WGO Practice Guideline
Osteoporosis and gastrointestinal diseases

7 October 2003, revised June 2004

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Sections

1. Definition

Osteoporosis is a systemic disease characterized by low bone mass (osteopenia) and micro-architectural deterioration, resulting in an increased risk of fracture. (1,2).

Gastroenterologists will encounter patients in their practices with osteoporosis/osteopenia, and practice guidelines about diagnosis, presentation and treatment would be useful.

Abbreviations:

BMD	Bone mineral density
CD	Crohn's disease
DXA	Dual-energy x-ray absorptiometry

FIT	Fracture intervention trial
FSH	Follicle stimulating hormone
GCS	Glucocorticosteroids
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HRT	Hormone replacement therapy
IBD	Inflammatory bowel disease
LH	luteinizing hormone
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PBC	Primary biliary cirrhosis
PSC	Primary sclerosing cholangitis
PTH	Parathyroid hormone
SERMs	Selective estrogen receptor modulators
SD	Standard deviation
UC	Ulcerative colitis

2. Epidemiology

Some simple facts:

- Peak bone mass is achieved by 30 years
- After skeletal maturity, bone is lost at a rate of 0.5 - 1.0% per year
- Women experience a phase of accelerated bone loss for 3-5 years after menopause
- When bone density falls with age, fracture risk increases
- The incidence of osteoporotic fracture increases dramatically with age, markedly so after the age of 60

Seriousness of osteoporotic hip fractures:

- 80% occur in women > 65 years
- mortality rate is increased by approximately 24% in the year following the fracture
- the risk of death associated with hip fracture is similar to that of breast cancer - for both the risk grows with age.
- vertebral fractures are of concern in Crohn's patients, and are associated with impaired quality of life, chronic pain, impaired ability to carry out activities of daily living, social isolation, increased hospital drugs, and increased mortality

3. Osteoporosis in gastrointestinal/liver associated conditions

3.1. Inflammatory Bowel Disease (IBD)

- Prevalence of reduced bone mineral density (BMD) in Crohn's Disease (CD) and chronic ulcerative colitis (UC) vary widely, but affect about 25% of CD and UC patients (3,4,5,6)
- Use of glucocorticosteroids (GCS) plays an important role (7,8)
- Low BMD is clinically relevant, since there is a 40% increase in fracture incidence in patients with IBD (9)
- Bone loss 3% per year in IBD without, and 6% with use of GCS (equal risk in males and females)
- 30-50% of chronic GCS users have fractures
- Prevalence and extent of osteopenia / osteoporosis in UC less than in CD
- Increased bone turnover (6)
- Unlike CD, in UC osteoporosis is not usually present at the time of diagnosis and is mostly seen in steroid users

3.2. Glucocortiocosteroids (GCS)

- BMD in person on GCS underestimates fracture risk. Increased relative risk of fracture in rheumatoid arthritis patients on GCS: hip, 2-fold; vertebral, 4-5 fold
- Bone loss most rapid in first year of use of GCS, and is similar in both lumbar spine and femoral neck
- Threshold dose for development of osteoporosis is 7.5 mg/day

3.3. Celiac Disease

- 30% prevalence of reduced BMD, and 25% of sprue patients with osteoporosis will have evidence of peripheral bone fractures (7,10)
- Malabsorption of calcium and vitamin D, with increased parathyroid hormone (PTH) levels

3.4. Liver disease

In liver disease there is decreased bone formation and increased bone resorption (11,12) with chronic liver disease, especially with cholestasis.

Liver disease associated with decreased BMD:

- Cholestatic liver disease: primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC)
    - 10-60% develop osteopenia/osteoporosis
    - Role of GCS/ursodeoxy cholic acid in development of osteoporosis unclear (13,14)
- Hemochromatosis
- Alcohol abuse
- Autoimmune hepatitis (including use of GCS)
- Liver transplantation
    - initially worsens BMD, possibly because of use of GCS/Cyclosporin A(CyA)/tacrolimus
    - 20% of patients suffer fractures within one year after liver transplantation (15)

4. Etiology

Osteoporosis from the GI perspective:

- All the usual risk factors (age, gender, alcohol usage, smoking)
- Sprue
- Chronic liver diseases
- Inflammatory Bowel Diseases
- Use of GCS
- Gastric / intestinal resection
- Pancreatic insufficiency
- Malabsorption

Risk factors for development of osteoporosis:

Primary: occurs independently of other disease or drugs

Secondary: woman, 40%; men, 60%

Personal history	History of fracture after age 40 dementia with increased likelihood of falls Poor general health/frailty (para- and tetraplegia, rheumatoid arthritis)
Genetic	family history of hip, wrist or vertebral fracture in first degree relative gender advanced age caucasian race
Lifestyle	smoking heavy alcohol or caffeine use sedentary lifestyle chronic low sunlight exposure
Endocrine	menopause estrogen deficiency hypogonadism hyperthyroidism hyperparathyroidism Cushing syndrome anorexia
Nutrition	calcium & vitamin D deficiency low peak BMD during growth period low body mass index malnutrition uncontrolled recurrent use of diets for treatment of obesity anorexia nervosa
Chronic use of medications	GCS anticonvulsants heparin antineoplastic drugs CyA/tacrolimus

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Potentially modifiable risk factors for osteoporosis and fracture:

- Known low BMD
- Low body weight
- Estrogen deficiency due to:
    - Early menopause (< age 45)
    - Bilateral oophorectomy
    - Prolonged premenopausal amenorrhea (> 6 months)
- Low calcium intake
- Malnutrition

- GCS use (at least 7.5 mg prednisone/day, or equivalent, for at least 3 months), or endogenous hypercortisolism
- Alcohol abuse
- Smoking
- Caffeine (daily intake > 190 mg, equivalent to > 1 cup)
- Recurrent falls
- Inadequate sunlight exposure
- Inadequate physical activity
- Impaired eyesight

5. Diagnosis

5.1. Diagnosis of osteoporosis:

- Suspect based on risk factors including GI disorders
- Confirm BMD measured by DEXA
    - gold standard (16)
    - DXA (Dual-energy X-ray absorptionmetry, g/cm^2)
    - Z-score - comparison with age-, race-, gender-matched populations
    - T-score - comparison with young adults at peak bone mass, gender- and race-matched populations
- WHO guidelines of osteoporosis on DXA: BMD 2.5 standard deviations or more below the mean value for young adults (17)
    - Osteopenia is a T-score from 1 to 2.5 SD below mean
    - In the elderly, the Z-score compares the patient's bone density with the age-, race-, and sex-matched mean of control subjects (18)

5.2. Diagnostic work-up of osteoporotic patient with GI/Liver disease:

- Diagnose and treat associated GI/liver disease
- Ca, PO_4, vitamin D, alkaline phosphatase, ALT or AST
- Thyroid function studies
- Parathyroid hormone (PTH) level
- Hypogonadism
    - F = estradiol and LH/FSH
    - M = free AM (=morning) testosterone or total testosterone / sex hormone binding globlulin; LH/FSH
- DXA scan; repeat after 1–2 yrs treatment

5.3. Indications for bone densitometry by Gastroenterologist

- Gastrointestinal/hepatic diseases with risk of development of osteoporosis
- Use of GCS
- Postmenopausal women aged 50 or older, with more than one risk factor other than being postmenopausal
- Women aged 65 or older, regardless of number of risk factors
- Postmenopausal women who present with fractures

Frequency of repeated DXA studies:

- Usually at 12- to 18- month intervals
- Assess perceived risk of fracture and make a patient-by-patient decision

- If DXA scan is not available, high risk patients may need to be treated empirically

6. Management of Osteoporosis

6.1. Suggested clinical approach

It is important to establish whether or not steroids are used and whether or not this concerns post-menopausal osteoporosis.

1. Steroid Use	bisphosphonates, other drugs second line
2. No steroids but fragility fracture history	bisphosphonates or raloxifene first, other drugs second line
3. No steroids, no fracture, no vasomotor symptoms	bisphosphonates or raloxifene first, other drugs second line
4. No steroids, no fracture, vasomotor symptoms present	HRT, other drugs second line (but NO raloxifene - worsens vasomotor symptoms

If these drugs are not easily available then the key approach is to increase vitamin D intake and to allow sun exposure. The possibility of adding vitamins to milk or other food products in low sunlight areas should be explored.

6.2. Key pharmacological options

Key pharmacological options are:

- Hormone replacement therapy
- SERMS
- Calcitonin
- Parathyroid hormone (PTH)
- Bisphophonates
- Combination therapy

The HRT mechanism of action is unknown and it should only be recommended with caution, taking into account the potential long term risks for the development of gynecological/breast cancers. It increases BMD by 5%, reduces risk of fracture by 50%. The best result is achieved if HRT is started before menopause, and continued for 10 yrs. It maybe useful to prevent bone loss in post-menopausal women on glucocorticosteroids.

Treatment with selective estrogen receptor modulators (SERMS) shows a 50% reduction in vertebral (but not hip) fracture rates (28, 29) and is useful in men with low estrogen levels

Calcitonin use in osteoporosis reduces the risk of vertebral fracture (30) but not non-vertebral; it is especially indicated for use in women who have been post-menopausal for 5 years and it is used primarily when first line drugs fail or are not tolerated

PTH use in osteoporosis is very expensive and only intended only for severe cases (T-score < 3.5)

Bisphosphonates are given for diseases with increased bone turnover, notably post-menopausal osteoporosis and GCS-associated osteoporosis

6.3. Treatment options for different patient categories

6.3.1. Treatment in postmenopausal women

- Calcium (1500 mg/day), vitamin D (800 IU/day)
  PLUS
  Pharmacotherapy (26)*
- Estrogens (combined with progestin if uterus is present), particularly in symptomatic women (27)
  OR
- A selective estrogen receptor modulator (raloxifene 60 mg.day)
  OR
- A bisphosphonate (alendronate 10 mg/day or 70 mg/week, or risedronate 5 mg/day) * when indicated, not necessarily routine therapy.

6.3.2. Treatment of GCS-associated osteoporosis

Bisphosphonates in the treatment of GCS-treated patients.

aAll three of the bisphosphonates have been proven to reduce fractures in glucocorticoid-induced osteoporosis, while this has not been shown for either estrogen (negative data) or raloxifene (no data).

6.3.3. Treatment for patients starting long-term GCS

- Initial evaluation
- Physical therapy
- Patient education

Table 2:

If DXA: T score ≥ -1 → HRT	If DXA: T score < -1 → HRT only in postmenopausal women

From: ACR Task Force on Osteoporosis Guidelines (37,38).

6.3.4. Treatment for patients on long-term GCS who have an osteoporotic fracture

- Initial evaluation
- Physical therapy
- Patient education

Table 3

DXA: T score ≥ -1 Normal lab results	**DXA: T score ≥ -1 Abnormal lab results**	**DXA: T score < -1 Normal lab results**	**DXA: T score < -1 Abnormal lab results**
Calcium & Vit D supplementation |	Reinforce physical therapy |	Calcium & Vit D supplementation |	Reinforce physical therapy |
HRT |	Treat underlying causes |	Reinforce physical therapy |	Treat underlying conditions |
Reinforce physical therapy	Calcium & Vit D supplementation |	HRT	Calcium & Vit D supplementation

	HRT

From: ACR Task Force on Osteoporosis Guidelines (37,38).

The main gastrointestinal adverse effects of bisphosphonates are:

- Esophagitis; heartburn, dysphagia, odynophagia
- Gastric/duodenal ulcers

6.4. Prevention

6.4.1. General Prevention

The following lifestyle changes can help prevent osteoporosis:

- Reduce excessive intake of alcohol, caffeine, and smoking
- Achieve ideal body weight
- Maintain an adequate exercise program
- Maintain an adequate intake of calcium and vitamin D for persons with malabsorption; monitor to prevent hypercalcemia or hypercaliuria

Table 4: Prevention and Treatment for GCS-Associated Osteoporosis:

Medical Therapy	Primary Prevention	Secondary Prevention & Treatment
Reduce dose of GCS where possible	✔	✔
Calcium & Vitamin D	NO	✔
Calcitrol	✔	-
Bisphosphonates	✔	✔
Hormone Replacement Therapy	-	✔
Calcitonin	✔	✔
Fluoride	±	✔

6.5. Guidelines for developing countries

- The main metastatic bone disease in the third world is often osteomalacia/rickets due to borderline malnutrition, in combination with cultural or religious practices involving covering the body
- Key approach is to increase calcium and vitamin D intake and to allow sun exposure

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8 Links to useful websites and consensus statements

American College of Rheumatology: http://www.rheumatology.org/

- Fact Sheet: Osteoporosis and Corticosteroid-induced osteoporosis: http://www.rheumatology.org/patients/factsheet/osteopor.html
- Treatment of Steroid-Induced Osteoporosis ACR Task Force on Osteoporosis Guidelines: http://www.rheumatology.org/research/guidelines/osteo/osteo.html

European Foundation for Osteoporosis: http://www.connect.ie/effo/index.htm

International Osteoporosis Foundation: http://www.osteofound.org/

- Position Papers and Guidelines: http://www.osteofound.org/publications/position_papers_guidelines.html

National Institutes of Health - Osteoporosis & Related Bone Diseases: National Resource Center: http://www.osteo.org/

- Research Bibliographies: http://www.osteo.org/research.asp
- NIH Consensus Statement: Osteoporosis Prevention Diagnosis and Therapy: http://odp.od.nih.gov/consensus/cons/111/111_intro.htm

National Osteoporosis Foundation (USA): http://www.nof.org

- Osteoporosis Clinical Practice Guideline: http://www.nof.org/professionals/clinical/clinical.htm

National Osteoporosis Society (UK): http://www.nos.org.uk/

- Position Statements for Health Professionals: http://www.nos.org.uk/healthprof.asp

Osteoporosis Australia: http://www.osteoporosis.org.au/html/index.php

- Position Papers: http://www.osteoporosis.org.au/html/healthpapers.php

Scottish Intercollegiate Guidelines Network (SIGN). www.sign.ac.uk:

- Management of Osteoporosis, No. 71: http://www.sign.ac.uk/pdf/sign71.pdf

9. Queries and Feedback from you

INVITATION TO COMMENT

The Practice Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some

procedures are associated with extra risk? Tell us about your own experience. You are welcome to click on the link below and let us know your views.

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