



Complete Summary

GUIDELINE TITLE

American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders.

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders. Gastroenterology 2003 Sep;125(3):937-40. [1 reference] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

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SCOPE

DISEASE/CONDITION(S)

Osteoporosis in hepatic disorders (hepatic osteodystrophy)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To present the official recommendations of the American Gastroenterology Association on osteoporosis and hepatic disorders
- To summarize current knowledge of bone disease in chronic liver disease and following liver transplantation, and to make recommendations on bone density testing and therapy

TARGET POPULATION

Adults with chronic liver disease

INTERVENTIONS AND PRACTICES CONSIDERED

1. Assessment
 - Bone mineral density (BMD) testing
 - Anti-mitochondrial antibodies
 - Serum gamma-glutamyltransferase and serum alkaline phosphatase
2. Patient education
 - Lifestyle changes such as regular exercise, smoking cessation
 - Vitamin D and calcium supplementation
3. Female hormone replacement therapy
4. Raloxifene
5. Testosterone
6. Bisphosphonates
7. Calcitonin, nasal or subcutaneous
8. Parathyroid hormone
9. Fluoride (not recommended)

MAJOR OUTCOMES CONSIDERED

- Bone loss
- Fracture rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers searched Medline and 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 hepatic disorders (liver/transplantation[MAJR] OR "liver diseases"[MAJR] OR "liver transplantation"[MAJR]). Recently published reviews, references from retrieved articles, and expert committee reports were manually searched for additional studies.

The technical review excluded skeletal disorders unrelated to osteoporosis such as avascular necrosis, hepatitis C-associated osteosclerosis, and hypertrophic osteoarthropathy. Hepatobiliary rickets and liver disorders of infancy and early childhood (such as extrahepatic biliary atresia) are quite different from skeletal disorders that present in adults and older children and were also excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The guideline authors graded evidence using guidelines adapted from the Practice Guidelines Committee of the American Association of the Study of Liver Diseases.

Quality of Evidence on Which a Recommendation is Based

Grade 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

Grade B

Evidence from at least one large well-designed clinical trial with or without randomization, cohort or case-control analytic studies, or well-designed meta-analysis

Grade C

Evidence based on clinical experience, descriptive studies, or reports of expert committees

Grade D

Not rated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Point estimates of prevalence of osteoporosis and mean bone density were extracted and combined (weighted for patient numbers) to give pooled estimates. Although not a formal meta-analysis, results can be taken to reflect general trends in the published data and should be useful for assessing the overall magnitude of the impact of various hepatic disorders on bone metabolism. Pooling of data was site specific but combines related technologies, different vendors, reference ranges, and sexes. The analysis did not show any major difference in results restricted to a technology or vendor. Against the many other assumptions inherent to bone densitometry, this simplification is not unreasonable.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The paper was approved by the Committee on May 18, 2003, and by the American Gastroenterological Association (AGA) Governing Board on July 25, 2003.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength of the evidence supporting each guideline statement is graded (A–D). Definitions of these grades are provided at the end of the "Major Recommendations" field.

Summary of Bone Disease in Chronic Liver Disease

1. On average, there is a mild bone mineral density (BMD) deficit in chronic liver disease, but considerable patient heterogeneity exists (level B evidence).
2. In the absence of concurrent corticosteroid therapy, rates of BMD loss are similar to predicted (level B evidence).
3. Vertebral and nonvertebral fracture rates are increased in chronic liver disease, especially in postmenopausal women (level A evidence).
4. Markers of greater osteoporosis and fracture risk include older age, hypogonadism, corticosteroid therapy, and established cirrhosis (level B evidence).
5. Eugonadal noncirrhotic patients generally have a low incidence of osteoporotic fractures (level A evidence).
6. Patients with primary biliary cirrhosis are at increased risk for osteoporosis due to predominant female sex and older age, but cholestatic disease per se does not differ significantly from noncholestatic disorders in terms of osteoporosis and fracture risk (level A evidence).
7. Prediction rules relying on multiple variables (such as body mass index, corticosteroid history, age, and sex) may be a useful aid in predicting the presence of osteoporosis and for risk stratification (level B evidence).

Summary of Bone Disease after Liver Transplantation

1. All pre-orthotopic liver transplantation (OLT) patients should be evaluated for osteoporosis and disorders of bone metabolism: history and physical examination with attention to risk factors for osteoporosis, thoracolumbar spine x-rays, serum calcium, phosphate, 25-hydroxyvitamin D, and free testosterone (for men). Thoracolumbar spine radiographs should be repeated if the patient reports loss of height or severe back pain (level D evidence).
2. Bone loss after OLT follows a biphasic course, with the greatest decrease during the first 3 to 6 months and then spontaneous stabilization or even improvement (level A evidence).
3. Most fractures develop in the first year, and very few fractures occur after the first 3 years (level A evidence).
4. The small but statistically significant decrease in BMD after OLT is insufficient to completely account for the high early fracture risk and usually does not worsen over time (level A evidence).
5. Posttransplant BMD can recover to above baseline, and this seems to be more common with cholestatic liver disease (level B evidence).
6. Pretransplant insufficiency fractures and low BMD are markers of high fracture risk after OLT (level A evidence).

Summary of Bone Density Testing and Therapy in Liver Disease

The following outlines a possible approach to managing osteoporosis in hepatic disorders:

1. Patients who have experienced a fragility fracture, who are postmenopausal, and who require long-term treatment with corticosteroids (>3 months) should undergo BMD testing. BMD should also be assessed when the diagnosis of primary biliary cirrhosis is first made, in patients with cirrhosis, and before liver transplantation (level D evidence).
2. Patients with risk factors and a normal initial BMD result should be retested after 2 to 3 years to exclude significant bone loss. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating high-dose corticosteroid therapy (level D evidence).
3. Osteoporosis can be the first clinical manifestation underlying cholestatic liver disease, and it may be worthwhile to screen for anti-mitochondrial antibody in osteoporotic patients with both an elevated gamma-glutamyltransferase and serum alkaline phosphatase level (level D evidence).
4. All patients require education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation) as well as vitamin D and calcium supplementation (level D evidence).
5. All patients should receive 1,000 to 1,200 mg of elemental calcium daily (depending on their age) and at least 400 to 800 IU of vitamin D daily. Vitamin D deficiency should be corrected by increasing serum 25-hydroxyvitamin D levels to at least 25 to 30 ng/mL (level D evidence). In patients with malabsorption, higher doses of calcium and vitamin D may be necessary.
6. If female hypogonadism or early menopause (before age 45 years) is evident, hormone replacement therapy (best via the transdermal route in patients with malabsorption or liver disease) is advised for the prevention of osteoporosis (level D evidence in hepatic disease, level A evidence for vertebral and nonvertebral fracture risk reduction in generally healthy postmenopausal women). Estrogen therapy is approved by the Food and Drug Administration for the prevention of osteoporosis in postmenopausal or hypogonadal premenopausal women but must be balanced against the significant risks. Non-estrogen-based therapy is generally preferred for older postmenopausal women.
7. Raloxifene, a selective estrogen receptor modulator, is approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women (level D evidence in hepatic disease, level A evidence for vertebral fracture risk reduction in osteoporotic postmenopausal women). A bone disease specialist should participate in the decision to choose raloxifene in patients with a hepatic disorder.
8. Testosterone should be used to treat hypogonadism in men (level D evidence).
9. Bisphosphonates should be considered in patients with known osteoporosis, with vertebral fractures, or who cannot withdraw from corticosteroids after 3 months of use (level D evidence). Bisphosphonates are approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in patients with known osteoporosis, with fragility fractures, or on prolonged corticosteroid therapy (level D evidence in hepatic disease, level A evidence regarding vertebral and nonvertebral fracture risk reduction in postmenopausal women, level A evidence regarding vertebral fracture risk reduction in osteoporotic men and corticosteroid-treated patients).

10. Nasal or subcutaneous calcitonin can be considered as an alternative when the preceding antiresorptive agents are contraindicated or poorly tolerated (level D evidence in hepatic disease, level A evidence regarding fracture risk reduction in osteoporotic postmenopausal women).
11. As in other organ transplant recipients, bone loss occurs rapidly, so therapy is optimally started before or at the time of OLT. There is conflicting evidence that intravenous administration of a bisphosphonate at the time of transplantation may reduce bone turnover and fractures, but its use should be directed by a bone disease specialist (level C evidence).
12. Parathyroid hormone is approved by the Food and Drug Administration for the treatment of severe osteoporosis (level D evidence in hepatic disease, level A evidence in osteoporotic postmenopausal women). Its use should be directed by a bone disease specialist.
13. Fluoride is not recommended for the treatment of osteoporosis associated with a hepatic disorder (level D evidence in hepatic disease, no consistent evidence for fracture risk reduction in other groups).

Definitions:

Quality of Evidence on Which a Recommendation is Based

Grade 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

Grade B

Evidence from at least one large well-designed clinical trial with or without randomization, cohort or case-control analytic studies, or well-designed meta-analysis

Grade C

Evidence based on clinical experience, descriptive studies, or reports of expert committees

Grade D

Not rated

CLINICAL ALGORITHM(S)

An algorithm for a general approach to clinical management of osteoporosis in patients with chronic liver disease is provided in the Technical Review that accompanies the guideline (see the "Companion Documents" field).

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Potential prevention of bone fractures in individuals with advanced hepatic disease and following liver transplantation
- Potential prevention of bone loss

POTENTIAL HARMS

Estrogen therapy must be balanced against the significant risks.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline has been developed under the aegis of the Clinical Practice Committee of the American Gastroenterological Association (AGA). It provides preferred approaches to specific medical problems or issues. The statements herein are derived from the data available at the time of their creation and may need to be modified as new information is generated. Unless otherwise stated, these statements are intended for adult patients. The strength of the evidence upon which the statements are based is noted, with prospective, randomized, controlled trials being the strongest. When adequate data are absent, expert consensus may be used and will be identified as such. This document is not to be construed as a standard of care. All decisions regarding the care of a patient should be made by the physician in consideration of all aspects of the patient's specific medical circumstances.
- There is a paucity of therapeutic intervention studies specifically aimed at bone health in hepatic diseases. Most well-powered treatment studies are in populations of postmenopausal women or corticosteroid-treated patients who do not have gastrointestinal or hepatic disease. Studies are required that assess interventions directed at bone health in these disorders specifically and that use fracture prevention as the primary end point. Although there is much enthusiasm to address bone disease in hepatic diseases, there is a pressing need for prospectively conducted research to define the magnitude of the problem and the interventions required.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders. Gastroenterology 2003 Sep;125(3):937-40. [1 reference] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Sep

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Not stated

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

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GUIDELINE AVAILABILITY

Electronic copies: Available from the [American Gastroenterological Association Institute \(AGAI\) Gastroenterology journal Web site](#).

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- W.D. Leslie, C.N. Bernstein, M.S. Leboff. AGA technical review on osteoporosis in hepatic disorders. *Gastroenterology*. 2003 Sep; 125(3):941-966.

Electronic copies: Available from the [American Gastroenterological Association Institute \(AGAI\) Gastroenterology journal Web site](#).

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

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