosis of celiac disease treated with a gluten-free diet, the prevalence of osteoporosis using DXA is still increased compared with controls (level B evidence).
- At diagnosis of celiac disease, children and adults have similarly low BMD; however, children are more likely to have fully restored bone mass after a gluten-free diet than adults (level B evidence).
- Patients with celiac disease increase their BMD after initiating a gluten-free diet (level A evidence). The greatest increase occurs in the first year (average of 5%), but final BMD remains below average, with a final Z score of approximately -1.0 for the spine and -0.5 for the hip (level B evidence).
- BMI consistently correlates with BMD at both diagnosis and follow-up (level A evidence).
- Axial bone mass increases more than appendicular mass during gluten-free diet therapy (level B evidence).
- Subjects with asymptomatic celiac disease are at increased risk for osteoporosis (level B evidence).
- The high prevalence of osteoporosis among patients with celiac disease, including asymptomatic subjects, provides a rationale for instituting gluten-free diet therapy for those who do not have overt malabsorption (level D evidence).
- Males and females are at equal risk for osteoporosis, and postmenopausal females are at the greatest risk (level B evidence).
- Typical serological abnormalities that correlate with diminished BMD include elevated PTH and $1,25(\text{OH})_2$ -vitamin D levels and diminished 25-OHD level. Levels of 25-OHD, calcium, and possibly PTH should be measured in patients with newly diagnosed celiac disease and in patients whose elevated levels warrant increased attention to bone health (level B evidence).
- The precise incidence of fractures in celiac disease is unknown but is estimated to be 40% by age 70 years, more than twice the expected incidence for the general population (level B evidence).
- The value of calcaneal ultrasound as a screening test for fracture risk in celiac disease is unknown (level D evidence).
- DXA is a marker of diminished bone mass but is not a proven marker of fracture risk in patients with celiac disease (level B evidence).
- DXA scans are likely unnecessary in newly diagnosed uncomplicated pediatric celiac disease, but should be considered for adults with newly diagnosed celiac disease 1 year after initiation of a gluten-free diet, to allow for stabilization of bone density (level D evidence).

Postgastrectomy

Introduction

The incidence of peptic ulcer disease has been decreasing simultaneously with improved medical therapy for this condition, including *Helicobacter pylori* and advanced acid-neutralizing drugs.¹⁸⁶ This has led to such a reduction in peptic ulcer surgery that postgastrectomy bone disease will soon be a rarity (excluding gastric cancer survivors). However, a large cadre of patients who have undergone partial or total gastrectomy remains, and these patients should still be considered at risk for postgastrectomy bone disease.

First identified more than 60 years ago, postgastrectomy bone disease may arise secondary to total gastrectomy or partial gastrectomy.¹⁸⁷ The exact nature of the bone defect is unknown, although both osteoporosis and osteomalacia have been found. Males predominate by a factor of at least 3 in studies that include both genders, and there are an additional 11 male-only studies,^{188–198} compared with just 1 female-only study.¹⁹⁹

Partial gastrectomy was once considered the most common cause of osteomalacia in Europe.²⁰⁰ The recent Mediterranean Osteoporosis Study evaluated hip fracture rates among 730 males over age 50 years from 6 countries in southern Europe.²⁰¹ Compared with age-matched controls without hip fracture, antiepileptic agent therapy

and senile dementia were the variables most strongly correlated with hip fracture risk. A history of past gastrectomy was prevalent in 3.6% of hip fracture patients; this equated to a RR of 1.79 (95% CI, 1.13–2.85).

A group at the University College of London assembled a cohort of postgastrectomy patients who underwent surgery between 1955 and 1960, including 186 who underwent Billroth II surgery and 41 who underwent Billroth I surgery.²⁰² In follow-up done after an average of 20 years, this group identified iron deficiency as the most common metabolic defect postgastrectomy, followed by vitamin B₁₂ deficiency and metabolic bone disease.²⁰²

A more recent study conducted through advertising in the Northwestern U.S. in the 1990s involved the recruitment of 355 males over age 60 from 3 rural communities.²⁰³ Seventeen had a previous total gastrectomy for gastric cancer. After adjustment for age and weight, previous gastrectomy was found to be associated with a reduced BMD as measured by DXA at the total hip (−9%), spine (−14.1%), and distal radius (−9.9%). Overall, gastrectomy accounted for 2% of the BMD variance at the femoral neck and distal radius and for 4% of the BMD variance at the spine ($P < 0.05$). Thus, even in more recent studies, gastrectomy remains a significant contributor to bone disease.

Pathogenesis of Postgastrectomy Bone Disease

The exact pathogenesis of the bone defect in postgastrectomy is unknown. Removal of the gastric antrum with anastomosis to the duodenum (Billroth I) or with anastomosis to a bypassed segment of duodenum or jejunum (Billroth II or Polya gastrectomy) alters normal GI physiology. Calcium is absorbed primarily in the duodenum, and calcium malabsorption can have several possible causes, including bypass of duodenal surface area due to intestinal “hurry” from gastric dumping or formation of insoluble calcium soaps due to fat malabsorption. However, calcium malabsorption has not proven to be a major problem for postgastrectomy patients. Serum calcium levels are often normal,^{188,190,191,193–195,197,204–207} although mean levels were found to be lower than those in controls in 3 studies^{198,208,209} and also in 1 study done only in males.²¹⁰ However, on average, these lower levels still fall within the normal range. In 1 study, 7.3% of a sample of 342 postgastrectomy patients had subnormal serum calcium levels, compared with only 0.5% of controls ($P < 0.05$).²¹¹ Similarly, in 10 of 12 studies in which it was assessed, serum phosphate levels were similar in postgastrectomy patients and controls.^{188–191,193,194,198,204,206,207} In some instances serum calcium and serum phosphate may

be maintained at the expense of bone mass. Bone-related hormones, such as PTH, likely play an important role in this process, although phosphate levels are generally normal or slightly reduced in the setting of secondary hyperparathyroidism.

Patients with partial or total gastrectomy may develop steatorrhea (and possibly also intestinal hurry), leading to malabsorption of vitamin D.¹⁸⁷ However, studies of vitamin D absorption in postgastrectomy patients reported mild vitamin D malabsorption at worst.²⁰⁰ Later studies have confirmed normal intestinal absorption of vitamin D in postgastrectomy patients, although patients with postgastrectomy steatorrhea had abnormal vitamin D absorption.²¹² Postgastrectomy patients may alter their diet,¹⁸⁷ and reduced serum 25-OHD level may in part reflect reduced dietary intake of vitamin D.¹⁸⁷

In postgastrectomy patients, 25-OHD levels were found to lie within the normal range in 5 studies^{191,193,205,206,208} but were subnormal in 4 others.^{189,190,197,209} The discrepancies in these results are not explained by differences in patient selection or type of gastric surgery. However, studies with subnormal 25-OHD levels generally had longer duration postsurgery. Two studies have reported normal 25-OHD levels after Billroth II surgery, but subnormal levels after Billroth I surgery.^{188,210} 1,25(OH)₂-vitamin D levels may be elevated (as a result of low phosphate and high PTH)^{189,209} or normal.^{193,206,210} Most studies report PTH levels within the normal range,^{189–191,193,194,210} although some have found PTH to be elevated.^{188,208} One study found elevations in patients post-Billroth II but not in patients post-Billroth I.¹⁸⁸ Secondary hyperparathyroidism, elevated 1,25(OH)₂-vitamin D level, and enhanced 25-OHD clearance can be reversed with oral calcium supplementation, but higher doses of vitamin D may be necessary.²¹³

Protein metabolism has an obvious role in the formation of the collagen matrix of bone. Impaired protein nutrition secondary to reduced intake may also play a role in postgastrectomy bone disease.²¹⁴ Generally, weight loss and nutrition stabilize over time postgastrectomy.

The role of gastrin in mediating bone disease has been controversial, because subjects with partial gastrectomies (hypergastrinemia) and those with total gastrectomies (hypogastrinemia) both may experience bone disease. One study has suggested that a fundal-derived factor, termed “gastrocalcin,” may shift calcium into bone in a gastrin-dependent manner.²¹⁵ This mechanism has yet to be fully proven, and animal models of partial gastrec-

tomy have raised questions as to the existence of this factor.^{216,217}

One study that evaluated the serum calcitonin level induced by a meal in postgastrectomy patients found it to be significantly reduced in post-Billroth I ($n = 10$) and post-Billroth II ($n = 10$) patients.¹⁸⁸ Calcitonin has osteoclast-inhibiting effects, and a blunting of this effect may favor bone resorption.

The abolition of gastric acid does not appear to be an important factor in the development of postgastrectomy bone disease; gastric acidity does not seem crucial to calcium absorption.²¹⁸ One study by DXA using histamine-2 receptor antagonists reported no difference in the rates of osteoporosis in ulcer patients and healthy controls.²¹⁹ This study did not report the degree of acid suppression, however, and similar studies using more complete acid neutralization with proton pump inhibitors are lacking. Three studies have shown no difference in BMD in postvagotomy patients compared with controls,^{189,198,220} but 2 of these studies had less than 5 years' average follow-up postoperatively.^{189,198}

Animal data. Several animal studies, most of which have been conducted in rats, have evaluated postgastrectomy bone disease.^{215,220–229} These animal models have confirmed the important role of the stomach (particularly, but not exclusively, the fundus) in bone health and confirm that loss of acid is not likely an important factor in postgastrectomy bone disease. An interesting study of bone mechanics in a rat model suggested that a decrease in the number of bone trabeculae occurred postgastrectomy.²²¹ Large areas without trabeculae were seen, and the direction of the trabecular network was dramatically changed. Aspects of the mechanics required to cause fracture (i.e., bending moment and energy absorption) were decreased by 30%. Of interest, was that DXA measures of BMD correlated better with bone strength in the femoral shaft ($r = 0.68–0.91$, $P < 0.001$) compared with the femoral neck ($r = 0.53–0.58$, $P < 0.05$), the site more often measured in humans.

Bone histomorphometry in postgastrectomy bone disease. A study of 11 postgastrectomy patients found that all had normal osteoid volume, but with a reduced percentage of osteoid and an extent of calcification front correlating with an elevated SAP level.²²² This lesion was shown to be responsive to vitamin D administration and thus suggestive of subclinical osteomalacia.

In a large study of 80 postgastrectomy patients who underwent bone biopsy including tetracycline labeling, 32.5% had an increased osteoid seam width, in comparison with none of the 9 peptic ulcer disease controls.²¹¹

The 80 patients who underwent bone biopsy were selected from a larger postgastrectomy cohort of 342 based on serological and/or radiological abnormalities. Thus, in this group with a mean postoperative follow-up period of 7.4 years, the possible prevalence of osteomalacia ranged from 7.6% to 32.5%.

Bone biopsy (without tetracycline labeling) was performed in 36 patients after gastric surgery from 3 to 9 years (Billroth I, $n = 10$; Billroth II, $n = 19$; vagotomy and pyloroplasty, $n = 7$).²²³ This group volunteered from an initial cohort of 125 patients who had undergone gastric surgery. Compared with a control group, gastric surgery patients had a lower total bone index and an increased osteoid index for both males ($P < 0.001$) and females ($P < 0.02$). Males and females both had an increased demineralization index ($P < 0.01$). Fifteen of 36 (14%) had an osteoid index > 2 SD from the normal mean, and 6 of 36 (17%) had a total bone index < 2 SD from the normal mean. Five of 36 (15%) had both an increased osteoid index and a decreased total bone index. Thus the prevalence of osteomalacia was at most 42% (15 of 36) and at least 12% (15 of 125), even though the diagnosis was not based on tetracycline labeling. There was no difference in incidence of osteomalacia based on surgical type, including vagotomy and pyloroplasty.

A more recent study evaluated bone biopsy with tetracycline labeling in 45 postgastrectomy patients (Billroth I, $n = 24$; Billroth II, $n = 39$; total gastrectomy, $n = 5$) and reported significantly lower trabecular bone volume ($P < 0.01$) and significantly greater osteoid thickness ($P < 0.01$) and mineralization lag time ($P < 0.01$) compared with controls.²⁰⁹ In this study, 24%–62% of patients had some evidence of increased bone remodeling. Using a conventional definition of osteomalacia (mineralization lag time and osteoid thickness that deviated by > 2 SD from normal), 8 of 45 patients (18%) met these diagnostic criteria. Most of these 45 patients had normal levels of serum calcium, alkaline phosphatase, and 25-OHD, suggesting that older studies that relied on these measures to exclude osteomalacia without biopsy confirmation in those with normal levels may have underestimated the prevalence of osteomalacia. Age was the strongest determinant of a mineralization defect on multivariate analysis ($P < 0.01$), followed by serum 25-OHD ($P < 0.02$). Because postgastrectomy patients had similar dietary intakes of vitamin D as controls, it was suggested that the vitamin D defect was malabsorptive and that all postgastrectomy patients should receive vitamin D prophylaxis.²⁰⁹ Clearly, with varying degrees of malabsorption, large amounts of oral or in some instances parenteral vitamin D might be necessary; care-

ful monitoring of 25-OHD, serum calcium, and urinary calcium levels is also necessary in such instances.

Bone biopsy without tetracycline labeling was performed on 36 postgastrectomy subjects who had undergone surgery within 7 years.²⁰⁵ There was a significant increase in osteoid seam width among gastrectomy patients compared with controls, although the osteoid seam percentage was within normal limits. Furthermore, patients actually had evidence of increased trabecular bone and no difference in resorption surface compared with controls.

Thirty-eight patients of the University College of London cohort ($n = 227$) underwent bone biopsy. The patients selected for biopsy had either elevated SAP level, diminished bone density on metacarpal X-ray, or bone pain with muscle weakness.^{224,225} Four of 38 (10%) reportedly had osteomalacia, and 6 others (16%) had biopsy results suggestive, but not diagnostic, for osteomalacia, although tetracycline labeling does not appear to have been performed on any of the biopsy samples. Thus, at most 26% of the selected cases had osteomalacia, representing 4% of the entire cohort (10 of 227). An additional 5 (2%) had probable osteomalacia, based on elevated SAP level that responded to oral vitamin D and calcium administration. The prevalence of biopsy-proven osteomalacia was more common among females (11%) than males (2%).

A study of postgastrectomy patients who sustained vertebral fractures found that 7 of 25 (28%) underwent bone biopsy with tetracycline labeling. None of these showed evidence of osteomalacia.¹⁹⁷ In 16 post-Billroth II gastrectomy patients with a mean of 1.7 fractures/patient, bone biopsy revealed no abnormalities on tetracycline labeling, so osteomalacia could not be confirmed on any biopsy sample.¹⁹² However, these patients had significantly higher osteoid volumes and greater total osteoid surface than controls. Thus, despite the fractures, low BMD, and histomorphometric changes found in these 2 studies, osteomalacia could not be confirmed in the patients with overt bone disease.

Osteomalacia or Osteoporosis?

As described previously, only 2 studies in the literature have used tetracycline labeling, the gold standard for diagnosing osteomalacia.^{209,211} These studies suggested a maximal prevalence rate of 32.5%, but realistic rates are likely closer to 10%–20%. A study from the 1960s suggested the importance of osteomalacia postgastrectomy in patients with compatible bone histomorphometry changes and also in those with normal bone histology and abnormal serum biochemistry (i.e., alkaline phosphatase and vitamin D metabolites) with a

serological response to vitamin D administration.²⁰⁰ Another study from the same era using similar diagnostic criteria (i.e., low serum calcium, low serum phosphate, and elevated SAP with a response to vitamin D administration) was conducted on 1228 patients postgastrectomy.²²⁶ Six of these (0.4%) had osteomalacia (defined as excessive osteoid on bone biopsy), which included 3% of females and <1% for males. It is not clear how many of the 1228 underwent biopsy, but this was the first study from this earlier era suggesting that postgastrectomy osteomalacia was uncommon. Others have not found a definite correlation between plasma vitamin D level and subclinical osteomalacia,²⁰² and early histological changes of osteomalacia may be evident in the presence of normal plasma alkaline phosphatase.²²⁷

The definition of osteomalacia or osteoporosis used in each study is critical, particularly in defining osteomalacia. In the University College of London group's cohort results for the 1988 follow-up,²⁰² the most common metabolic defect identified was iron deficiency anemia (in 92% of females and 68% of males), followed by vitamin B₁₂ deficiency (in 83% of females and 70% of males) and osteomalacia (in 33% of females but in no males). The study definition of osteomalacia was based on serological evidence (elevated alkaline phosphatase level [with isoenzyme measurements after 1974] in the absence of Paget's disease, liver disease, metastases, or recent fractures) and not on biopsy. In suspected cases, a therapeutic trial of oral calcium and vitamin D was given, and osteomalacia was considered present if the SAP level subsequently normalized. Vitamin D deficiency occurred in 7.5% of Billroth II patients and 7.3% of Billroth I patients and was more prevalent in females (19%) than males (4%). Metacarpal X-rays of the right hand at the 1982 follow-up revealed osteoporosis in 86% of females and 22% of males. This study supported the finding that osteoporosis was more common than osteomalacia; however, the study definition of osteomalacia was "soft," and hence the magnitude of the incidence of osteomalacia is unclear.

Studies using tetracycline labeling for diagnosing osteomalacia are somewhat lacking in postgastrectomy bone disease. Most data point to the fact that osteomalacia represents a small portion of postgastrectomy bone disease.^{209,211,226} The paucity of large-scale studies of bone biopsies with tetracycline labeling makes it impossible to accurately define the incidence of postgastrectomy osteomalacia.

Prevalence of Bone Disease Postgastrectomy

Osteoporosis in excess of normal aging may be more prevalent in postgastrectomy patients,^{202,214} but

the data quantifying the magnitude of this reduced BMD are discordant (Table 13). Thirteen studies reported that postgastrectomy patients had significantly lower BMD than controls, whereas 4 studies reported no difference. (In 4 other studies, statistical comparison with controls was not done.) There have been only 6 studies done using DXA; 4 of these reported the prevalence of spinal osteoporosis (T score < -2.5) as 30% ($n = 10$),¹⁹³ 37% ($n = 59$),²²⁸ 22% ($n = 18$),²²⁹ and 30% ($n = 26$).²⁰⁶ Femoral neck osteoporosis (T-score < -2.5) was present in 10%¹⁹³ and 61%.²²⁹ These rates seem high, but they must be interpreted with caution in view of the absence of age-matched control data. These patients were mostly elderly, and matched controls would also be expected to have significant rates of osteoporosis in the absence of earlier gastric surgery. A pooled analysis of studies revealed a mean lumbar Z score of -1.09 and a mean hip Z score of -0.56 .

A number of variables have been assessed in an attempt to identify factors that would predispose to reduced BMD postgastrectomy. Post-Billroth II surgery had significantly lower BMD than post-Billroth I surgery in 2 studies,^{188,197} but most studies found similar BMDs in these 2 forms of partial gastrectomy.^{189,195,198,204,211,230-232} Three studies reported no difference in BMD between total gastrectomy and partial gastrectomy.^{194,204,230}

Increased time from surgery was significantly correlated with lower BMD in 2 studies,^{204,233} with a similar trend in a third¹⁹⁸ but not in 2 others.^{194,229} Eight studies with less than 10 years' follow-up postgastrectomy showed a significant reduction in BMD,^{191,192,194,196,198,229,231,234a} but 4 such studies did not.^{189,205-207} All studies with 10-20 years' follow-up showed significant reductions in BMD,^{188,197,220,231} as did 2 studies with greater than 20 years' follow-up.^{190,197} The results of the latter 2 long-term studies are not unexpected, because 20 years of follow-up is also associated with 20 years of aging—a process associated with obligatory BMD losses. Osteopenia should be considered in patients at any time postgastrectomy, particularly beyond 10 years from the time of surgery. The surgical indication (e.g., neoplasia vs. peptic disease) did not correlate with ultimate BMD in the 1 study in which this was assessed.²³⁰

Importantly, BMD correlated directly with body weight or BMI in 2 studies^{193,197} but not in a third study.¹⁹¹ Greater reductions in BMD were seen in older subjects^{204,228,234a} and in females,^{228,231,233} although no gender effect was seen when BMD was expressed as percentage of age- and sex-matched controls.^{234a} Although postgastrectomy patients may be more likely to be smokers than age-matched controls,¹⁹⁵ smoking status

did not correlate with BMD.²¹⁰ Similarly, no correlation between alcohol use and BMD was seen.²¹⁰

Serum measures have been assessed in relation to BMD. SAP is often used as a measure of potential bone disorders. In early studies done before isoenzyme measurements or rigorous searches for abnormal liver enzymes were available, some elevated reports of elevated alkaline phosphatase level may not have derived from bone. In a study from 1971, Paget's disease was ruled out as an explanation for the elevated alkaline phosphatase level, but isoenzymes were not measured, and the method for assessing liver status was not reported.²¹¹ In another study, alkaline phosphatase levels were directly correlated with γ -glutamyltransferase levels, raising the possibility that alkaline phosphatase was more hepatic than bone.¹⁹⁷ With these caveats in mind, elevated mean SAP level was reported in 7 of 14 studies.^{188-191,193,194,197,198,204,205,208-211} One study found an elevated mean SAP level only in post-Billroth II patients, not in post-Billroth I patients.¹⁹⁵ SAP level was elevated over preoperative levels in 50 patients, but not in comparison to normal controls.²⁰⁷ Some studies reported that BMD was inversely related with SAP^{189,193,204,229,230} and 1,25(OH)₂-vitamin D,^{188,189,192} and directly related with 25-OHD,^{192,220} but other studies found no significant correlations.

Fracture Prevalence and Incidence in Postgastrectomy States

A population-based study from Olmsted County,^{234b} assessed 438 subjects who underwent peptic ulcer surgery between 1956 and 1985 with an average follow-up of 15.6 years. This surgery included Billroth I ($n = 78$), Billroth II ($n = 132$), drainage procedures including gastroenterostomy and pyloroplasty ($n = 146$), and other procedures ($n = 82$). At 30 years postoperation, the estimated incidence of hip fracture was 25% with an RR of 2.5 (95% CI, 1.9-3.3), the estimated incidence of vertebral fracture was 41% with an RR of 4.7 (95% CI, 3.8-5.7), and the estimated incidence of forearm fracture was 20% with an RR of 2.2 (95% CI, 1.5-3.1). The cumulative incidence of any fracture at 30 years was 72% in females and 48% in males ($P < 0.001$). Fracture risk was not related to smoking, alcohol intake, or BMI. Among those operated on for peptic ulcer disease, the cumulative incidence of any fracture at 30 years was 58%. No relationship was found between fractures and the premorbid diagnosis or the type of gastric surgery, but other factors proved to have significant association with fracture risk. Vertebral fractures had an increased risk with advancing age, with a hazard ratio (HR) of 1.8 per 10 years (95% CI, 1.3-2.5). An increased risk

Table 13. Cross-Sectional Studies of Bone Density in Adults Postgastrectomy

Reference	BMD instrument	Subjects	Follow-up period (mean)	Mean bone density
Adachi ²²⁸	DXA	Distal gast n = 49 Total n = 10	16 yrs	BMD % controls 88%
Aukee ²³²	SPA	Control not stated Bl n = 36 BII n = 60 Control n = 30	Bl: 3.3–8.5 yrs ^a BII: 15–18 yrs	BMD % controls <i>P</i> value vs. controls M BI: 97.6% NS BII: 88% ^b <0.001 F BI: 89.2% ^b <0.001 BII: 89.6% ^b <0.001 BMD% controls <i>P</i> value vs. controls
Blichert-Taft ¹⁹⁸	SPA	Bl n = 47 BII n = 39 Vagotomy n = 67 Control n = 54	Bl: 5.3 yrs BII: 4.6 yrs Vagotomy: 4.8 yrs	Bl: 92.2% ^b <0.001 BII: 93.3% ^a <0.05 Vagotomy 95.3% NS Spine BMD% controls Bl: 96.3% BII: 88.9% ^a Mean Z Spine; -0.83 ^a Femoral neck; -1.54 ^a Mean Z-score Spine; -0.52 Distal radius; -0.37 Radius; -0.37 Heel; +0.14 BMD % controls At resection 99.3% 5–7 yrs post-op 100% Microdensitometry >3 Postgast: 53% Vagotomy: 40%
Filipponi ¹⁸⁸	DPA	Bl n = 10 BII n = 10 Control n = 16	Bl: 12.7 yrs BII: 13.5 yrs	Bl: 96.3% BII: 88.9% ^a
Heiskanen ²²⁹	DXA	Total gast n = 18 Control n = 46	6 yrs	Mean Z Spine; -0.83 ^a Femoral neck; -1.54 ^a Mean Z-score Spine; -0.52 Distal radius; -0.37 Radius; -0.37 Heel; +0.14 BMD % controls At resection 99.3% 5–7 yrs post-op 100% Microdensitometry >3 Postgast: 53% Vagotomy: 40%
Hirano ¹⁹⁹	DXA pDXA pQCT	Partial gast n = 15 Total gast n = 5 Control n = 126		Mean Z Spine; -0.52 Distal radius; -0.37 Radius; -0.37 Heel; +0.14 BMD % controls At resection 99.3% 5–7 yrs post-op 100% Microdensitometry >3 Postgast: 53% Vagotomy: 40%
Hoikka ²⁰⁵	SPA	Bl n = 42 Control none	6 yrs (median)	Mean Z Spine; -0.52 Distal radius; -0.37 Radius; -0.37 Heel; +0.14 BMD % controls At resection 99.3% 5–7 yrs post-op 100% Microdensitometry >3 Postgast: 53% Vagotomy: 40%
Imamura ²⁰⁴	SPA Microdensitometry	Bl n = 14 BII n = 13 Total n = 7 Prox gast n = 5 Other n = 11 Vagotomy n = 10	Bl: 7 yrs BII: 8 yrs Total: 7 yrs Prox gast: 6 yrs Other: 17 yrs Vagotomy: 10 yrs	Mean Z Spine; -0.52 Distal radius; -0.37 Radius; -0.37 Heel; +0.14 BMD % controls At resection 99.3% 5–7 yrs post-op 100% Microdensitometry >3 Postgast: 53% Vagotomy: 40%
Inoue ¹⁹⁴	DXA	Control not stated Within 5 yrs post-op Bl n = 24 BII n = 8 Total n = 2 6–10 yrs post-op Bl n = 8 Total n = 3 Control n = 115 BII n = 16 Control n = 24	Within 5 yrs and 6–10 yrs	BMD % controls Spine Within 5 yrs 87.5% ^a 6–10 yrs post op 87.5% ^a
Klein ¹⁹²	SPA QCT	Bl n = 15 Control n = 15 Total gast n = 26 Control: company data	8.9 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Kwon ¹⁹¹	QCT	Bl n = 15 Control n = 15 Total gast n = 26 Control: company data	9.4 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Leidman ²⁰⁶	DXA	Bl n = 15 Control n = 15 Total gast n = 26 Control: company data	5 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Marcinowska ²²⁰	DXA	Bl n = 20 V+P n = 22 Post chole n = 20	Bl: 10 yrs V+P: 9 yrs Post chole: 10 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Mellstrom ¹⁹⁷	DPA	Bl n = 26 BII n = 103 Control n = 216 Bl n = 70 Total n = 28	28.5 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Nihei ²³⁴	QCT	Bl n = 15 BII n = 19 Vagotomy n = 23 Control n = 74 Bl n = 31 BII n = 28 Total n = 39 Control n = 151	Bl: 8.8 yrs BII: 10.4 yrs Vagotomy: 4.3 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Nilas ¹⁸⁹	SPA	Bl n = 15 BII n = 19 Vagotomy n = 23 Control n = 74 Bl n = 31 BII n = 28 Total n = 39 Control n = 151	Bl: 8.8 yrs BII: 10.4 yrs Vagotomy: 4.3 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Nishimura ²³¹	SPA	Bl n = 15 BII n = 19 Vagotomy n = 23 Control n = 74 Bl n = 31 BII n = 28 Total n = 39 Control n = 151	Bl M: 10.5 yrs Bl F: 12.3 yrs BII M: 13.8 yrs BII F: 15.6 yrs Total BI type: M: 6.2 yrs F: 5.4 yrs Total BI type: M: 9.1 yrs F: 8.3 yrs	BMD % controls Prox radius: 96.3% Dist radius: 90.6% Spine: 72.2% ^a BMD % controls 82.1% ^a Mean T Spine: 0 Femoral neck; -0.21 Total body; -0.51 BMD % controls Spine Bl 80% Post V+P 94% Post chole 95% Femoral neck Bl 94% Post V+P 100% Post chole 98% Heel BMD % controls Bl: 92.4% BII: 80.5% ^a BMD % controls Within 6 mos op: 92.6% 6–12 mos post-op: 79.6% 12–24 mos post-op: 70.5% ^a BMD % controls <i>P</i> value vs. controls
Paakinen ²⁰⁷	SPA	Bl n = 50 Control n = 50	3.4 yrs	BMD % controls M: 98.7% F: 100%
Resch ¹⁹⁰	SPA QCT	Bl n = 15 Control n = 19	23 yrs	BMD % controls SPA: 92.3% QCT: 80.9% ^a Mean Z Spine; -1.44 Femoral neck; -0.82 BMD % controls <i>P</i> value vs. controls 87.8% × control ^a <i>P</i> < 0.01 BMD % controls 13.4% ^a Mean Z Bl: -0.93 BII: -0.71 Total gast: -0.78 Grade 2 vertebral deformity Bl: 22% BII: 33% Total gast: 69%
Schniedl ¹⁹³	DXA	Total gast n = 11 Control: company data	8.9 yrs	BMD % controls M: 98.7% F: 100%
Tougaard ²⁰⁸	SPA	BII n = 27 Control not stated Total n = 17	13 yrs	BMD % controls SPA: 92.3% QCT: 80.9% ^a Mean Z Spine; -1.44 Femoral neck; -0.82 BMD % controls <i>P</i> value vs. controls 87.8% × control ^a <i>P</i> < 0.01 BMD % controls 13.4% ^a Mean Z Bl: -0.93 BII: -0.71 Total gast: -0.78 Grade 2 vertebral deformity Bl: 22% BII: 33% Total gast: 69%
Wetschler ¹⁹⁶	DPA	Control: company data Total n = 17	3 yrs	BMD % controls 13.4% ^a Mean Z Bl: -0.93 BII: -0.71 Total gast: -0.78 Grade 2 vertebral deformity Bl: 22% BII: 33% Total gast: 69%
Zittel ²³⁰	QCT routine x-ray	Bl n = 19 BII n = 12 Total n = 18	Bl: 13 yrs BII: 12 yrs Total: 18 yrs	BMD % controls 13.4% ^a Mean Z Bl: -0.93 BII: -0.71 Total gast: -0.78 Grade 2 vertebral deformity Bl: 22% BII: 33% Total gast: 69%

^a*P* < 0.05 controls.^b*P* < 0.001 vs. controls.^cMicrodensitometry >3: a score >3 is considered to equate with greater than 2 standard deviations from the normal mean and qualitatively slight changes but pathologically thin bone. Bl, Billroth I; BII, Billroth II; V+P, vagotomy and pyloroplasty; Gast, gastrectomy (Distal gast is distal gastrectomy when exact type is not stated); post chole, post cholecystectomy.

was also seen in females (HR, 1.8; 95% CI, 1.3–2.5), corticosteroid users (HR, 2.3; 95% CI, 1.0–5.2), and those receiving chronic anticoagulation therapy (HR, 2.3; 95% CI, 1.1–4.6). A notable finding was that an earlier Billroth II procedure proved protective for overall fracture incidence (HR, 0.5; 95% CI, 0.3–0.9); however, there was an increased risk of vertebral fractures (HR, 3.6; 95% CI, 2.4–5.4). For hip fractures, an increased risk was found with age (HR, 2.7 per 10 years; 95% CI, 2.1–3.5), corticosteroid use (HR, 5.8; 95% CI, 2.2–15.3), and anticonvulsant use (HR, 4.6; 95% CI, 1.8–12.0), whereas a previous Billroth I procedure exerted a weak protective effect (HR, 0.9; 95% CI, 0.8–0.96). For distal forearm fractures, there was an increased risk for females (HR, 4.7; 95% CI, 2.2–10.1) and chronic anticoagulant use (HR, 2.8; 95% CI, 1.1–7.3). The authors of the foregoing study concluded that the postgastrectomy population of 1952–1985 had independent risk factors for bone disease and increased fracture risk, which may be related to specific patient characteristics rather than to the adverse effects of the surgical procedure per se. Regardless, previous gastric surgery was a marker for bone disease and, most importantly, for fractures, and thus these patients should be followed closely for this potential complication.

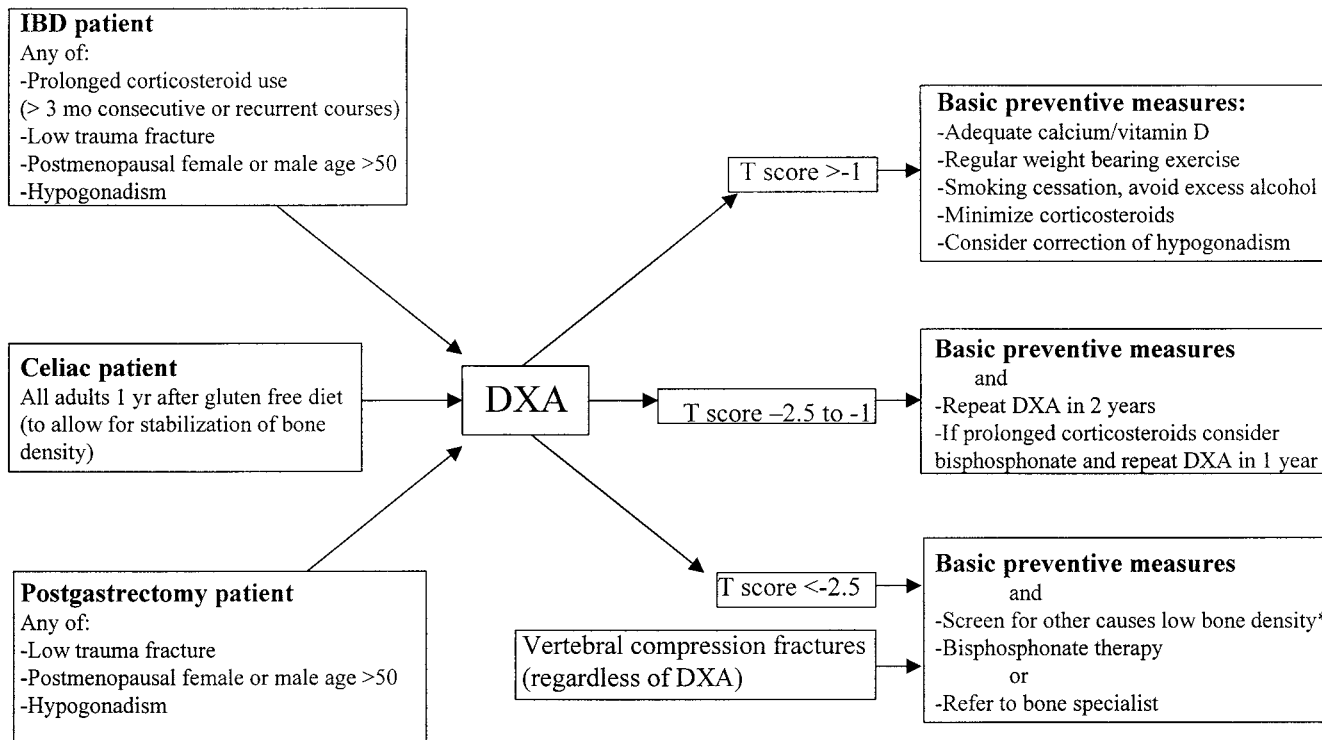
Another large study was conducted in 549 Swedish males who underwent Billroth II gastrectomy during 1948–1952 and were followed-up in 1969 and compared with an age-matched population that did not undergo a gastric resection procedure.²³⁵ Fractures were almost twice as common in postgastrectomy subjects (35%) than in controls (19%) with an RR of 1.83 ($P < 0.01$). This was also true for fragility fractures, defined as vertebral compression or fracture of the pelvic bone, upper femur, tibia condyle, humeral neck, or distal forearm (10% vs. 3%; RR, 3.3, $P < 0.01$). This study did not control for alcohol use, smoking status, or comorbidity. A Swedish population-based case-control study of 129 males who had undergone partial gastrectomy compared with 216 age- and sex-matched controls revealed that 19% of postgastrectomy patients sustained vertebral fractures versus only 4% of controls (RR, 4.3; 95% CI, 1.05–17). This remained statistically significant after adjusting for smoking status and BMI. There was no apparent difference between Billroth I and Billroth II procedures.

Other, smaller studies confirm the Olmsted County and Swedish experience of a significantly increased fracture burden after gastrectomy. A study evaluating 342 postgastrectomy patients after a mean of 7.4 years from surgery found pathological fractures on routine chest,

pelvis, and spine X-rays in 5.8% of this group but in none of the control group of peptic ulcer patients.²¹¹ One study reporting a high rate of osteoporosis by DXA (22% at the spine and 61% at the femoral neck) found no fractures after a mean follow-up of nearly 6 years.²²⁹ However, 6 years may not be sufficiently long for fractures to become apparent in this group. Conversely, in a group of 40 postgastrectomy patients who underwent spinal X-rays 12–13 years after Billroth I ($n = 9$) and Billroth II procedures ($n = 15$) and 8 years after total gastrectomy ($n = 16$), 31 vertebral fractures were found in 13 patients (mean, 2.4 fractures/patient).²³⁰ Vertebral fractures occurred in 22% of Billroth I patients, 40% of Billroth II patients, and 31% of total gastrectomy patients. Seven patients with fractures had normal BMD on QCT. In a cohort of 449 70-year-old Swedish males from the 1970s, 45 had undergone previous gastrectomy.¹⁹⁵ The fracture rate was 40% in the 16 males with a Billroth I and 33% in the 27 males with a Billroth II, significantly greater than the 12% fracture rate seen in the 404 controls. At nearly 9 years' follow-up, the post-Billroth II patients had an average of 1.7 spinal fractures, compared with an average of 0.6 fracture in the controls ($P = 0.017$), representing a threefold increase in risk.¹⁹²

Summary of Bone Disease in Postgastrectomy States

1. Postgastrectomy patients typically have a number of risk factors for osteoporosis, and bone disease may not necessarily be a sequela of the surgery per se. Nonetheless, postgastrectomy patients are at risk for bone disease (level A evidence).
2. Both osteoporosis and osteomalacia may occur postgastrectomy. The incidence of osteomalacia is approximately 10%–20% (level B evidence). The incidence of osteoporosis is unknown, but may be as high as 32%–42% (level B evidence).
3. Postgastrectomy states are associated with an increased risk of fracture and thus should be evaluated for possible underlying bone disease (level B evidence).
4. There is no difference in risk for postgastrectomy bone disease between a Billroth I procedure and a Billroth II procedure (level A evidence).
5. There is no difference in risk for postgastrectomy bone disease between partial gastrectomy and total gastrectomy (level A evidence).
6. There is no apparent risk for postgastrectomy bone disease from acid-reducing procedures such



* complete blood count, serum calcium, alkaline phosphatase, creatinine, 25-OH-vitamin D, protein electrophoresis, testosterone [males]

Figure 1. A management approach for osteoporosis in gastrointestinal diseases.

as vagotomy in the absence of gastrectomy (level B evidence).

7. Serum calcium and phosphate levels are most often normal in postgastrectomy states, although calcium levels may be normal as a result of mobilization of calcium from bone (level A evidence).
8. SAP, vitamin D metabolite, and PTH levels are variable in postgastrectomy states (level A evidence).
9. Patients who are at least 10 years postgastrectomy (especially postmenopausal females, males age >50 years, and patients with low-trauma fractures), should undergo DXA testing.

When to Measure Bone Density in GI Disease

The path of least resistance is to simply order a DXA on all patients with GI disease in one's practice. This would identify subjects with low BMD but no other obvious risk factors for osteoporotic fracture, but would lead to a considerable number of unnecessary tests. As discussed previously, however, some subjects with BMD

within the normal range may still have other risk factors making them susceptible to fracture. A clinician might be lulled into a false sense of security when a BMD T score result > -1 is reported. DXA T scores between -1 and -2 might create more confusion than benefit. Should those patients be treated? If so, with what medication?

Clearly, testing should be done in patients with the GI disorders reviewed earlier who have experienced a vertebral fracture, are postmenopausal, or have been on chronic corticosteroid therapy (>3 months) (Figure 1). There is an urgent need for the development and validation of a risk factor grading system for GI disorders. For IBD, such a system could incorporate data on body weight (possibly skin-fold thickness), smoking, exercise, disease activity, menstrual status, corticosteroid use, dietary calcium intake, family history of osteoporosis, and personal history of fractures. In the absence of an available scoring system, clinicians must use common sense in deciding when to pursue DXA testing. Patients with 1 or more known risk factors probably should undergo initial screening with DXA and, if levels are within the

normal range, repeat testing after 2–3 years to exclude significant bone loss (Figure 1). A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy, although in general, 1 year is not long enough to determine the effectiveness of any treatment of bone disease in adults.²³⁶ An alternative approach is to screen all patients, but third-party payors will have to decide whether this is cost-effective, and clinicians will have to decide whether the current state of therapy is sufficiently evidence-based to warrant intervention for borderline cases.

Therapy

Overview of Osteoporosis Therapy

General. Education on the importance of lifestyle changes (e.g., regular exercise, smoking cessation) and vitamin D and calcium supplementation should be given. Vitamin D deficiency should be identified and treated aggressively to maintain serum levels of 25-OHD within the normal range. For individuals found to be at high risk for osteoporotic fractures, therapy with an approved agent should be considered. Major abnormalities in BMD, calcium level, vitamin D metabolism, or PTH level warrant referral to a specialist in metabolic bone diseases.

Calcium. The National Academy of Sciences²³⁷ has provided age-stratified recommendations for daily calcium intake required to prevent negative calcium balance. These recommendations are 1000 mg/day of elemental calcium for men and premenopausal women and 1200 mg/day for women and men over age 50. These calcium intake levels are considered safe. In patients with malabsorption, higher calcium intake may be needed to maintain calcium balance. These patients have an increased risk for kidney stone formation, and measurement of urinary calcium level is advised. For a patient with a urinary calcium excretion >4 mg/kg per 24 hours, a thiazide diuretic can be given to reduce the risk of hypercalciuria and nephrolithiasis. Thiazide diuretics have been reported to increase bone density at the spine and hip²³⁸ and to reduce the risk of hip fracture.²³⁹ Today, the ready availability of calcium-fortified juices, cereals, dairy products, and other foods makes it possible to achieve an adequate daily calcium intake. Calcium carbonate (containing 40% elemental calcium) is the most commonly prescribed calcium supplement preparation. Calcium citrate, which contains 24% elemental calcium, is more bioavailable and can produce fewer GI symptoms (e.g., bloating and constipation). Calcium

phosphate or calcium and magnesium may produce less constipation.

Vitamin D. Inadequate dietary intake of vitamin D and sunlight exposure leads to vitamin D deficiency.²⁴⁰ In patients with acute hip fractures, a recent study showed that 50% had vitamin D deficiency, a preventable and treatable contributing factor.²⁴¹ Vitamin D and calcium supplementation reduces bone loss and the incidence of nonvertebral fractures by 50% in community-dwelling subjects²⁴² and the incidence of hip fractures by 43% in nursing home patients.²⁴³ Vitamin D, 400–800 IU/day, is usually an adequate replacement dose in healthy individuals and can be obtained from many multivitamin preparations. Higher doses may be needed for those with malabsorption or overt vitamin D deficiency; this requires high-concentration capsules (50,000 IU), liquid formulations (200 IU/drop), or parenteral administration. Earlier studies showed that high doses of calcitriol [1,25(OH)₂-vitamin D₃], the active metabolite of vitamin D, can lead to increments in bone mass²⁴⁴ and reduced rate of fracture.²⁴⁵ However, calcitriol has a narrow safety margin, with a risk for hypercalcemia and hypercalciuria. Alfacalcidol [1 alpha(OH)-vitamin D₃] is another activated form of vitamin D that has not been as thoroughly evaluated as calcitriol.

Estrogen. Estrogen therapy in postmenopausal women produces a 4%–5% increase in bone mass, possibly through direct interaction with estrogen receptors on bone cells^{246,247} or a reduction in cytokines that stimulates bone resorption (e.g., IL-1, IL-6).^{248–250} Hormone replacement therapy is currently approved by the FDA for the prevention, but not the treatment, of osteoporosis. The Women's Health Initiative in the United States is a very large randomized trial evaluating the effects of ovarian hormone replacement therapy, calcium, and vitamin D on fractures, cardiovascular events, and breast cancer.²⁵¹ Users of daily combined estrogen and progestin (0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate) exhibited reduced rates of hip fracture (34%), clinical vertebral fracture (34%), and total fractures (24%). This benefit was offset by an even greater increased risk for cardiac events, strokes, pulmonary emboli, and invasive breast cancers. Any possible benefit of hormone replacement therapy will have to be carefully balanced against the significant risks.

Selective estrogen receptor modulators (SERMs). The SERM raloxifene has antagonistic effects on the endometrium and breast, decreasing the risk of breast cancer by 76% in women treated for osteoporosis. It also exerts an estrogen-like effect on the lipid profile, decreas-

ing low-density lipoprotein LDL cholesterol by 12% and increasing high-density lipoprotein₂ cholesterol by 15%. In the Multiple Outcomes of Raloxifene trial,^{252,253} raloxifene 60 mg/day increased bone density by 1%–2% per year and decreased vertebral fractures by 40%–50% but did not affect nonvertebral fractures (including hip fractures). The side effects of raloxifene include increased deep venous thrombosis, hot flashes, and rarely leg cramps. The FDA has approved raloxifene for the prevention and treatment of osteoporosis.

Calcitonin. The Prevent Recurrence of Osteoporotic Fractures study²⁵⁴ was a 5-year, randomized, placebo-controlled comparison of nasal calcitonin vs. placebo in postmenopausal women with severe osteoporosis. The data demonstrated a 33% reduction in the risk of new vertebral fractures with calcitonin nasal spray, 200 IU/day, with no decrease in non-spine or hip fractures. No significant reduction in vertebral fractures occurred at doses of 100 IU/day or 400 IU/day, although increases in lumbar spine bone density and inhibition of biochemical markers of bone turnover (serum C-telopeptide) were seen at all doses. Nasal calcitonin, 200 IU/day, is FDA-approved for the treatment (but not prevention) of postmenopausal osteoporosis.

Bisphosphonates. Bisphosphonates are potent inhibitors of bone resorption with varying side chains that determine potency. Alendronate is FDA-approved for the prevention and treatment of osteoporosis at doses of 5 mg/day (35 mg/week) and 10 mg/day (70 mg/week), respectively. In postmenopausal women with osteoporosis, alendronate, 10 mg/day, increases spinal bone density overall by 7% and femoral neck bone mass by 6%.²⁵⁵ Data from multicenter studies show that alendronate reduces the incidence of vertebral, nonvertebral, and hip fractures.³⁸ Gastroesophageal reflux and other abdominal symptoms may be exacerbated by alendronate; rarely, erosive esophagitis may occur. To minimize side effects, the patient must remain in an upright position for at least 30 minutes after taking this medication. Like all bisphosphonates, alendronate is poorly absorbed and must be taken on an empty stomach at least 30 minutes before the first food, beverage, or medication of the day. Alendronate has been used to treat patients with osteoporosis in combination with estrogen-replacement therapy. It results in an additional 2.5%–3% increase in bone density, although an additive benefit in terms of anti-fracture effect has not yet been established. Risedronate is another bisphosphonate approved for the prevention and treatment of osteoporosis. Data show that 2 years of treatment with risedronate 5 mg/day in postmenopausal women with spinal fractures increases spinal bone den-

sity by 7% and femoral neck bone density by 2%.^{256,257} Vertebral fractures are reduced by 40%–50%; nonvertebral fractures, by 33%–39%. Preliminary data indicate that risedronate is well tolerated and can be used in select patients who cannot tolerate other medications for osteoporosis.²⁵⁸ Adverse effects were similar in both placebo and treatment groups, and no increase in GI symptoms was observed.

Although less well studied, intermittent cyclic therapy with etidronate (400 mg/day for 14 days, followed by 500 mg/day of supplemental calcium for 76 days) clearly increases bone density of the spine and hip, and evidence indicates that vertebral fractures may also be prevented.²⁵⁹ Other bisphosphonates are currently being tested in clinical trials.

Sodium fluoride. Sodium fluoride stimulates bone formation and produces large increments in bone density. The incidence of adverse events with fluoride is 40% and includes GI irritation and lower extremity pain with stress fractures. Therapy with a slow-release fluoride preparation increases spine and hip bone mass; 1 study reported reduced vertebral fractures.²⁶⁰ However, a controlled study of high-dose (75 mg/day) sodium fluoride for treating osteoporosis found no significant decrease in vertebral fractures, and an actual increase in nonvertebral fractures.²⁶¹ At present, fluoride therapy should be limited to investigative protocols.

Parathyroid hormone. The latest therapy for the treatment of osteoporosis, PTH is anabolic to bone. Early studies showed that low doses of recombinant human PTH (1–34, the active amino terminus), administered by daily injection and given with calcitriol, increased trabecular bone in the spine,²⁶² but with possible small losses of cortical bone. Recent studies²⁶³ have shown that in postmenopausal women taking estrogen replacement therapy, calcium, and vitamin D, the addition of PTH (1–34) for 2 years produces a dramatic (29%) increase in spinal bone density and a 9%–10% increase in hip bone density. Results from a large multicenter, placebo-controlled trial show that recombinant human PTH (rhPTH) (1–34) produces a marked increase in bone mass over 21 months and decreases the risk of new vertebral fractures by >65% and the risk of non-spine fractures by 53%.²⁶⁴ Future investigation into osteoporosis treatment may include combinations of rhPTH and antiresorptive agents.

Corticosteroid-Induced Bone Loss

General. Long-term corticosteroid use is a major risk factor for osteoporosis and fractures. The conventional definition of long-term use is continuous exposure beyond 3 months, though the administration of multiple

shorter courses of corticosteroids given intermittently is probably also a risk factor despite the breaks in use. Factors associated with greater bone loss include corticosteroid dose (both daily and cumulative), duration of exposure, and possibly, the underlying disease for which the corticosteroids are being given. Persons of both sexes and all ages are at risk for corticosteroid-induced bone loss.²⁶⁵ A number of strategies are used to reduce the potential adverse effects of corticosteroids on skeletal homeostasis, although it should be recognized that most of the literature on the prevention or treatment of corticosteroid-induced osteoporosis is in patients with non-GI diseases. Strategies include using the lowest effective corticosteroid dose, administering corticosteroid therapy for the shortest duration possible, using those corticosteroids with fewer systemic effects (e.g., budesonide), and using alternate medications (e.g., azathioprine) that do not affect bone mass.

As discussed previously, not all corticosteroid-treated patients develop osteoporosis. In patients who are (or are predicted to be) corticosteroid-dependent (prednisone ≥ 7.5 mg/day for more than 3 months), a baseline bone density should be obtained. If bone mass is significantly reduced at baseline, then it is particularly important to identify and treat any underlying secondary causes of bone loss and consider therapy to protect the skeleton from further corticosteroid-induced osteoporosis. Those with normal or only mildly reduced bone density can be offered preventive treatment (especially those at higher risk, such as older individuals and patients on high-dose corticosteroid therapy) or followed closely for rapid bone loss with annual bone density measurements. All patients are advised to modify any lifestyle factors that increase the risk of osteoporosis (e.g., smoking, excessive alcohol consumption) and institute a program including weight-bearing exercises and fall-prevention strategies.

Calcium and vitamin D. To avoid negative calcium balance, we recommend adequate calcium intake (at least 1000 mg/day of elemental calcium, up to 1500 mg/day in postmenopausal females) and vitamin D, 800 IU/day. Supraphysiologic doses of vitamin D (e.g., 50,000 U once weekly or bimonthly) may be needed to maintain a serum 25-OHD level >25 ng/mL. Careful monitoring of the serum and urinary calcium concentrations is essential whenever high-dose vitamin D is prescribed, to prevent the development of hypercalcemia, hypercalciuria, and nephrolithiasis. Hydrochlorothiazide (25 mg twice daily) may reduce the hypercalciuria associated with corticosteroid therapy.²⁶⁶

In patients with rheumatoid arthritis taking >5 mg of prednisone daily, Buckley et al.²⁶⁷ showed that calcium,

1 g, with vitamin D₃, 500 IU/day, prevented bone loss at the spine and hip and actually increased bone density at these sites by 0.72% and 0.82%, respectively, over 2 years. Earlier studies found that calcitriol was ineffective in treating established corticosteroid-induced osteoporosis.²⁶⁸ However, as a primary prevention strategy, calcium and calcitriol (with or without calcitonin) reduced vertebral bone loss in corticosteroid-treated subjects.²⁶⁹ In rheumatic patients taking corticosteroids, Hahn et al.²⁷⁰ showed that vitamin D (50,000 U 2–3 times weekly) and 25-hydroxyvitamin D (40 μ g/day), each with 500 mg of elemental calcium, had beneficial effects on bone density (8% and 16% increments, respectively), although further long-term studies are needed. To offset the negative calcium balance resulting from corticosteroid therapy, raising vitamin D levels to the upper range of normal can improve calcium absorption and inhibit the action of PTH on bone.

Gonadal replacement therapy. Treating hypogonadism is essential provided that the patient has no contraindications for such treatment. Gonadal steroid replacement can be used to both prevent and treat corticosteroid-induced bone loss in premenopausal women, postmenopausal women, and hypogonadal men. Corticosteroids may decrease sex corticosteroid levels, and women and men may benefit from hormone replacement. Reid et al.²⁷¹ randomized men with subnormal free testosterone levels on long-term corticosteroid therapy to 250 mg testosterone or placebo injected intramuscularly every 4 weeks for 1 year and then crossed-over this therapy for the second year. Free testosterone levels were restored to the high-normal range. In the treatment group, bone density increased by 5% at the spine, but not at the hip. There was no adverse effect on prostate cancer risk or lipid profiles, and, as expected, there was an increase in lean body mass and decrease in total body fat.²⁷¹ Thus, in men with testosterone deficiency in association with corticosteroid therapy, treatment with an intramuscular or transdermal testosterone preparation may have beneficial effects on bone density.²⁷² Titration of the free testosterone levels, monitoring of prostate-specific antigen levels, and prostate examination every 6–12 months is advised.

In a retrospective, case-controlled study of postmenopausal women receiving 5–15 mg of prednisone daily, therapy with estrogen and cyclic progesterone prevented bone loss and produced a small increase in spine BMD at 1 year.^{265,273} In a randomized controlled study of women with rheumatoid arthritis, some of whom were treated with corticosteroids, Hall et al.²⁷⁴ reported that transdermal estradiol, 50 μ g day, increased BMD in the spine

by 3.7% but produced no change in the hip.²⁷⁵ Premenopausal women with amenorrhea or low estradiol levels should be treated with a birth control pill unless contraindicated.¹⁶ Further prospective randomized controlled studies of the effects of hormone replacement therapy on corticosteroid-induced bone loss are needed.

Calcitonin. The presence of corticosteroid-induced bone resorption led investigators to determine the effects of calcitonin, an osteoclast inhibitor. Adachi et al.²⁷⁶ showed that patients with polymyalgia rheumatica treated with prednisone for 1 year had 3.7% less bone loss at the spine when treated with intranasal calcitonin than those on placebo. A study of asthmatic patients²⁷⁶ with osteoporosis receiving corticosteroids, calcium, and intranasal calcitonin or placebo showed a 10.6% greater spinal BMD at 2 years, but no significant reduction in fractures. Nasal calcitonin is not currently approved for treating corticosteroid-induced bone loss.

Bisphosphonates. Bisphosphonates as antiresorptive therapy are proving highly beneficial in treating corticosteroid-induced bone loss. In patients receiving long-term corticosteroid therapy, a prospective placebo-controlled study of oral pamidronate and calcium produced almost a 20% increment in lumbar spine trabecular bone density as measured by QCT over 1 year,²⁷⁷ with subsequent stable bone densities. However, oral pamidronate is not FDA-approved for use in the United States. Pamidronate²⁷⁸ was studied as a primary preventive therapy in patients commencing long-term, low-dose (<10 mg/day) prednisone therapy.²⁷⁸ Treatment involved 90 mg administered intravenously at the start of corticosteroid therapy, followed by 30 mg given intravenously every 3 months. At 1 year, 3.6% and 2.2% increases in BMD were noted in the spine and femoral neck, respectively. A pooled data analysis from Roux et al.²⁷⁹ showed that intermittent cyclic etidronate is effective in preventing corticosteroid-induced bone loss in subgroups as defined by sex, menopausal status, and disease state.

Saag et al.²⁸⁰ pooled data from 2 randomized, double-blind trials comparing the effects of alendronate (5 and 10 mg) and placebo on BMD in patients treated with prednisone, ≥ 7.5 mg/day, for various disorders. All patients received calcium, 800 to 1000 mg/day, and vitamin D, 250 to 500 IU/day. During the study, the median prednisone dose in each treatment group decreased. Over 48 weeks, spinal BMD increased 2.1%–3.0%, compared with a 0.4% decrease in the control group. Femoral neck bone density increased by 1%–1.2% in the alendronate groups, compared with a 1.2% decrease in the control group. After 2 years of therapy,

the vertebral fracture rate was 0.7% in alendronate-treated patients, compared with 6.8% controls. A slight increase in nonserious upper GI symptoms was seen in patients treated with alendronate, 10 mg/day.

Risedronate was studied for prevention purposes in postmenopausal women initiating prednisone therapy (at least 7.5 mg/day for less than 3 months), and for treatment purposes in subjects receiving chronic corticosteroid therapy (at least 7.5 mg/day for 6 months or longer).²⁸¹ All patients received calcium 500–1000 mg/day, vitamin D 400 IU/day, and either risedronate 5 mg/day or placebo. The prevention study showed that risedronate resulted in a 0.5%–1.3% increase in BMD at the lumbar spine and hip sites. In the treatment group, risedronate increased BMD by 2%–2.8% in the spine and hip. Vertebral fracture rates were significantly lower in the risedronate-treated group.²⁸¹ Risedronate was well tolerated, with no significant increase in GI side effects.

Sodium fluoride. In contrast to antiresorptive drugs, fluoride stimulates bone formation. The use of monofluorophosphate plus calcium, for example, produced a 9.3% increase in spine BMD in patients treated with prednisone for 6 years.²⁸² Rickers et al.,²⁸³ in a prospective randomized trial over 2 years, was unable to show an effect of calcium, fluoride, and vitamin D in the prevention of corticosteroid-induced bone loss.

Using histomorphometric analyses of iliac crest biopsy samples in corticosteroid-treated patients, Meunier et al.²⁸⁴ observed a 63% increment in trabecular bone. This increase is consistent with the anabolic effect of fluoride on trabecular bone. Unfortunately, the increments in bone mass seen with fluoride therapy have not been shown to produce a decreased risk of fracture in patients with osteoporosis. Long-term, randomized controlled studies that demonstrate a reduction of fractures would be necessary to support the use of fluoride in the treatment of corticosteroid-induced bone loss.

Parathyroid hormone. Lane et al.²⁸⁵ studied the role of PTH in the treatment of corticosteroid-induced bone loss in postmenopausal women. All women were treated with 5–20 mg/day of prednisone and were also receiving estrogen replacement therapy. Patients were randomized to receive PTH 400 IU/day or placebo with calcium and vitamin D. After 1 year of this therapy, BMD was increased by 9% at the lumbar spine. This study did not assess fracture endpoints.

Summary. Corticosteroid-dependent patients with evidence of increased fracture risk, either reduced bone mass or previous fractures, benefit from therapy. Some authors advocate preventive treatment in even low-risk patients and/or those with normal bone density, al-

though proof of long-term benefit in terms of fracture prevention is lacking. Untreated patients with a normal BMD should have a follow-up BMD at 1 year to exclude rapid bone loss. The American College of Rheumatologists¹⁶ recommends administering bisphosphonates to patients with corticosteroid-induced osteoporosis. Note, however, that the bioavailability, tolerability, and safety of bisphosphonates in IBD has not yet been adequately studied. Premenopausal women and young men should not be treated with bisphosphonates in the absence of fractures or evidence of accelerated bone loss. Alendronate 10 mg/day (available as 70 mg/week) and risedronate 5 mg/day are FDA-approved therapies for corticosteroid-induced osteoporosis. In patients who cannot take alendronate because of GI symptoms, oral risedronate 5 mg/day or intravenous pamidronate may be considered. In a patient treated with corticosteroids, persistent bone loss or development of fractures while receiving an approved modality to protect bone mass should prompt an evaluation of other secondary causes of bone loss and consideration of alternative treatment options.

Gastrointestinal Disease-Specific Therapy

Therapy for bone disease in inflammatory bowel disease. As summarized earlier, men and women with Crohn's disease or ulcerative colitis are at equal risk for the development of osteoporosis with a 40% increased risk of fracture. Administration of corticosteroid therapy increases the risk of osteoporosis in patients with IBD. Thus, the treatment of patients with IBD should be directed toward preventing bone loss, controlling disease activity, maintaining adequate nutrition, giving the lowest effective corticosteroid dose, administering immunomodulation therapy to minimize or discontinue corticosteroid therapy, and reducing fractures in those with established osteoporosis.

Data on therapeutic interventions to prevent bone loss in patients with IBD are limited. In a pilot study of 17 corticosteroid-treated IBD patients, including both men and women, supplemental calcium 1000 mg/day and vitamin D 250 IU/day had no effect on bone mass after 1 year.¹³⁰ This study also found that patients with IBD on average ingest considerably less than the recommended daily intake of dietary calcium and vitamin D. Thus, supplementing oral calcium and vitamin D intake may be indicated for many patients with IBD. In a randomized placebo-controlled study of 75 women and men with Crohn's disease, Vogelsang et al.²⁸⁶ reported that 1000 IU/day of vitamin D prevented bone loss in the forearm. Bone density increases in the group receiving vitamin D were independent of baseline serum 25-

OHD level. This group reported elsewhere that their Crohn's disease patients ingest only 1 $\mu\text{g/day}$ of vitamin D on average.²⁸⁷ This is only 20% of the recommended daily intake of vitamin D and also is much lower than the average oral vitamin D intake found in 1 U.S. study.¹³⁰ Thus, the effect of supplemental vitamin D on subjects who have sufficient dietary intake remains unclear. One randomized controlled study of 33 patients with Crohn's disease compared the effects of therapy comprising calcium 1000 mg/day plus vitamin D 1000 IU/day with this combination plus sodium fluoride 75 mg/day.²⁸⁸ This study also found no impact of calcium and vitamin D alone on bone mass; however, the fluoride group exhibited a significant increase in mean spine Z score (-1.39 — -0.65 , $P < 0.05$). Problems with using fluoride to treat osteoporosis have been reported elsewhere.¹⁷⁷ Greenstein et al.²⁸⁹ found kidney stones in 7.6% of 700 patients with IBD. Hypercalciuria commonly occurs in corticosteroid-treated subjects, and hyperoxaluria and calcium oxalate stones may develop in patients with malabsorption. Therefore, when urine calcium levels are elevated (>4 mg/kg), adding a thiazide diuretic in IBD, as outlined earlier, should be considered.

In a randomized study of 117 patients with Crohn's disease, low-impact aerobic exercise did not lead to a significant increase in bone mass at the hip or the spine.²⁹⁰ Nonetheless, an increase in spine or hip BMD was positively associated with the number of exercise sessions completed ($r = 0.35$, $P = 0.01$). Another study found that exercise is safe and possibly beneficial from a general health perspective in patients with mild or inactive Crohn's disease²⁹¹; thus exercise should be considered as a means to at least maintain, if not improve, bone health. In 47 postmenopausal women with IBD, hormone replacement therapy produced small increases in bone mass at the spine and forearm over 2 years.¹⁸ The benefit of hormone replacement therapy in IBD has never been tested in a randomized controlled fashion. Finally, Haderslev et al.,²⁹² in a placebo-controlled trial in 32 patients with osteopenia and Crohn's disease, found that alendronate 10 mg/day increased bone mass by 3%–5% over 1 year. Thus, based on reports in the literature, treatment strategies for patients with IBD and osteoporosis could include exercise, vitamin D therapy, hormone replacement therapy (when appropriate), and bisphosphonate therapy. Although there is a general paucity of data on enhancing bone mass in patients with IBD, and all studies reported to date and reviewed herein have been small, it is also significant that no study has yet been conducted with fracture as the primary endpoint. Thus, the current approach to managing osteoporosis in IBD is extrapolated mainly from approaches to postmenopausal osteoporosis and

is almost wholly empiric. In this regard, common-sense approaches, including exercise, nutritional maintenance, and supplementation, where appropriate, should be the cornerstones of routine management.

Therapy for bone disease in celiac disease. Osteoporosis and vitamin D deficiency are common in both male and female patients with untreated celiac disease. In these patients, institution of a strict gluten-free diet is critically important, particularly when the diagnosis was made in childhood. Increased public awareness about the high prevalence of low bone mass in asymptomatic subjects with celiac disease may encourage earlier identification, treatment, and reversal of low bone mass in subjects with this disease. In patients who have vitamin D deficiency with low 25-OHD levels (<15 ng/mL), treatment should focus on restoring vitamin D level to >25–30 ng/mL—a level that prevents the rise in PTH and PTH-mediated bone resorption.¹⁵⁵ In patients with intestinal malabsorption, very large doses of vitamin D (i.e., 50,000 U 1–3 times weekly) may be needed in the early stages of a gluten-free diet until the malabsorptive process has resolved. Because of the increased fracture risk, particularly in older patients, other therapeutic interventions to reduce fractures might be considered after sufficient vitamin D levels are achieved.

Therapy for bone disease in postgastrectomy states. A study of postgastrectomy bone disease found that weekly intramuscular administration of vitamin D in doses ranging from 700 to 10,000 U were ineffective in correcting biochemical changes. This may have been because osteomalacia was not the underlying skeletal abnormality in most of the patients.²⁹³ Strategies to minimize the nutritional deficiencies should be implemented before other therapies are considered to treat the osteoporosis that may develop postgastrectomy.

Conclusions

Bone disease has become a well-recognized problem in patients with GI disorders. The rising prevalence of IBD and more frequent diagnosis of asymptomatic celiac disease (aided by serological testing) will increase the number of patients with potential bone disease in all gastroenterology practices. The widespread accessibility to DXA testing has led to more gastroenterology patients with diagnoses of osteopenia and osteoporosis. There is a clear need to better define the implications of a DXA diagnosis of “osteopenia” in these patients. The risk of fracture is the critical endpoint, a fact that is frequently overlooked. Further research is urgently needed to better define the magnitude of the excessive risk of fracture

in patients with GI and hepatic disorders. Furthermore, defining who among these patient groups is at greatest risk of fracture is critical, because, as has been shown in IBD, this risk may be only mildly increased. Thus, prospective data are needed to determine the relative importance of known risk factors in each patient group. This will lead to a more efficient use of screening with such techniques as DXA. Finally, there is a paucity of therapeutic intervention studies specifically aimed at bone health in GI diseases. Most therapy studies of sufficient size have been conducted in postmenopausal women or patients on corticosteroid therapy who do not have GI disease. Future studies should be required to assess interventions directed at bone health in these patients specifically and to use fracture prevention as endpoints. Although there is much enthusiasm to address bone disease in GI diseases, there is a pressing need for prospectively conducted research to define the magnitude of the problem and the interventions required.

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