

# Bone Mineral Density Thresholds for Pharmacological Intervention to Prevent Fractures

Ethel S. Siris, MD; Ya-Ting Chen, PhD; Thomas A. Abbott, PhD; Elizabeth Barrett-Connor, MD; Paul D. Miller, MD; Lois E. Wehren, MD; Marc L. Berger, MD

**Background:** Treatment intervention thresholds for prevention of osteoporotic fractures can be derived from reports from the World Health Organization (diagnostic criteria) and National Osteoporosis Foundation (treatment criteria). It is not known how well these thresholds work to identify women who will fracture and are therefore candidates for treatment interventions. We used data from the National Osteoporosis Risk Assessment (NORA) to examine the effect of different treatment thresholds on fracture incidence and numbers of women with fractures within the year following bone mineral density measurement.

**Methods:** The study comprised 149 524 white postmenopausal women aged 50 to 104 years (mean age, 64.5 years). At baseline, bone mineral density was assessed by peripheral bone densitometry at the heel, finger, or forearm. New fractures during the next 12 months were self-reported.

**Results:** New fractures were reported by 2259 women, including 393 hip fractures; only 6.4% had

baseline T scores of  $-2.5$  or less (World Health Organization definition for osteoporosis). Although fracture rates were highest in these women, they experienced only 18% of the osteoporotic fractures and 26% of the hip fractures. By National Osteoporosis Foundation treatment guidelines, 22.6% of the women had T scores of 2.0 or less, or  $-1.5$  or less with 1 or more clinical risk factors. Fracture rates were lower, but 45% of osteoporotic fractures and 53% of hip fractures occurred in these women.

**Conclusions:** Using peripheral measurement devices, 82% of postmenopausal women with fractures had T scores better than  $-2.5$ . A strategy to reduce overall fracture incidence will likely require lifestyle changes and a targeted effort to identify and develop treatment protocols for women with less severe low bone mass who are nonetheless at increased risk for future fractures.

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From the Toni Stabile Osteoporosis Center, Columbia-Presbyterian Medical Center, and Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY (Dr Siris); Department of Outcomes Research and Management, Merck & Co Inc, West Point, Pa (Drs Chen, Abbott, and Berger); University of California, San Diego, La Jolla (Dr Barrett-Connor); Colorado Center for Bone Research, Lakewood, and University of Colorado, Denver (Dr Miller); and University of Maryland, Baltimore (Dr Wehren). Drs Siris, Barrett-Connor, Miller, and Wehren receive consulting fees from Merck & Co Inc to compensate them for time spent working on the NORA project.

**O**STEOPOROTIC FRACTURES cause substantial clinical and economic burdens for society.<sup>1,2</sup> More than 50% of women with hip fractures never completely return to their prefracture function; 25% are admitted to nursing homes and 20% die within 1 year after fracture.<sup>3</sup> Vertebral fractures are also associated with increased morbidity and mortality.<sup>1,4</sup> The number of osteoporotic fractures and cost for their treatment are expected to continue to rise because of the aging of the population and secular increases in the incidence of fractures.<sup>5,6</sup>

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The single most important predictor of osteoporotic fractures in postmenopausal women without a previous fracture is bone mineral density (BMD). There is a strong, continuous relationship between BMD and osteoporotic fractures,<sup>7,8</sup>

with a 1.5- to 2.6-fold increase in fracture risk for every standard deviation decrease in BMD; differences depend on the site where BMD is measured and the location of the fracture.<sup>9-11</sup>

Although it is well established that the risk of fracture is highest in women with the BMD levels usually used for the diagnosis of osteoporosis, women with higher BMD levels, such as those used for the diagnosis of osteopenia, are also at increased risk for fracture. In a previous analysis of 200 160 postmenopausal women in the National Osteoporosis Risk Assessment (NORA) study, women with osteoporosis (BMD levels at peripheral sites,  $\leq -2.5$ ) had 2.74 times higher 1-year risk of fracture, and women with osteopenia (BMD,  $-1$  to  $-2.49$ ) had 1.73 times higher risk of fracture, compared with women with normal BMD, independent of demographic and clinical factors.<sup>12</sup>

The BMD level appropriate for intervention with pharmacological treatment in postmenopausal women at increased

fracture risk is a critical issue when assessing the potential for reducing the overall fracture rate in the population. Several medications have been shown to prevent bone loss or reduce the risk of fracture in postmenopausal women with low bone mass or osteoporosis.<sup>13-20</sup> However, there is no agreement on the ideal BMD measurement at which to initiate pharmacological therapy. The lack of consensus on treatment intervention thresholds reflects the trade-offs between the known and potential benefits and risks of these treatments, the willingness of patients to initiate and continue therapy, and the available resources to pay for medications.

Treatment threshold levels available for consideration in clinical practice emerge principally from 2 sources. The first is derived from reports developed by the World Health Organization (WHO), and the second is from the National Osteoporosis Foundation (NOF). The WHO provided an operational definition of osteopenia and osteoporosis in 1994.<sup>21</sup> A postmenopausal woman with a BMD 2.5 SDs or more below the young adult mean (ie, T score,  $\leq -2.5$ ) at any site (spine, hip, or mid radius) is considered to have osteoporosis, and a woman with a BMD between  $-2.49$  and  $-1.0$  is considered to have osteopenia. Although the WHO cutpoints were designed as diagnostic thresholds and were not developed to provide criteria for selecting patients in whom to initiate therapy, many clinicians and reimbursement sources use the WHO level for osteoporosis (T score,  $\leq -2.5$ ) as the treatment intervention threshold.

The NOF developed treatment thresholds by combining BMD measured at the hip with clinical risk factors for fracture (eg, prior fracture as an adult, family history of fracture, body weight  $<127$  pounds, cigarette smoking).<sup>2,22</sup> According to NOF recommendations, women with a T score of  $-2.0$  or less or  $-1.5$  or less with at least 1 risk factor should be considered for treatment. The rationale for these particular threshold levels was evidence-based and influenced by cost-effectiveness considerations.<sup>2</sup>

It is not known how well the WHO- and NOF-derived treatment cutpoints identify women who will fracture in the near future and are therefore candidates for therapy to reduce fracture risk. In this article, we use information from NORA in an initial attempt to address this question. We examine fracture incidence and numbers of women with fractures within the year following a peripheral BMD measurement, comparing BMD thresholds derived from WHO and from NOF.

## METHODS

NORA is a longitudinal, observational study. The cohort is composed of 200 160 postmenopausal women (defined as having no menstrual period, bleeding, or spotting during the 6 months before enrollment), residing in 49 states who were at least 50 years old who did not have a previous diagnosis of osteoporosis or a BMD measurement within the 12 months preceding enrollment. Participants were recruited from the practices of 4236 primary care physicians in 34 states and the District of Columbia between September 1997 and March 1999. Physicians were identified based on having large numbers of postmenopausal women in their practices and not having in-office bone densitometry equipment. Approximately 17% of invited physicians

agreed to consider participating, and 75% to 80% of this group participated. With scientific support from NORA personnel, each physician office generated randomly selected names of up to 300 eligible women, of whom between 40 and 100 agreed to enter the study. There were no general health or preexisting medical condition exclusions, although women had to be ambulatory and able to visit their physicians' offices. Women treated with a bisphosphonate, calcitonin, or raloxifene hydrochloride were ineligible for participation, but current estrogen use was not an exclusion criterion. The study protocol and consent documents were approved by the national Essex Institutional Review Board, Lebanon, NJ. A detailed description of the study design and initial results of BMD and fracture outcomes have been reported previously.<sup>12,23,24</sup>

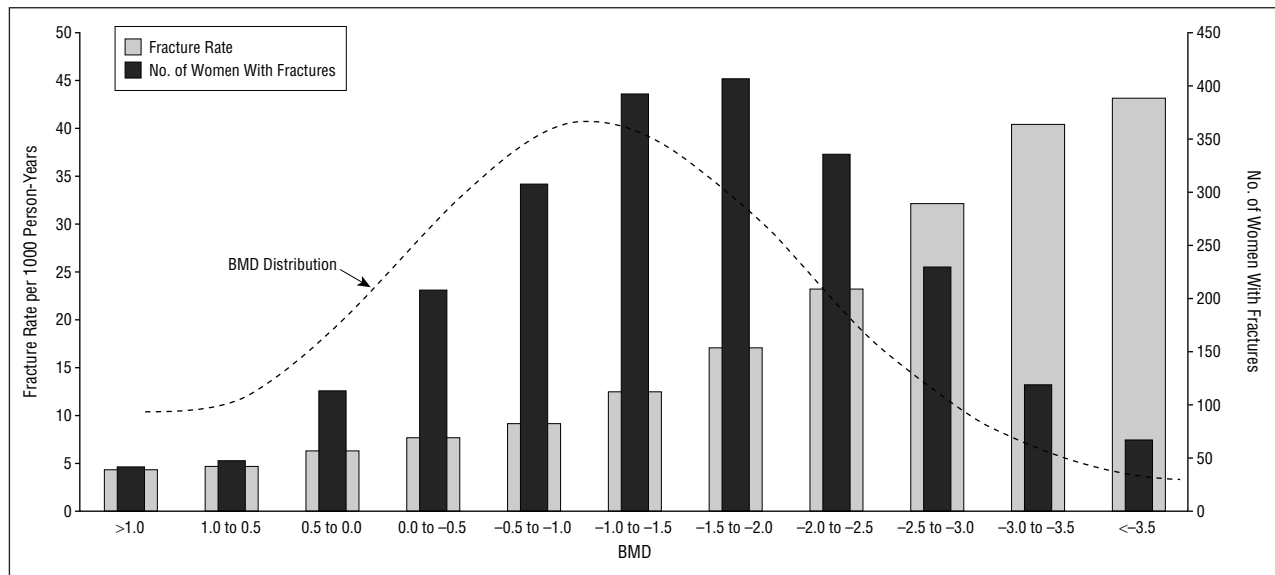
At baseline, each woman completed questionnaires that included demographic data and risk factors for osteoporosis, including personal and family history of fracture, lifestyle behaviors, and medication use. The questionnaires had been pilot tested before use in NORA to assure comprehensibility of the questions. Each subject had one of the following BMD measurements at a peripheral site conducted in her primary care physician's office: heel, using single x-ray absorptiometry (Osteoanalyzer; Norland Medical Systems Inc, White Plains, NY) or ultrasonography (Sahara; Hologic Inc, Bedford, Mass); forearm, using peripheral dual-energy x-ray absorptiometry (DXA) (pDEXA; Norland Medical Systems Inc); or finger, using peripheral DXA (AccuDEXA; Schick Technologies Inc, Long Island City, NY). Instruments were calibrated daily and in each new location and were standardized with device-specific phantoms. Testing was performed by NORA field personnel who were licensed technicians who had completed training by the equipment manufacturers and by the International Society for Clinical Densitometry. Quality assurance was maintained by staff at the quality assurance center at Synarc Inc, Portland, Ore, who monitored scans from all technicians according to a rigorous formal protocol.<sup>25</sup> T scores were calculated from the young adult normal white reference databases as reported by the equipment manufacturers. Our group has previously reported that each of these peripheral BMD measurements was equally predictive of increased risk of fracture during the year after the baseline evaluation.<sup>12,23</sup>

Approximately 12 months after enrollment, each participant received a follow-up questionnaire that included the following questions about new fractures:

Since you joined NORA, have you broken any bone? Please tell us which bone(s) you broke and the month and year you broke the bone. If you were hospitalized for broken bone(s), please tell us about how many days you stayed overnight in the hospital. (a) Hip; (b) Spine; (c) Rib; (d) Wrist; (e) Forearm; (f) Other Bone.

Reported new fractures were compared with fractures that had been described at baseline. If the sites were identical, the fracture was considered to be preexisting and was not included in the present analysis. If a participant reported 4 or more new fractures, these data were also excluded from analysis because these fractures were likely to be due to major trauma. For these analyses, osteoporotic fractures included self-reported fractures at the wrist or forearm, rib, spine, or hip. Patients who reported hip fractures were contacted by telephone for confirmation. This analysis was limited to white women (89.7% of the NORA cohort) to minimize any effect of ethnic variation. Among these 179 471 white women, 149 524 (83%) completed the follow-up survey and reported fracture status.

Proportions of women, fracture incidence rates, and proportions of fractures were calculated for the following BMD T-score thresholds:  $\leq -2.5$ ;  $\leq -2.0$ ;  $\leq -2.0$  or  $\leq -1.5$  with at least 1 additional risk factor such as prior fracture as an adult, family history of fracture, low body weight ( $<127$  lbs [57 kg]), and ciga-



Bone mineral density (BMD), osteoporotic fracture rate, and number of women with fractures.

rette smoking (NOF treatment criteria); and  $\leq -1.0$ . Proportions of women, fracture incidence rates, and proportions of fractures were also computed and displayed graphically for BMD T scores of  $>1.0$ ,  $<-3.5$ , and every 0.5 increment between 1.0 and  $-3.5$ . Fracture rates and proportions of fractures were computed for all osteoporotic fractures (including hip fractures) and specifically for hip fractures. Fracture rates were calculated per person, not total number of fractures (ie, if a participant reported 2 new fractures, this was counted as 1 fracture event), and weighted for duration of follow-up. All analyses were conducted using SAS version 6.12 (SAS Institute, Cary, NC).

## RESULTS

The mean  $\pm$ SD age of these women was  $64.5 \pm 9.3$  years (range, 50-104 years). Bone mineral density T scores were obtained using single x-ray absorptiometry (heel) in 79 185 women (53%), peripheral DXA (distal forearm) in 51 941 women (35%), peripheral DXA (finger) in 10 836 women (7%), and ultrasonography (heel) in 7 562 women (5%). New osteoporotic fractures ( $n=2340$ ) were reported by 2259 women. Of these, 393 reported a hip fracture, representing 17.4% of all women who reported a fracture.

The **Figure** illustrates graphically the strong continuous relationship between lower BMD and higher fracture rate, expressed as the number of women who fractured per 1000 person-years of follow-up. The Figure also shows the distribution of BMD T scores within the NORA population, which approximates a normal distribution. The absolute number of women who sustained an incident fracture within a given T-score range is a function of the fracture rate multiplied by the population distribution within that T-score range. The fracture rates were highest in women with the lowest T scores, as expected. Nevertheless, 82% of the 2259 women who reported fractures at 1 year had peripheral T scores greater than  $-2.5$ , and 67% had T scores greater than  $-2.0$ .

Estimates of the fracture rate and proportion of all osteoporotic fractures and hip fractures occurring at various levels of BMD thresholds are shown in the **Table**. Only 6.4% of participants had T scores of  $-2.5$  or less.

Although fracture rates were 35.7 per 1000 person-years for osteoporotic fracture and 8.8 per 1000 person-years for hip fracture in these women, they contributed only 18% of the osteoporotic fractures and 26% of the hip fractures. Twenty-three percent of women met NOF treatment guidelines (ie, T score,  $\leq -2.0$ , or  $\leq -1.5$  with  $\geq 1$  risk factors); fracture rates were somewhat lower in this group (24.7 per 1000 person-years for osteoporotic fracture and 5.1 per 1000 person-years for hip fracture). However, 45% of the osteoporotic fractures and 53% of hip fractures occurred in these women who met the NOF treatment guidelines. If a T-score cutpoint of  $-1.0$  or less was applied, 70% of women with osteoporotic fractures and 77% of those with hip fractures were identified; however, fracture rates for osteoporotic fracture and hip fracture were even lower: 17.4 per 1000 person-years and 3.6 per 1000 person-years, respectively.

## COMMENT

In this large cohort recruited from primary care practices in the United States, 82% of women who sustained osteoporotic fractures of the wrist or forearm, hip, rib, or spine within 1 year after peripheral BMD testing had T scores greater than  $-2.5$ . Only 18% of the NORA women who had fractures would have been treatment candidates if the intervention threshold had been set at  $-2.5$  or less. This would result in no intervention in 82% of the women who actually experienced a new fracture during the first year after BMD was measured. Therefore, treatment of only women with T scores of  $-2.5$  or less would have a limited effect on reducing the number of women who sustain osteoporotic fractures, including hip fractures. Recent results from the Study of Osteoporotic Fractures showed a similar observation in older women (lowest age, 65 years), in which 54% of the women with hip fractures and 74% of the women with any nonvertebral fracture had a total hip T score greater than  $-2.5$ .<sup>26</sup>

The NOF guidelines recommend pharmacological intervention in women with T scores of  $-2.0$  or less, or

### Fracture Rates, Proportions of Population, and Percentages of Fractures, According to T-Score Groups

T Score	Proportion of Population, %	Osteoporotic Fracture Rate*	Osteoporotic Fracture, %†	Hip Fracture Rate*	Hip Fracture, %
≤-2.5	6.4	35.7	18	8.8	26
≤-2.0	14.5	28.6	33	6.5	44
National Osteoporosis Foundation Guidelines‡	22.6	24.7	45	5.1	53
≤-1.0	45.3	17.4	70	3.6	77

\*Per 1000 person-years.

†Self-reported fractures of wrist or forearm, hip, spine, or rib.

‡T score ≤-2.0 or ≤-1.5 with ≥1 risk factors.

-1.5 or less with prior fracture as an adult, family history of fracture, low body weight (<127 pounds), or cigarette smoking. Cutpoints in the present study based on these recommendations identified 45% of women with osteoporotic fractures and 53% of those with hip fractures. This threshold increased the number of candidates for medical intervention to 22.6% of the NORA population, capturing nearly half of those who fractured with intervention in less than a quarter of the population. If the treatment threshold is shifted further to below -1.0, 70% of the women who experienced osteoporotic fractures and 77% of those with hip fractures would have been identified as treatment candidates, but this would require treating nearly half of the women, substantially increasing cost.

The observation that more than half (52%) of the NORA women experiencing an incident osteoporotic fracture within 1 year had a BMD T score of -1.0 to -2.5 underscores the unmet need to identify those women who are most likely to fracture and might benefit from targeted pharmacological intervention. Although the fracture rate per 1000 person-years is lower than that for women with T scores below -2.5, most of the fractures occur in this middle area of the BMD distribution (Figure), because most the women are in this T-score range. It will be necessary to determine methods for risk stratification, based on combining BMD data with those risk factors that best serve to predict the risk of future fracture, to allow more efficient application of therapeutic resources. Other risk factors have been reported to be predictive of fractures independent of BMD, including age,<sup>11,27</sup> prior fracture,<sup>28,29</sup> body size,<sup>8,29</sup> and factors related to falls.<sup>30</sup>

Fracture prevention will require not only better targeting of high-risk women with less severe BMD T-score levels but also evidence that treatments lower fracture risk in those women. Most clinical trials with fracture outcomes have been conducted in women with T scores of -2.0 or less, measured at the spine or hip, or in women with prevalent vertebral fractures.<sup>13,14</sup> Little data exist to show that available agents are effective at reducing the risk of fracture in women with BMD T scores greater than -2.0, because such women have not been the focus of most clinical trials with first-fracture outcomes. In prevention trials, antiresorptive agents maintain or increase BMD in women with low bone mass, contrasted with the loss of bone density observed with placebo.<sup>31-33</sup> Preservation of bone mass with attendant preservation of bone architecture over time would be expected to afford protection against fracture. Recent findings from the Women's Health Initiative trial<sup>17</sup>

showed a reduction of clinical fractures and hip fractures with hormone therapy in women unselected for osteoporosis by BMD or prior fracture criteria, which suggests that treatment of women with osteopenia reduces fracture risk. With large enough studies or long enough studies, other antiresorptives would be expected to provide similar benefit to women with osteopenia.

Despite the advantages of a large population of women ranging from age 50 to 104 years from throughout the United States, this study has some limitations. First, NORA included only women with personal physicians and excluded women who had a prior diagnosis of osteoporosis or were receiving specific treatment for osteoporosis. Therefore, NORA women may be healthier, with lower fracture rates and better BMD, than the US population. Second, peripheral devices were used to assess BMD in NORA, and comparability of these peripheral BMD test to the gold standard measurements of central hip and spine BMD is still under study. However, the WHO diagnostic criteria were established based on central (hip and spine) and peripheral (forearm) BMD measurement devices.<sup>21</sup> T scores obtained by peripheral devices may not always be as low as T scores determined from central DXA devices, resulting in prevalences of WHO-defined osteoporosis using peripheral device-specific databases of 3% to 14%, compared with prevalences based on hip measurements for white women of 16% to 20%.<sup>34,35</sup> The discrepancies between T-score calculations among various BMD devices are well recognized and exist among different central DXA skeletal sites and devices as well.<sup>36-40</sup> As previously reported, prediction of fracture risk in NORA, including risk of hip fracture, with peripheral BMD measurements was similar to that reported in other studies<sup>12,23</sup> with hip BMD measurements. Third, fractures in NORA were self-reported, without radiological confirmation, so fractures may have been overestimated (eg, sprains or arthritis reported as fractures) or underestimated (unrecognized or subclinical fractures). It has previously been shown, however, that self-report of fractures is generally reliable.<sup>41-43</sup> Because most spine fractures are asymptomatic or at least unrecognized, NORA cannot address the value of risk factors or peripheral BMD to predict nonclinical spine fractures. Over the long term, clinical and subclinical vertebral fractures are associated with increased morbidity and mortality.<sup>4,44</sup> Finally, the data in this analysis are derived from information from white postmenopausal women, and generalization to other ethnic groups should be made with caution, if at all, until analyses from those groups become available.



We conclude that substantial reductions in the population burden of osteoporotic fractures experienced by postmenopausal women cannot be accomplished simply by aggressively treating women with T scores of  $-2.5$  or less. There will have to be a targeted effort toward better identification and treatment of women with moderate levels of low bone mass, who are nonetheless at an increased risk for future fracture. We believe that non-pharmacological approaches, including weight-bearing exercise, strength training, and a healthy diet, including adequate calcium, should continue to be encouraged. The NOF treatment intervention guidelines, as defined in the present study, provide a reasonable strategy for targeting and treating women at high risk for fractures. Future research is required to develop strategies to risk-stratify women with osteopenia (T scores,  $-2.5$  to  $-1.0$ ) who are at substantial risk for fracture and who constitute most of those who sustain fractures.

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Corresponding author and reprints: Ethel S. Siris, MD, Metabolic Bone Disease Program, Toni Stabile Osteoporosis Center, Columbia-Presbyterian Medical Center, 180 Fort Washington Ave, New York, NY 10032-3784 (e-mail: es27@columbia.edu).

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## 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada

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# 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada

Jacques P. Brown, Robert G. Josse, for the Scientific Advisory Council of the Osteoporosis Society of Canada

## Abstract

**Objective:** To revise and expand the 1996 Osteoporosis Society of Canada clinical practice guidelines for the management of osteoporosis, incorporating recent advances in diagnosis, prevention and management of osteoporosis, and to identify and assess the evidence supporting the recommendations.

**Options:** All aspects of osteoporosis care and its fracture complications — including classification, diagnosis, management and methods for screening, as well as prevention and reducing fracture risk — were reviewed, revised as required and expressed as a set of recommendations.

**Outcomes:** Strategies for identifying and evaluating those at high risk; the use of bone mineral density and biochemical markers in diagnosis and assessing response to management; recommendations regarding nutrition and physical activity; and the selection of pharmacologic therapy for the prevention and management of osteoporosis in men and women and for osteoporosis resulting from glucocorticoid treatment.

**Evidence:** All recommendations were developed using a justifiable and reproducible process involving an explicit method for the evaluation and citation of supporting evidence.

**Values:** All recommendations were reviewed by members of the Scientific Advisory Council of the Osteoporosis Society of Canada, an expert steering committee and others, including family physicians, dietitians, therapists and representatives of various medical specialties involved in osteoporosis care (geriatric medicine, rheumatology, endocrinology, obstetrics and gynecology, nephrology, radiology) as well as methodologists from across Canada.

**Benefits, harm and costs:** Earlier diagnosis and prevention of fractures should decrease the medical, social and economic burdens of this disease.

**Recommendations:** This document outlines detailed recommendations pertaining to all aspects of osteoporosis. Strategies for identifying those at increased risk (i.e., those with at least one major or 2 minor risk factors) and screening with central dual-energy x-ray absorptiometry at age 65 years are recommended. Bisphosphonates and raloxifene are first-line therapies in the prevention and treatment of postmenopausal osteoporosis. Estrogen and progestin/progesterone is a first-line therapy in the prevention and a second-line therapy in the treatment of postmenopausal osteoporosis. Nasal calcitonin is a second-line therapy in the treatment of postmenopausal osteoporosis. Although not yet approved for use in Canada, hPTH(1-34) is expected to be a first-line treatment for postmenopausal women with severe osteoporosis. Ipriflavone, vitamin K and fluoride are not recommended. Bisphosphonates are the first-line therapy for the prevention and treatment of osteoporosis in patients requiring prolonged glucocorticoid therapy and for men with osteoporosis. Nasal or parenteral calcitonin is a first-line treatment for pain associated with acute vertebral fractures. Impact-type exercise and age-appropriate calcium and vitamin D intake are recommended for the prevention of osteoporosis.

Dr. Brown is with the Division of Rheumatology, Centre de recherche du CHUL, Université Laval and Dr. Josse is with the Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto

Lists of the members of the Scientific Advisory Council, the Guidelines Steering Committee and the section committees appear at the end of the article.

## Endorsing organizations

Canadian Association on Gerontology

Canadian Society of Endocrinology and Metabolism

Canadian Society for Exercise Physiology

Canadian Orthopaedic Association

Dietitians of Canada

Canadian Rheumatology Association

*This article has been peer reviewed.*

**Validation:** All recommendations were graded according to the strength of the evidence; where the evidence was insufficient and recommendations were based on consensus opinion alone, this is indicated. These guidelines are viewed as a work in progress and will be updated periodically in response to advances in this field.

**O**steoporosis is a major public health problem in Canada (and worldwide) and its prevalence is increasing. In Canada, approximately 1 in 4 women and 1 in 8 men have osteoporosis.<sup>1</sup> Because some 25% of the population will be over 65 years of age by 2041, the incidence of osteoporosis is expected to rise steeply over the next few decades.<sup>2</sup> The public health and clinical importance of osteoporosis lies in the fractures associated with the disease. According to conservative estimates, a 50-year-old Caucasian woman has a remaining lifetime risk of 40% for hip, vertebra or wrist fractures.<sup>3</sup>

This morbidity burden has considerable medical, social and financial implications. Many vertebral fractures are occult and asymptomatic; however, an increased mortality rate is associated with them, as for hip fractures.<sup>4-6</sup> Mortality rate is 20% higher on average within 1 year of a hip fracture.<sup>7</sup> Put another way, for women, the 1-in-6 lifetime risk of hip fracture is greater than the 1-in-9 risk of developing breast cancer, and the death rate associated with hip fracture is higher.<sup>8,9</sup> Moreover, 50% of women who sustain a hip fracture do not return to their previous functional state and become dependent on others for daily activities. About 20% require long-term care.<sup>7</sup>

The greatest direct expenditures associated with osteoporosis arise from treatment of fractures and their sequelae. Although difficult to assess accurately, these costs are substantial. According to estimates,<sup>10</sup> in 1993 the total acute care cost for osteoporosis (admission to hospital, outpatient care and drug therapy) was over Can\$1.3 billion. Over the past decade, these costs have increased and in the United States have risen to Can\$17–20 billion a year. These burgeoning costs may outstrip the resources designated to deal with osteoporotic fractures (i.e., orthopedic surgeons, operating room time and space, rehabilitation programs, drug budgets).

Although osteoporotic fractures are an important cause of morbidity, disability and mortality, they are preventable. With this in mind, the Scientific Advisory Council (SAC) of the Osteoporosis Society of Canada (OSC) set itself the task of updating and expanding the 1996 consensus statements<sup>1,11</sup> into evidence-based guidelines.

## Methods

### Process

In 1999, in consultation with its SAC, the OSC created a Guidelines Steering Committee and identified the following areas

related to osteoporosis for review: risk factors, diagnosis, nutrition, physical activity, drug therapies and alternative or complementary therapies. The task of the steering committee, which was made up of members of the SAC, was to direct the organization of the guidelines. Sixty-five stakeholders were recruited to participate in the process; they included additional members of the SAC, family physicians, dietitians, therapists and representatives of the various medical specialties involved in osteoporosis care (geriatric medicine, rheumatology, endocrinology, obstetrics and gynecology, nephrology and radiology), and methodologists from across Canada. These stakeholders were divided into section committees, each comprising 4–9 members and a chair. Each section committee was to review the literature and develop recommendations in one of the identified areas.

The section committees identified key questions within their review area to be addressed in the guidelines. A decision was made to focus on management of *primary* osteoporosis. However, although no formal review of the literature was undertaken regarding risk factors for, or management of, secondary osteoporosis, the committees chose to review certain papers regarded as pivotal in this area — in particular, trials evaluating glucocorticoid-induced osteoporosis. In addition, the search for risk factors focused on *risk factors for fragility fracture*, the most important clinical outcome of osteoporosis. Therefore, no formal review of the literature was undertaken regarding risk factors for low bone mineral density (BMD).

Under the direction of the steering committee, the section committees carried out an extensive literature search for articles relevant to each of the key questions. Searches for both review and original articles were carried out in the following databases: Medline, Embase, HealthStar, Cancerlit, Cinahl, Grateful Med, Toxline, Psycinfo and the Cochrane Collaboration. All review articles were scanned for additional original papers. Each database was searched as far back as records existed and forward to May 2000. In addition, some singularly important and pivotal studies published after our cut-off date were selected and addressed in these guidelines. All abstracts retrieved were reviewed by the chair and one other member of the appropriate section committee to determine their applicability to each question. If an abstract or title was deemed applicable, the full article was obtained, numbered and distributed to 2 or 3 committee members for review.

A total of 89,804 abstracts were retrieved; from these, 6941 full articles were obtained for review. Two or 3 reviewers independently reviewed each article using a standardized form. Each article was assigned a level of evidence based on the question addressed and the design of the study (Table 1).<sup>12</sup> If the reviewers did not achieve consensus, the article was reviewed again. If there was still no consensus, members of the steering committee were asked to review the article and make a decision.

The principles used for developing these guidelines, assigning levels of evidence to the relevant articles and making and grading recommendations were drawn from the guidelines literature.<sup>13,14</sup>



Once all key articles had been reviewed and assigned a level of evidence, each section committee reviewed the data and developed recommendations. Recommendations were graded according to the system used to grade recommendations for diabetes,<sup>12</sup>

**Table 1: Criteria used to assign a level of evidence to articles<sup>12</sup>**

Level	Criteria
<b>Studies of diagnosis</b>	
1	i. Independent interpretation of test results ii. Independent interpretation of the diagnostic standard iii. Selection of people suspected, but not known, to have the disorder iv. Reproducible description of the test and diagnostic standard v. At least 50 people with and 50 people without the disorder
2	Meets 4 of the Level 1 criteria
3	Meets 3 of the Level 1 criteria
4	Meets 1 or 2 of the Level 1 criteria
<b>Studies of treatment and intervention</b>	
1+	Systematic overview or meta-analysis of randomized controlled trials
1	1 randomized controlled trial with adequate power
2+	Systematic overview or meta-analysis of Level 2 randomized controlled trials
2	Randomized controlled trial that does not meet Level 1 criteria
3	Non-randomized clinical trial or cohort study
4	Before–after study, cohort study with non-contemporaneous controls, case–control study
5	Case series without controls
6	Case report or case series of < 10 patients
<b>Studies of prognosis</b>	
1	i. Inception cohort of patients with the condition of interest, but free of the outcome of interest ii. Reproducible inclusion and exclusion criteria iii. Follow-up of at least 80% of participants iv. Statistical adjustment for confounders v. Reproducible description of the outcome measures
2	Meets criterion i and 3 of the 4 other Level 1 criteria
3	Meets criterion i and 2 of the 4 other Level 1 criteria
4	Meets criterion i and 1 of the 4 other Level 1 criteria

**Table 2: Grades of recommendation for clinical practice guidelines<sup>12</sup>**

Grade	Criteria
A	Need supportive level 1 or 1+ evidence plus consensus*
B	Need supportive level 2 or 2+ evidence plus consensus*
C	Need supportive level 3 evidence plus consensus
D	Any lower level of evidence supported by consensus

\*An appropriate level of evidence was necessary, but not sufficient to assign a grade in recommendation; consensus was required in addition.

which incorporates both level of evidence *and* expert consensus (Table 2). Recommendations were assigned a grade of D when they were based only on committee consensus in the absence of clear supporting evidence or when evidence was weak. Before a final grade was assigned, all recommendations were reviewed by the steering committee, which included several methodologists who were neither directly involved in the initial assessment of evidence nor with the grading of the recommendations. If appropriate, the assigned level of evidence or grade of recommendation was modified on the basis of this final assessment.

## Definitions

Osteoporosis was defined at a 1993 consensus conference as “a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a resultant increase in fragility and risk of fracture.”<sup>15</sup> Recently a United States National Institutes of Health consensus conference modified this definition as follows: “a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of 2 main features: bone density and bone quality.”<sup>16</sup> Probably the only clinically applicable index of bone quality at present is a patient’s history of a fragility fracture. In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low bone density. (Note: The World Health Organization (WHO)<sup>17</sup> defines fragility fracture as “a fracture caused by injury that would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone.” Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma.)

In interpreting BMD results, the OSC decided to adopt the widely used WHO<sup>18,19</sup> study group’s definitions, which are based on a comparison of a patient’s BMD with the mean for a normal young adult population of the same sex and race. The patient is assigned a “T-score,” which is the number of standard deviations above or below the mean BMD for normal young adults as follows:

1. Normal BMD is defined as a T-score between +2.5 and –1.0, inclusive (i.e., the patient’s BMD is between 2.5 standard deviations [SDs] above the young adult mean and one SD below the young adult mean, inclusive).
2. Osteopenia (low BMD) is associated with a T-score between –1.0 and –2.5, inclusive. Osteopenia is also a term used by radiologists to indicate that the bones on a plain x-ray film appear to be of decreased mineral content.
3. Osteoporosis is defined as a T-score at or below –2.5.

The WHO study group added a 4th category “severe osteoporosis” to describe patients whose T-score is at or below –2.5 and who also have suffered a fragility fracture. The recommendations concerning risk factors in this document should make the importance of fracture history in assessing a patient for osteoporosis very clear.

The term “efficacious” is used in reference to evidence from a randomized controlled trial (RCT); the term “effective” refers to evidence from a nonexperimental observational study. “Perimenopause” describes the several years of change before and during the first year beyond final menstrual flow. “Menopause” refers to one or more years following the final menstrual flow. There has been a change from previous terminology about therapy with

estrogen and progestin or progesterone for postmenopausal women. Approximately 10 years ago, the OSC adopted the term “ovarian hormone therapy” (OHT) to reflect its awareness that the hormonal changes during the menopause transition and menopause are entirely normal. Although the SAC maintains this position, to aid in understanding by those who use these guidelines, it was decided to use the terms “estrogen and progestin/progesterone therapy” and the abbreviation for hormone replacement therapy, “HRT.”

Finally, a recommendation that a specific therapy be used as “first-line” therapy for osteoporosis relies on Level 1 evidence for prevention of fragility fracture (mainly vertebral fracture), but this may be modified by other extenuating circumstances (e.g., unfavorable risk–benefit profile). “Second-line” therapy is the term used when adequate evidence exists for preventing loss of BMD, but inadequate data are available regarding fracture prevention or there are problems with the study or its interpretation.

## Identifying those at high risk

The OSC recommends that all postmenopausal women and men over 50 years of age be assessed for the presence of risk factors for osteoporosis. The selected key risk factors should aid physicians in identifying those who require further assessment and investigation to determine whether medical intervention is needed to reduce their risk of osteoporotic (fragility) fracture. The main areas of concern are wrist, humerus, ribs, vertebral body, pelvis and hip. When a patient is identified as having a high risk for fracture, a discussion regarding treatment is recommended. Clinical judgment and the patient’s preference, as well as evidence-based clinical trial data, will determine if, when and what treatment is initiated.

### Selection of risk factors for clinical use

Many factors other than a low BMD have been suggested as predictors of risk of future fracture. In elderly women with no history of hip fracture, such variables as bone density, calcium intake, maternal history and even hair colour were related to the incidence of hip fracture during 4 years of follow-up.<sup>20</sup> Important predictive factors were bone density in combination with age, fracture history, various drug treatments, weight loss and physical fitness. A review of 94 cohort studies and 76 case–control studies revealed about 80 factors considered to be related to future fracture risk.<sup>21</sup> However, when classified according to their strength of association with fracture, only 15% had relative risk ratios greater than 2. Most were associations with primary disorders such as hyperparathyroidism or with treatments such as glucocorticoid therapy. The remaining important factors included low body weight, physical inactivity and aging.

The presence of a key risk factor should alert the physician to the need for further assessment and possibly active intervention, such as pharmacologic therapy, to prevent fracture. BMD is the best quantifiable predictor of osteoporotic fracture, and low BMD and other major risk factors

combine to further increase a person’s risk of fracture. Therefore, BMD should be measured in a postmenopausal woman or a man over the age of 50 with 1 of the other major risk factors for fracture.

Risk factors for osteoporotic fracture should not be considered to be independent of one another; they are additive and must be considered in the context of baseline age and sex-related risk of fracture. For example, a 55 year old with low BMD is at significantly less risk than a 75 year old with the same low BMD. A person with low BMD and a prior fragility fracture is at considerably more risk than another person with the same low BMD and no fracture.

Osteoporotic fractures occur most commonly in men and women over 65 years of age, and medical interventions have only been demonstrated to be effective in preventing fractures in populations with an average age over 65 years. However, most currently approved therapies for osteoporosis prevent or reverse bone loss when initiated at or soon after the age of 50 years. Therefore, it seems prudent to begin the identification of people at high risk for osteoporosis in their 50s, if they are willing to accept a treatment.

### Four key risk factors for fracture

After reviewing the literature and considering the effect of potential confounders, we identified 4 key factors as predictors of fracture related to osteoporosis: low BMD, prior fragility fracture, age and family history of osteoporosis. Other factors that are commonly cited — weight < 57 kg, weight loss since age 25, high caffeine intake and low calcium intake — were not found to be consistent independent predictors of fracture risk, after taking into consideration age and/or BMD.

### Bone mineral density

The relation between BMD and fracture risk has been calculated in a large number of studies. A meta-analysis by Marshall and colleagues<sup>22</sup> of some of the earlier studies probably still represents the best estimate. BMD is clearly the most readily quantifiable predictor of fracture risk for those who have not yet suffered a fragility fracture. For each standard deviation of BMD below a baseline level (either mean peak bone mass or mean for the reference population of the person’s age and sex), the fracture risk approximately doubles. This risk should always be viewed in the context of the person’s age. A 25 year old with a low BMD (e.g., a T-score of –2.5) has a very low 10-year risk of fracture that is not appreciably greater than that of a 25 year old with a high BMD. However, a person with the same BMD at age 65 has a much higher 10-year risk of fracture.

What are the risk factors for low BMD? Or, for practical purposes, who should be selected for BMD measurements? This is a question with major economic implications. What criteria should be used to select people for BMD measurements?

Risk factors for osteoporosis are summarized in Table 3. A BMD measurement is recommended for those with at least one major or 2 minor risk factors (Figure 1; Table 3). Several attempts have been made to develop decision tools to aid physicians in selecting patients for BMD testing<sup>23-25</sup> using a variety of combinations of risk factors, including age, prior fractures, estrogen use, rheumatoid arthritis, smoking, low body weight and family history of osteoporotic fracture.

None of these decision tools is without problems and, if applied to the general population of postmenopausal women over the age of 50, will result in a significant number being selected for BMD measurement.<sup>26</sup> However, all of these decision tools seem to identify at least 90% of women over 65 years of age as candidates for BMD measurement. The National Osteoporosis Foundation guidelines<sup>25</sup> suggest it is also cost-effective to measure bone density in all women over age 65, but this recommendation was based on the assumption that patients would receive low-cost estrogen-progesterone therapy.

It is abundantly clear from epidemiology studies that age is a major risk factor for fracture. Because low BMD is also a major risk factor for fracture and BMD decreases with age, there must also be an age at which it is worthwhile to begin using BMD as a screening tool. The OSC has taken the position that BMD testing is appropriate for targeted case-finding among people under age 65 and for all women age 65 and older because of the high risk of osteoporosis and fracture after that age.

### Prior fragility fracture

A prior fragility fracture places a person at increased risk for another one.<sup>20,27-30</sup> The increased risk is 1.5- to 9.5-fold depending on age at assessment, number of prior fractures and the site of the incident fracture.<sup>27,28,30-34</sup>

Vertebral fractures have been best studied in this regard. The presence of a vertebral fracture increases the

risk of a second vertebral fracture at least 4-fold.<sup>35-36</sup> A study of the placebo group in a recent major clinical trial<sup>37</sup> showed that 20% of those who experienced a vertebral fracture during the period of observation had a second vertebral fracture within 1 year. Vertebral fractures are also indicators of increased risk of fragility fractures at other sites, such as the hip.<sup>38</sup> In a clinical trial of risendronate,<sup>38</sup> the combination of a vertebral fracture and low bone density was associated with a doubling of the 3-year risk of hip fracture (from 3% to 6%) in women over the age of 70. Similarly, wrist fractures predict vertebral and hip fractures.<sup>30</sup> Patients with a hip fracture are at increased risk of a second hip fracture. Pooling the results from all studies (women and men) and for all fracture sites, the risk of subsequent fracture among those with a prior fracture at any site is 2.2 times that of people without a prior fragility fracture (95% confidence interval [CI] 1.9-2.6).<sup>30</sup>

### Age

Age is clearly a major contributor to fracture risk.<sup>20,26,34,39</sup> As summarized in a recent review by Kanis and others,<sup>40</sup> the 10-year probability of experiencing a fracture of forearm, humerus, spine or hip increases as much as 8-fold between ages 45 and 85 for women and 5-fold for men (Table 4).

### Family history of osteoporotic fracture

This factor has been best studied with respect to hip fracture. The Study of Osteoporotic Fractures,<sup>20</sup> for example, identified a maternal history of hip fracture as a key risk factor for hip fracture in a population of elderly women. A history of hip fracture in a maternal grandmother also carries an increased risk of hip fracture.<sup>41</sup>

Although most studies have focused on the index person's mother or other female family members, genetic influence on risk of osteoporosis is multifactorial, and one should not ignore a history of osteoporotic fracture in first- or second-degree male relatives. The emphasis on the presence of osteoporotic fractures in patients' female relatives in epidemiology studies probably reflects the belief that osteoporosis is mostly a disease of women. It is now clear that osteoporosis is common in men; therefore, although the recommendations focus on hip fractures in a patient's mother or grandmother, other family members should be included during assessment of genetic contribution to osteoporosis risk.

Genetic influence on osteoporosis and BMD is extremely impor-

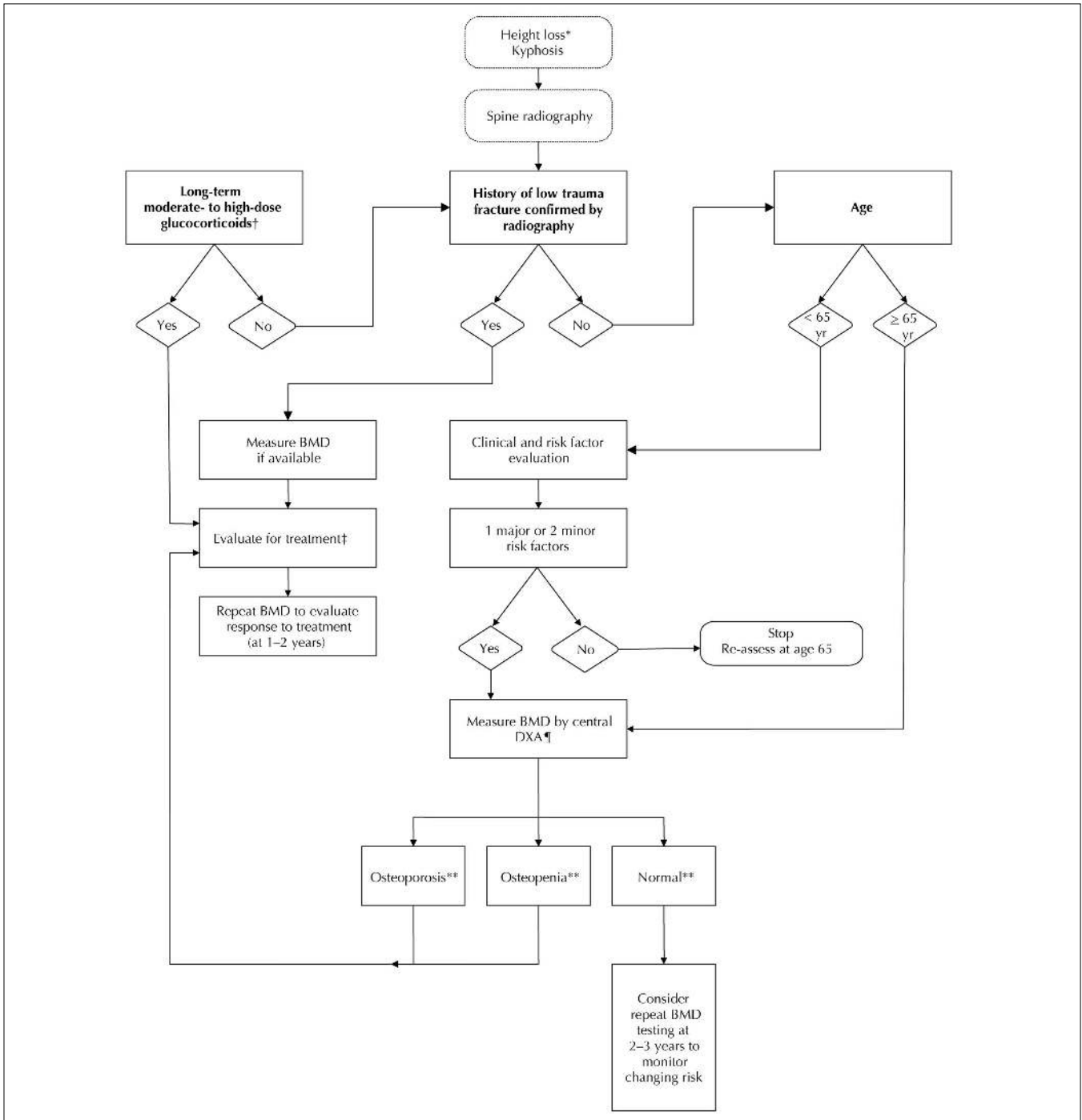
**Table 3: Factors that identify people who should be assessed for osteoporosis**

Major risk factors	Minor risk factors
<ul style="list-style-type: none"> <li>• Age ≥ 65 years</li> <li>• Vertebral compression fracture</li> <li>• Fragility fracture after age 40</li> <li>• Family history of osteoporotic fracture (especially maternal hip fracture)</li> <li>• Systemic glucocorticoid therapy of &gt; 3 months duration</li> <li>• Malabsorption syndrome</li> <li>• Primary hyperparathyroidism</li> <li>• Propensity to fall</li> <li>• Osteopenia apparent on x-ray film</li> <li>• Hypogonadism</li> <li>• Early menopause (before age 45)</li> </ul>	<ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• Past history of clinical hyperthyroidism</li> <li>• Chronic anticonvulsant therapy</li> <li>• Low dietary calcium intake (see nutrition section)</li> <li>• Smoker</li> <li>• Excessive alcohol intake</li> <li>• Excessive caffeine intake (see nutrition section)</li> <li>• Weight &lt; 57 kg</li> <li>• Weight loss &gt; 10% of weight at age 25</li> <li>• Chronic heparin therapy</li> </ul>

tant; it has been estimated that heredity accounts for 50–80% of the variability in BMD.<sup>42</sup> Genetic influences on bone have been the subject of major scientific investigations, and a number of genes have been associated with osteoporosis. However, these discoveries have not yet resulted in a clinical application in the diagnosis and treatment of osteoporosis at the practitioner level; thus,

we have chosen not to review the genetics of osteoporosis in this document, beyond emphasizing the importance of a family history of osteoporosis.

Fewer studies have considered risk factors for osteoporotic fractures in men, but, as in women, age, low BMD and prior fragility fractures increase this risk. Although we do not list family history of fracture as a risk factor for men,



**Fig. 1: Who should be tested for osteoporosis?** (Note: \*4 cm historical height loss; 2 cm prospective height loss [Grade D]. †Low to moderate: 2.5–7.5 mg prednisone/day; moderate to high: > 7.5 mg prednisone/day. ‡See Fig. 2. ¶ Central DXA = spine and hip. \*\*As defined by the World Health Organization.)

it should not be ignored. We identified 3 studies,<sup>43-45</sup> of osteoporotic fracture in men that provided Level 1 evidence for osteoporosis risk factors, but 2 of these<sup>44,45</sup> did not focus on family history of fragility fracture.

**Table 4: Average 10-year probability (%) of an osteoporotic fracture\* by sex, age and BMD expressed as T-score (adapted from Kanis et al.<sup>40</sup>)**

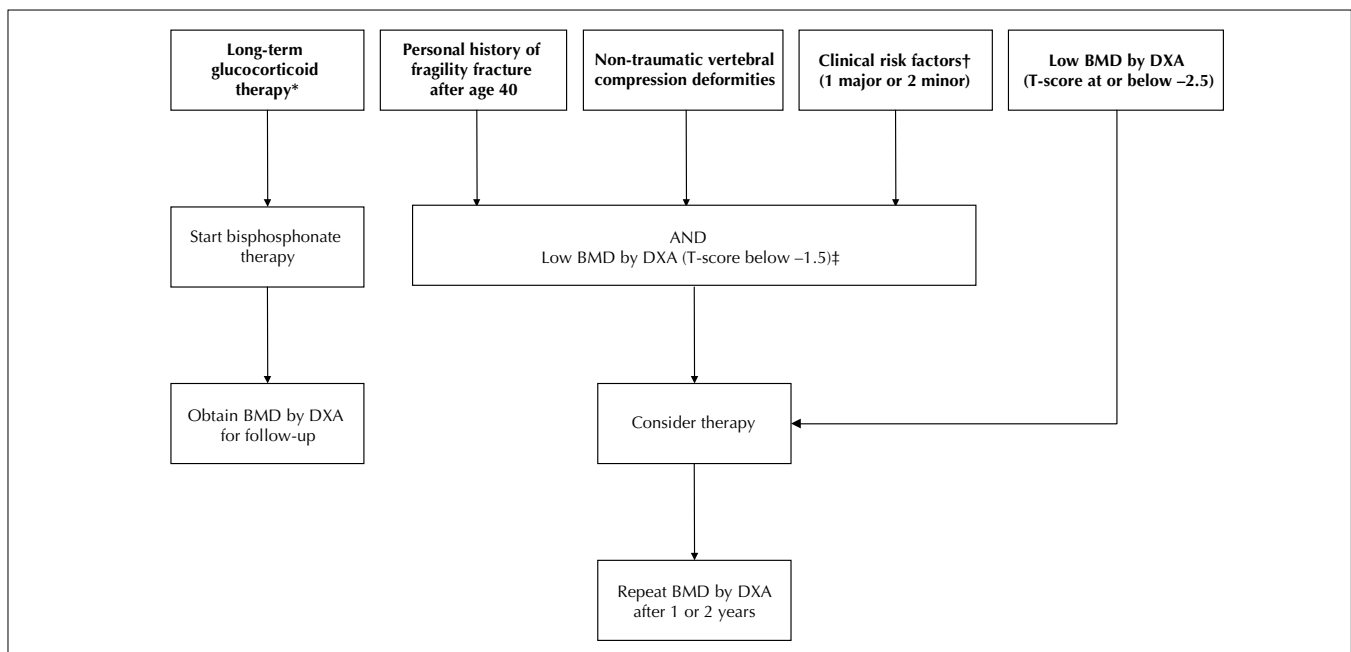
Age; years	Overall average probability	T-score				
		1	0	-1	-2	Below -2.5
<b>Men</b>						
50	3.3	1.8	2.7	4.2	6.3	9.2
55	3.9	1.9	3.0	4.6	7.0	10.4
60	4.9	2.5	3.6	5.4	7.9	11.6
65	5.9	3.0	4.3	6.2	8.8	13.0
70	7.6	3.4	5.1	7.4	10.9	16.2
75	10.4	4.1	6.3	9.6	14.4	21.5
80	13.1	5.3	7.7	11.1	15.8	23.2
85	13.1	5.3	7.5	10.4	14.3	21.4
<b>Women</b>						
50	6.0	2.4	3.8	5.9	9.2	13.9
55	7.8	2.6	4.1	6.7	10.7	16.8
60	10.6	3.2	5.1	8.2	13.0	20.5
65	14.3	4.0	6.3	10.0	15.6	24.9
70	18.9	4.3	7.1	11.5	18.3	29.8
75	22.9	4.2	7.0	11.8	19.4	32.6
80	26.5	4.6	7.7	12.7	20.5	34.4
85	27.0	4.5	7.4	12.0	19.1	33.1

\*Wrist, hip, proximal humerus, vertebra.

**Other major risk factors**

**Falls**

Because fractures are frequently associated with falls, a history of falls or factors that increase the risk of falling should be included in an assessment of risk. Risk factors for falling include those associated with general frailty, such as reduced muscle strength (inability to rise from a chair without assistance), impaired balance and low body mass.<sup>20</sup> Reduced visual acuity also increases risk of falling.<sup>20</sup> A prospective study<sup>46</sup> of elderly, ambulatory women identified 3 factors that were significantly predictive of risk for subsequent hip fracture and were independent of proximal femur BMD: a slower gait, difficulty in performing a heel-to-toe walk and reduced visual acuity. In a subsequent study<sup>47</sup> in the same group of women, DXA, ultrasound, gait speed and age were equally effective in identifying women at high risk of fracture. Combination of the various predictors increased sensitivity, but not to a level that would be useful for population screening. It should be noted that falls cause fractures irrespective of whether a patient has osteoporosis, but a person who has



**Fig. 2: Who should undergo a fracture risk assessment and be treated for osteoporosis? (Note: \*≥ 7.5 mg prednisone for more than 3 months. †See Table 3. ‡We have arbitrarily chosen T-score below -1.5; non-traumatic vertebral compression deformities [Grade A]<sup>117</sup>; personal history of fragility fracture after age 40 [Grade D]; clinical risk factors [Grade D].)**



osteoporosis is at even greater risk of fracture if he or she also has a propensity to fall.

### Glucocorticoid use

Systemic glucocorticoid therapy lasting more than 2–3 months for any disorder is a major risk factor for bone loss and fracture, particularly among postmenopausal women and men over age 50.<sup>48</sup> Most reviews and guidelines focus on a daily dose of prednisone of  $\geq 7.5$  mg (or equivalent) as the threshold for assessment and clinical intervention to prevent or treat glucocorticoid-induced osteoporosis.<sup>48</sup> Two major groups of high-risk patients can be identified.

- Patients whose physician is planning to prescribe  $\geq 7.5$  mg prednisone daily for more than 3 months or has already done so should be assessed for initiation of a bone-sparing therapy (see Figure 1).
- Patients who have received glucocorticoid therapy for more than 3 months at a dose  $< 7.5$  mg prednisone daily should be assessed for risk of osteoporosis and should at least have BMD measured, as doses slightly higher than 2.5 mg/day over a prolonged period are associated with increased fracture risk.

A retrospective cohort study<sup>49</sup> of data derived from the United Kingdom's General Practice Research Database, compared 244 235 patients receiving prednisone with 244 235 patients matched for age, sex and type of office practice; doses between 2.5 mg/day and 7.5 mg/day were associated with an increased risk of fracture. Regardless of whether the prednisone or the disease for which the prednisone was given caused the increased risk of fracture, the lesson from this large case-control study is that patients receiving more than 2.5 mg of prednisone daily should be viewed as being at increased risk and further assessment should be carried out (at least BMD measurement).

### Other conditions

A variety of clinical conditions are associated with bone loss and secondary osteoporosis, and clinicians should consider the individual patient's risk for osteoporosis. Such conditions that are likely to be encountered by a family physician include hypogonadism, early menopause (before age 45), chronic heparin therapy, malabsorption syndromes, rheumatoid arthritis and a past history of clinical hyperthyroidism. The risk factors listed in Table 3 should be used to assess people with these conditions for risk of developing osteoporosis or for the presence of osteoporosis. The identification of these people is predicated on the fact that a proven therapeutic intervention is available.

### Summary statements

1. Four key factors — low bone mineral density (BMD),<sup>22</sup> prior fragility fracture,<sup>27,28,30–34</sup> age<sup>20,26,34,41</sup> and family history of osteoporosis<sup>20,41</sup> — stand out as predictors of fracture related to osteoporosis [Level 1].

2. Low BMD should be considered a major risk factor, but those who have suffered a vertebral fracture or other osteoporotic fracture should be considered to have osteoporosis even if their BMD is not in the range associated with osteoporosis<sup>50</sup> [Level 1].
3. Glucocorticoid therapy is a major risk factor for osteoporosis and fracture if it is continued beyond 3 months<sup>48</sup> even if the dose is slightly higher than 2.5 mg of prednisone daily<sup>49</sup> [Level 2].

### Recommendations

1. The major risk factors listed in Table 3 are most predictive of osteoporosis in postmenopausal women, but where applicable, are also relevant to the assessment of men over 50 years of age. These risk factors have a cumulative effect such that, for example, if a person has a low BMD in addition to a fragility fracture or is over 65 and has a BMD in the range associated with osteoporosis, he or she should be considered to be at high risk for fracture and a candidate for therapy [Grade A].
2. People receiving  $\geq 7.5$  mg of prednisone daily for more than 3 months should be assessed for initiation of a bone-sparing therapy [Grade A].
3. People receiving more than 2.5 mg of prednisone daily should be regarded as being at increased risk of fragility fracture and require further assessment (at least BMD measurement) [Grade B].
4. People with other conditions or medications known to be associated with osteoporosis should be assessed for other risk factors. Those with low bone density or a prior fragility fracture are candidates for therapeutic intervention [Grade D].

## The diagnosis of osteoporosis

Historically, osteoporosis was diagnosed late in the course of the disease when bone had become weakened to the point of fracturing. By virtue of the WHO study group definition of osteoporosis,<sup>17</sup> diagnosis now depends on measurement of BMD. The WHO classification is based on risk of fracture, but the available evidence and, therefore, the classification was developed for use in postmenopausal Caucasian women. We were careful not to take a position on gender and racial matching. There is still debate over the reference group to be used to derive T-scores in men. The measured BMD is compared with the mean BMD in young adults of the same sex and race.

### Fracture recognition

Established osteoporosis may still be recognized on radiographs of the spine. However, because some two-thirds of spinal fractures are not diagnosed clinically, one cannot rely on radiographs obtained to investigate back pain. Although there is some debate over what constitutes

a vertebral fracture, deformity — the most widely used criterion — is derived from measurements of the vertical height of a vertebra at its anterior margin, centre (or mid-position) and posterior margin on lateral spine radiographs. If these measurements differ from each other or from the same measurements in the supra- or sub-adjacent vertebrae by 20% or more, the vertebra is considered to have a fracture deformity if congenital, developmental, degenerative or other causes of such deformities are excluded.<sup>33</sup> Level 1 evidence shows that the presence of one such prevalent fracture implies a risk of further fracturing that is equal to the risk associated with a BMD of one standard deviation below the mean peak density. Better recognition and measurement of vertebral deformities presents a major opportunity for increased early recognition of osteoporosis.

### **Bone measurement**

In general, there is a paucity of good prospective trials of diagnostic technology for measuring bone, compared with trials of interventions. Most reported investigations are either cross-sectional studies (Level 2) or comparisons of 2 or more technologies in populations that are usually predominantly Caucasian postmenopausal women. Data for men and people of other races are few.

The techniques for measuring bone may be divided into those that measure the central skeleton (spine, proximal femur, whole skeleton, etc.) and those that measure some part of the peripheral skeleton. Measurement of the central skeleton is most widely carried out using dual-energy x-ray absorptiometry (DXA). There is Level 1 evidence that DXA bone measurement (with consideration of age) is the most effective way to estimate fracture risk in postmenopausal Caucasian women.<sup>22,41</sup>

Density measurement in the peripheral skeleton by quantitative ultrasound (QUS) is a widely reported technique. Large-scale, prospective, evidence-based studies<sup>51,52</sup> of the efficacy of calcaneal QUS measurements were carried out in 2 groups of women, one aged  $\geq 65$  and one aged  $\geq 75$  years. Meta-analysis of these studies<sup>53</sup> indicated a relative risk per standard deviation (RR/SD) of 1.6 (95% CI 1.4–1.8) for hip fracture, whereas direct hip measurement yielded a stronger prediction: RR/SD of 2.4. Although prediction of fracture risk at other sites (wrist and spine) on the basis of calcaneal ultrasound was about the same as direct measurement at these sites,<sup>52</sup> it seems that BMD of the hip is preferred for predicting its fracture risk.

Before calcaneal ultrasonometry can be considered as a replacement for central DXA, large prospective studies must be undertaken to demonstrate that it is at least as good as DXA for fracture prediction in perimenopausal and postmenopausal women and that treatment based on calcaneal ultrasound results is at least as efficacious. Although there is Level 1 evidence that QUS provides measurements of bone density that can be used to estimate risk with

power similar to DXA, all studies have been carried out in elderly populations.<sup>54,55</sup>

There are at least 6 commercial quantitative ultrasound devices designed to measure bone “quality” of the calcaneus. Crossover studies have shown that there is good correlation between the 6 different devices for both the speed of sound (SOS) and broadband ultrasound attenuation (BUA) parameters; the correlation coefficients were significant at 0.73–0.93 for SOS and 0.71–0.92 for BUA. However, the results from the various ultrasound devices were not interchangeable.<sup>52</sup> To compare the results from different ultrasound devices, standardization equations must be developed through crossover studies as was done to compare Hologic, LUNAR and Norland central DXA measurements.<sup>54,55</sup>

Monitoring response to treatment of osteoporosis by ultrasonic measurements of the calcaneus as a surrogate for direct measurement of the lumbar spine and femoral neck or total hip has not proved useful. Correlations between changes in BUA, SOS and mathematical combinations of the 2, so-called “stiffness” and mineral changes in the central regions were either not significant or were too small to be clinically helpful.<sup>56</sup> This lack of association may be a function of at least 2 factors. The precision error of calcaneal ultrasonometry may not be sufficiently low to disclose mineral changes in the calcaneus over relevant intervals such as 1–3 years following treatment. For example, with a stiffness precision error of 2.3%, a positive or negative change of 6.4% must be achieved for it to be considered significant at the 95% confidence level. Also, the calcaneus may respond differently to treatment than the lumbar spine and femur. Other techniques for measuring peripheral bone density — peripheral quantitative tomography (pQCT), calcaneal and radial DXA, radiographic absorptiometry, etc. — have been found to discriminate between those with and those without prevalent fractures in postmenopausal Caucasian women. However, the studies do not provide Level 1 evidence. In men of all races and in non-Caucasian postmenopausal women, it is likely that the same relation between QUS and fracture exists, but the data are too few to make this statement with confidence. Data suggest that combining bone measurement with other means of risk estimation or combining permutations of bone measurement methods can improve risk estimation, but consensus on this approach has yet to emerge in the literature.

Most experience in estimating fracture risk has been gained from axial (central) DXA measurements of BMD. However, DXA equipment for spine and femur BMD measurement is not readily accessible in remote areas or where population densities are low. In such cases, less expensive, portable alternatives such as ultrasound, radiogrammetry, radiographic absorptiometry and single-photon absorptiometry (SPA) are available, but the relation between reduced BMD at an appendicular bone site and increased fracture risk is less well known for these techniques.

SPA measurements of radius BMD predict future fragility fracture in both men and women.<sup>57</sup> When a large population of older white women was followed after baseline measurements of axial and appendicular BMD, BMD at peripheral sites was found to be predictive of future fracture risk.<sup>58</sup> The relative risk of future hip fracture per population standard deviation reduction in BMD was the same for the mid-radius (RR 1.7), the distal radius (RR 1.8) and the spine (RR 1.7). In this same study, the relative risk was found to be greater when measurements were made at the calcaneus (RR 2.3) or the hip (RR 3.0). In another study,<sup>59</sup> the odds ratio for risk of vertebral deformity was similar when measured using metacarpal radiographic absorptiometry, spine DXA, radius SPA, calcaneus DXA or calcaneus ultrasound. Odds ratios were 1.4–1.9 per standard deviation reduction after accounting for age, and all measurements provided useful information regarding the probability of vertebral deformity.

The propagation of ultrasound through bone depends on bone mass, bone structure and bone material properties. BUA is a measure of the variation in ultrasound attenuation with the frequency of the incident sound wave. SOS in bone can be measured by observing the time required for ultrasound to travel a given distance. Prospective studies have shown that, in older women, both BUA and SOS predict the occurrence of fracture with a strength similar to that of DXA.<sup>60,61</sup>

Radiogrammetry is the geometric measurement of bone dimensions on high-resolution radiographs. The recent introduction of computer-controlled analysis of digital x-ray images has improved the precision of radiogrammetry, making it comparable to that obtained with DXA and suggesting a possible diagnostic role for such measurements where DXA is not available. Radiogrammetric results correlate with both axial and appendicular DXA results.<sup>62</sup> Radiogrammetry also yields similar cross-sectional information about BMD and fracture risk to that obtained using SPA and quantitated computed tomography.<sup>63</sup> No data are available relating the results of computer-controlled radiogrammetry to estimation of fracture risk.

BMD measured by radiographic absorptiometry of the phalanges correlates with BMD of the distal forearm and BMD of the lumbar spine and proximal femur.<sup>64</sup>

During treatment for osteoporosis, changes in axial and appendicular BMD are not strongly related to changes in fracture risk.<sup>65</sup> Only a fraction of the decrease in fracture risk produced by anti-resorptive therapy can be accounted for by the small increase observed in BMD.

### **Precision and serial measurements**

Evaluating changes in BMD over time can determine the rate of bone loss (differentiating “fast losers” from “slow losers”) and confirm a positive response to treatment. However, the average rate of bone loss in postmenopausal women is 0.5–2% per year and most treatments lead to an

increase in BMD of 1–6% over 3 years. Given these relatively small changes, only a very precise test will detect short-term changes. A clear understanding of the interpretation of serial measurements and the statistical principles surrounding their interpretation is necessary to determine whether a change is clinically meaningful and to avoid mistaking random fluctuations for real changes. In turn, this understanding will help in determining the time interval required between measurements to allow for accurate assessment of response to treatment or progression of disease.

Human factors (in both operator and patient) rather than instrumentation are usually the major source of variation. A quality assurance program to monitor the performance of both operator and equipment will ensure optimum testing and appropriate procedures.<sup>66–68</sup>

Techniques have been described for comparing results from different machines and vendors. Although DXA results from different devices are highly correlated, methods are too inexact to apply to individual patients and are still best suited for group comparisons, such as in clinical trials.<sup>54,55</sup> Results from DXA scanners from the same vendor and of identical design can show significant calibration differences. Even after cross-calibration, the precision error between different machines is greater than the error obtained when a single machine is used.<sup>69</sup> Thus, the same device should be used for baseline and follow-up measurements.

There is some debate over the method for expressing changes in measurements and their interpretation. A change can be reported as the absolute difference in bone density measurements ( $\text{g}/\text{cm}^2$  for DXA) or as a relative change (%), which is seen most frequently. Evidence indicates that error in absolute measurements is as great (if not greater) in the elderly and osteoporotic patients as in young, normal patients and that the absolute difference between measurements expressed in  $\text{g}/\text{cm}^2$  be used to determine significance rather than the difference in relative changes expressed in percentage.<sup>70</sup> Measurement precision is affected by clinical setting, patient population, site of measurement and device design. When young patients with normal BMD are studied in a research setting, the short-term variability in lumbar spine BMD measured by DXA is about 1%. In an older population with a high prevalence of disease and underlying osteoporosis, this number can be as high as 1.7%.<sup>71</sup> Long-term variability is greater (2–3%) and that number is more important in clinical care. Variability in the femoral neck is higher (up to 3.2%) than that of the total hip region (up to 2.5%).<sup>72</sup> It is not sufficient to accept vendor-supplied estimates of precision, as these are usually derived under optimal conditions and typically underestimate the error encountered in the clinical setting. Each BMD laboratory should determine its own measurement precision for each site commonly assessed in a typical clinical population and use this as the basis for interpreting change. Standardized methods for calculating precision are

well described<sup>73,74</sup> and should be familiar to the BMD laboratory.

### **BMD and fracture risk in men**

There are insufficient data on the relation between BMD and fracture risk in men. A few prospective studies<sup>75</sup> suggest that men fracture at a higher BMD than women; others<sup>76,77</sup> suggest that the BMD–fracture risk relationship is similar for men and women. Data from prospective large-scale trials are needed to understand the BMD–fracture risk relationship in men. The risk of fracture depends not only on BMD, but also on other factors such as the likelihood of falls and bone size and geometry. Bone size is greater in men than women even after adjusting for height and weight.<sup>78</sup> The pattern of age-related bone loss is also different in men. Endocortical thinning increases with age in women, but not in men,<sup>79</sup> which also affects bone strength. The relation between BMD and fracture risk may also differ in men because bone size creates an artifact that affects areal BMD (areal BMD is bone mineral content divided by bone area and corresponds to what is measured by current DXA machines), and DXA overestimates BMD in men relative to women. As a result, areal BMD provided by current DXA machines may be of advantage in evaluating fracture risk in men as the larger bone may have a greater biomechanical advantage compared with the smaller bone size in women.

As the lifetime risk of a fragility fracture after age 50 in men is approximately 13%,<sup>75</sup> this risk is best estimated by using a male-reference database. This is currently being done across Canada. Based on male reference data, if BMD is measured at hip, spine and radius by DXA and the lowest measure used to make the evaluation using the criterion of a T-score below  $-2.5$ , approximately 19% of the male population over the age of 50 years has been found to have osteoporosis.<sup>75</sup>

There are even fewer data on the BMD–fracture risk relationship in the non-Caucasian population. However, it is becoming apparent that men are as prone to fracture as women at a given BMD.<sup>80,81</sup> Asian Americans have been found to have a lower BMD than Caucasians but also have a lower hip fracture rate.<sup>82</sup> However, correcting for differences in skeletal size, their apparent BMD is actually higher than white women, which is consistent with the observed lower hip fracture rate. The appropriate cut-off points for diagnosis have not yet been established due to insufficient data.

Figures 1 and 2 outline who should be tested and treated. Significant height loss, kyphosis, personal history of fragility fracture after age 40, long-term use of glucocorticoids, clinical risk factors and age 65 and older (see Table 3) should all be considered as potential triggers for ordering a BMD measurement, spinal radiography or both. A non-traumatic vertebral height reduction of 20–25% should be considered as a vertebral fracture.<sup>33</sup>

The following laboratory tests are recommended in all patients with osteoporosis to exclude secondary causes: complete blood count, serum calcium, total alkaline phosphatase, serum creatinine and serum protein electrophoresis. These laboratory tests are discussed in further detail in the OSC's 1996 clinical practice guidelines for the diagnosis and management of osteoporosis.<sup>11</sup> Clinical suspicion of other secondary causes will determine the need for further investigation.

### **Summary statements**

4. Dual-energy x-ray absorptiometry (DXA) is the most widely investigated tool for estimating fracture risk in women and is the single best tool for assessing risk<sup>22,80</sup> [Level 1]. There are sufficient and consistent data to support the use of central DXA in case finding.
5. Screening of all postmenopausal women or all men over age 50 is not justified according to available data. However, measuring bone density in men and women after the age of 65, recognizing that after this age fracture risk increases, is justifiable<sup>25</sup> [Level 3].
6. All bone density measurement techniques predict the risk of all low-trauma fractures<sup>22,40,41,51,52</sup> [Level 1].
7. The best predictor of relative risk of fracture at the proximal femur is measurement of bone density at that site<sup>22,53</sup> [Level 1].
8. Clinical evaluation combined with BMD assessment out-performs any single method of risk-assessment; age, BMD and prevalent fracture(s) are the best risk indicators<sup>20,21,26,30,39</sup> [Level 1].
9. The most accurate indicator of BMD is the actual measurement of BMD. BMD is not well predicted by "osteopenia" on skeletal radiographs or by risk factors for low BMD<sup>21,26</sup> [Level 1]. Although current decision tools are useful in highlighting the risk factors for low BMD, they are not meant to replace BMD measurement. The decision to measure BMD should be based on age-related risk, the presence of other risk factors for fracture and consultation with the patient [consensus]. BMD should be measured only if it will affect management decisions.
10. Because fractures of the spine and hip are the most clinically important low-trauma fractures resulting from osteoporosis and because DXA provides the best measurements of bone at the spine and hip reflecting fracture risk, DXA is the optimum technology at present for use in risk assessment<sup>22,40,41,53</sup> [Level 1].
11. DXA can be used to assess sites that are responsive to therapy<sup>83–86</sup> [Level 1].
12. Justification for the clinical use of DXA assumes a clear understanding of its application, the need for quality assurance and careful determination of BMD with sufficient precision to provide clear indications of the least significant change<sup>67,69–74</sup> [Level 4].
13. Calcaneal quantitative ultrasonometry (QUS) appears to be effective in estimating risk of fracture in post-

menopausal women over 65 years of age<sup>52,59-61</sup> [Level 1]. Evidence for the use of QUS in men and younger women is limited. QUS data appear to be machine specific to a greater degree than data from DXA machines.<sup>52,59-61</sup>

14. Calcaneal QUS is not sufficiently precise for follow-up at clinically relevant intervals<sup>56</sup> [Level 1].
15. Other bone measurements (radiogrammetry, radiographic absorptiometry, quantitative ultrasonometry, etc.) may have particular application in risk assessment (but not follow-up) in situations where geography and population size limit access to DXA. However, there is no Level 1 evidence for their widespread use [consensus].
16. Uncertainty about the definition of a vertebral fracture and marked variation in observer performance in this context contribute to much of the variation in findings especially in cross-sectional studies<sup>33</sup> [consensus].
17. Consistency in measuring, recognizing and reporting vertebral fractures presents an opportunity in osteoporotic fracture-risk assessment [consensus].
18. Evidence for the use of bone measurement in men and in non-Caucasian women is meager. Existing data do not contradict the inferences already made [consensus].

### Recommendations

5. Targeted case-finding strategies for those at increased risk (at least one major or 2 minor risk factors) are recommended, and BMD measurement with central DXA at age 65 is recommended [Grade A].
6. Central (hip and spine) DXA remains the most accurate tool for evaluating BMD in clinical settings. Access to BMD measurement should not be limited by decision tools based on clinical risk factors [Grade A].
7. Patients should be monitored using central (total hip and spine) DXA in clinical settings 1–2 years after initiating therapy [Grade A].
8. Quantitative ultrasonometry may be considered for diagnosis of osteoporosis, but not for follow-up at this time [Grade C].
9. A height loss of > 2 cm in a year or historical height loss of > 4 cm should be followed by thoracolumbar spine radiography to determine the presence of vertebral fractures [Grade D].

### Role of biochemical markers of bone turnover

Remodeling is a normal, natural process that maintains skeletal strength, enables repair of microfractures and is essential for calcium homeostasis. During the remodeling process, osteoblasts synthesize a number of cytokines, peptides and growth factors that are released into the circulation. Their concentration thus reflects the rate of bone formation. Bone formation markers include serum

osteocalcin, bone-specific alkaline phosphatase and procollagen I carboxyterminal propeptide (PICP).

Osteoclasts produce bone degradation products that are also released into the circulation and are eventually cleared via the kidney. These include collagen cross-linking peptides and pyridinolines, which can be measured in the blood or urine and enable estimation of bone resorption rate. Bone resorption markers include urinary hydroxyproline, urinary pyridinoline (PYR), urinary deoxypyridinoline (D-PYR) as well as collagen Type I cross-linked N telopeptide (NTX) and collagen Type I cross-linked C telopeptide (CTX).

Markers of bone formation and resorption are of value in estimating bone turnover rates. These biochemical markers may be used to identify fast bone losers.<sup>87</sup> Numerous cross-sectional studies<sup>88,89</sup> have shown that bone turnover rates as evaluated by markers increase at menopause and remain elevated. Bone turnover rate in postmenopausal women correlates negatively with BMD.<sup>90</sup>

Most of the prospective studies evaluating the relationship between bone turnover and rates of bone loss have been short-term and have been limited by the precision error of the densitometer.<sup>91-95</sup> The utility of bone markers to identify fast bone losers was prospectively evaluated in a large cohort of healthy postmenopausal women over 4 years.<sup>87</sup> Higher levels of bone formation and resorption markers were significantly associated with faster and possibly greater BMD loss.

In population studies, it appears that markers of bone resorption may be useful predictors of fracture risk and bone loss. Elevated bone resorption markers may be associated with an increased fracture risk in elderly women<sup>96,97</sup> although the data are not uniform. The association of markers of bone resorption with hip fracture risk is independent of BMD, but a low BMD combined with high bone resorption biomarker doubled the risk associated with either of these factors alone.<sup>96</sup> However, the predictive value of biomarkers in assessing individual patients has not yet been confirmed.<sup>91</sup> Biomarker measurements are also currently limited by their high variability within individuals.<sup>97</sup>

Biomarkers may be of value in predicting and monitoring response to potent antiresorptive therapy in clinical trials. Normalization of bone formation and resorption markers following antiresorptive therapy has been prospectively observed.<sup>92,98,99</sup> Reduction in biochemical markers appears to be correlated with a decrease in vertebral fracture incidence<sup>99</sup> in some studies, but is not necessarily always predictive of response to therapies.

A weak inverse correlation between BMD and NTX has been observed in men.<sup>100</sup> Other studies have shown resorptive markers to be poorly correlated with BMD. Thus the situation in men is less clear and more large-scale prospective trials are required.

### Summary statements

19. Bone turnover markers appear to be of value in the as-



assessment of fracture risk in elderly postmenopausal women in population studies<sup>96</sup> [Level 2]. Additional studies with fracture endpoints are needed to confirm the usefulness of these markers in individual patients. Bone turnover markers may have a future role in the clinical management of osteoporosis.

20. In population studies, the combination of low BMD and high bone turnover markers may provide a superior indication of fracture risk to either BMD or bone turnover markers alone<sup>96</sup> [Level 2].

### Recommendations

10. Bone turnover markers should not yet be used for routine clinical management. Additional studies are needed to confirm their use in individual patients. However, with refinement of assay technology and better understanding of biological variability, we believe they will become a useful adjunct for risk assessment and management [Grade B].

## Prevention and treatment of osteoporosis

### Pharmacologic interventions

Because osteoporosis is a multifactorial condition, its prevention and management are complex. From prevention to treatment of established disease, the goal is to intervene as early as possible to ensure retention of bone mass and to preserve structural integrity of the skeleton, thus preventing fragility fractures.

The results of large prospective RCTs, carried out over the last 10 years, have helped guide our therapeutic options, which include non-pharmacologic approaches that should be recommended for all patients. Currently available drug therapies are all anti-resorptive and focus on decreasing bone turnover. They have been shown to reduce fracture risk for some, although not necessarily all, fragility fractures. Newer therapies aimed at increased bone formation are being studied and are about to be released. It is difficult to assess the relative anti-fracture efficacy of the various therapies, as they have not been compared directly in trials.

### Bisphosphonates

Several anti-resorptive agents have been used successfully in the treatment of postmenopausal osteoporosis. However, recent trials of the bisphosphonates consistently provide the best evidence of efficacy in preventing both vertebral and non-vertebral fractures. Bisphosphonates are stable analogues of naturally occurring pyrophosphate. They contain 2 phosphonate groups attached to a single carbon atom to give a P-C-P structure. This structure renders them chemically stable and is responsible for the strong affinity of the bisphosphonates for bone.<sup>101</sup>

Bisphosphonates inhibit bone resorption through their

effects on osteoclasts.<sup>102</sup> They interfere with osteoclast recruitment, differentiation and action as well as enhancing osteoclast apoptosis.<sup>102</sup> Bisphosphonates can be classified into 2 groups based on their mode of action<sup>102</sup>: those that most closely resemble pyrophosphate (such as clodronate and etidronate) can be incorporated into cytotoxic adenosine triphosphate (ATP) analogues; the more potent nitrogen-containing bisphosphonates (alendronate and risedronate) induce apoptosis in osteoclasts by interfering with protein prenylation through their effects on the mevalonate pathway and, therefore, the intracellular trafficking of key regulatory proteins. These 2 mechanisms of action may help explain some of the pharmacologic differences between the 2 classes of bisphosphonates.

Currently the bisphosphonates approved for the treatment of osteoporosis in Canada are etidronate, alendronate and risedronate. Although all bisphosphonates, these drugs vary considerably in potency, their ability to inhibit bone resorption, toxicity and dosing regimens. Oral absorption of bisphosphonates is poor, at only 1–5%, even when the medication is taken on an empty stomach. The plasma half-life is 1 hour with 40–80% clearance by the kidneys. The remaining drug is taken up by the bone where it has a long half-life. The most common side effect of bisphosphonates is gastrointestinal upset, which is often dose-related.

**Etidronate:** Etidronate was the first bisphosphonate to show a benefit in the treatment of osteoporosis.<sup>103–113</sup> It is generally well tolerated; reports of gastrointestinal upset are few, diarrhea being the most common complaint. When administered continuously for long periods, etidronate can cause impaired mineralization of bone with results similar to osteomalacia. As a result, etidronate is given in an intermittent fashion, typically 400 mg/day for 2 weeks every 3 months.

Two RCTs<sup>111,113</sup> examined the anti-fracture efficacy of cyclical etidronate in postmenopausal women with prevalent vertebral fractures. In both, etidronate produced significant increases in lumbar spine BMD with variable reductions in vertebral fracture rates. These studies indicate that etidronate has some effect in preventing new vertebral fractures in postmenopausal women with severe osteoporosis. There is no evidence of a beneficial effect of etidronate on risk of hip or non-vertebral fracture.

**Alendronate:** Alendronate is a nitrogen-containing bisphosphonate, which is given continuously at a dose of 5 mg/day for the prevention of osteoporosis and 10 mg/day for the treatment of established osteoporosis. Recently, a weekly dose of alendronate (70 mg) was shown to have an effect on BMD that was comparable to that of a 10-mg daily dose regimen.<sup>114</sup> Alendronate is generally well tolerated, although rare cases of esophagitis have been reported.<sup>115</sup>

Alendronate has been studied extensively for the treatment of osteoporosis.<sup>84–86,114,116–132</sup> In an initial 3-year study, alendronate significantly reduced the incidence of new fractures.<sup>85</sup> Its efficacy has since been examined in two large

populations of postmenopausal women, one with and one without pre-existing vertebral fractures.<sup>117</sup> In the group with vertebral fractures, treatment with alendronate reduced the incidence of vertebral, hip and wrist fractures by about 50% over 3 years; the risk of multiple vertebral fractures was reduced by 90%. This was the first RCT to show hip fracture benefits in calcium- and vitamin D-replete osteoporotic women. In a post-hoc analysis,<sup>133</sup> a reduction in the rate of clinical vertebral fractures was demonstrated as early as 1 year into the study.

The anti-fracture efficacy of alendronate has also been examined in postmenopausal women with no prior vertebral fractures.<sup>118</sup> Alendronate increased BMD at all measured sites and significantly reduced (36%) the clinical vertebral fracture rate among women with initial T-scores below -2.5. The Fosamax International Trial Study Group (FOSIT)<sup>127</sup> demonstrated a reduction in non-vertebral fracture incidence within 1 year in postmenopausal women with a T-score below -2.0. Alendronate prevents bone loss in normal postmenopausal women but anti-fracture efficacy in this context has not been demonstrated.

In summary, alendronate is beneficial in the prevention of vertebral, hip and non-vertebral fractures in postmenopausal women. It consistently increases bone mass at all measured sites. Alendronate has been used in patients who were also taking estrogen or raloxifene and had an additive effect in increasing BMD; however an additional anti-fracture benefit has not been demonstrated.<sup>124</sup>

**Risedronate:** Risedronate is generally well tolerated, with occasional reports of headache and diarrhea as side effects. Many studies have demonstrated risedronate efficacy, using both daily and once-weekly treatment regimens.<sup>38,83,134-138</sup> Recently, 2 large, 3-year, multicentre RCTs<sup>136,137</sup> evaluated the efficacy of risedronate in the treatment of postmenopausal osteoporosis. After 3 years of treatment at 5 mg/day, risedronate reduced the incidence of vertebral fractures by 41-49% and non-vertebral fractures by 39-33%. In a preplanned analysis, treatment with risedronate at 5 mg/day was shown to reduce the incidence of vertebral fractures within the first year of therapy by 61-65%. No significant differences in adverse events were seen between the risedronate and placebo groups.

In a large RCT<sup>38</sup> designed to determine the efficacy of risedronate in the prevention of hip fractures, the drug was shown to reduce hip fracture rates in those with low femoral neck BMD by 40%. Among the latter women, risedronate reduced hip fracture by 60% in those with prior vertebral fracture. Risedronate did not significantly reduce the risk of hip fracture among elderly women selected primarily on the basis of risk factors other than low BMD.

In conclusion, risedronate at 5 mg/day, given over 3 years, is well tolerated and reduces the incidence of both vertebral and non-vertebral fractures in women with established postmenopausal osteoporosis. Furthermore, these studies were the first to show a significant reduction in the

incidence of vertebral fractures (clinical and subclinical fractures) within 1 year of therapy.

A comprehensive evaluation of the evidence to date for the efficacy of these bisphosphonates is outlined in Hodson et al.<sup>139</sup>

**Combination therapy:** Cyclic etidronate has been used in combination with estrogen therapy in postmenopausal women.<sup>140,141</sup> In a randomized study,<sup>141</sup> at the end of 4 years, combination therapy produced a greater increase in BMD than either estrogen or etidronate alone; patients on estrogen or etidronate alone had lesser increases in spine and hip BMD.

The combined effect of alendronate and estrogen in postmenopausal women was studied in women who had been receiving estrogen replacement therapy for at least 1 year.<sup>124</sup> They were randomly assigned to receive either 10 mg/day of alendronate or placebo. After 12 months, the patients taking alendronate in addition to estrogen showed significantly greater increases in BMD of the lumbar spine and trochanter; however, no conclusions about fracture rate reduction could be drawn. The results of this trial were supported by a 2-year trial of postmenopausal women who were randomly chosen to be treated with placebo, 10 mg/day of alendronate, conjugated estrogen or both treatments.<sup>121</sup> Lumbar spine BMD in the placebo group remained stable over the 2 years. The alendronate and conjugated estrogen groups had similar gains in BMD, whereas the group given both treatments had a significantly greater gain than either of the single-treatment groups. These results suggest that, in those initiating therapy, the combination of alendronate and estrogen is more effective than either treatment alone. Although increases in BMD have been demonstrated with combination therapies, no direct evidence of fracture rate reduction has been shown.

**Bisphosphonate treatment in men:** There is no RCT evidence of benefit from treatment with etidronate. Alendronate has been studied in the treatment of osteoporosis in men and has been shown to increase BMD significantly,<sup>142</sup> while reducing vertebral fractures. One large study of risedronate in men on glucocorticoid therapy demonstrated a significant decrease in vertebral fractures after 1 year.<sup>143</sup>

**Bisphosphonates and glucocorticoid-induced osteoporosis:** Studies of glucocorticoid-induced osteoporosis are directed at 2 groups: those starting preventive therapy at the time of glucocorticoid initiation and those on chronic long-term glucocorticoid therapy who require treatment for osteoporosis. There is ample evidence that etidronate therapy maintains BMD in patients taking glucocorticoids.<sup>144-156</sup> Etidronate on initiation of glucocorticoid therapy has resulted in a slight increase in lumbar spine BMD, compared with bone loss with placebo.<sup>144,145,147,149,151</sup> One study<sup>144</sup> suggested that etidronate might be of benefit in preventing vertebral fractures. Two-year RCTs<sup>146,149</sup> of etidronate in patients on long-term glucocorticoids demonstrated increases in BMD. These results suggest that etidronate is

beneficial in the prevention and treatment of glucocorticoid-induced bone loss and may reduce the risk of fractures in glucocorticoid-treated postmenopausal women.

Alendronate has been studied in glucocorticoid-treated patients<sup>157-159</sup> and in those with Cushing's syndrome.<sup>160</sup> Statistically significant benefit has been shown in the spine, trochanter and femoral neck at doses of 5 and 10 mg/day. Alendronate benefitted all groups, including men, premenopausal and postmenopausal women; in postmenopausal women who were on HRT, alendronate therapy provided added benefit.<sup>158</sup> Alendronate was effective in both the prevention and treatment of glucocorticoid-induced osteoporosis and reduced vertebral fracture risk.<sup>159</sup>

Risedronate has been studied in both the prevention and treatment of glucocorticoid-induced osteoporosis,<sup>161-163</sup> and significant differences in lumbar spine and hip BMD have been observed compared with placebo. Analysis of pooled data from these studies revealed a significant reduction in the incidence of vertebral fractures among those taking 5 mg of risedronate daily.<sup>163</sup>

The newer nitrogen-containing bisphosphonates — alendronate and risedronate — should be considered first-line therapy for postmenopausal women with established osteoporosis who are at high risk for fracture. There is good evidence that they prevent both vertebral and non-vertebral fractures, including hip fractures. Bisphosphonates are the only therapy shown to be efficacious in reducing vertebral fracture in glucocorticoid-induced osteoporosis.

Bisphosphonates, particularly the more potent alendronate and risedronate, are effective in reducing risk of fracture in high-risk patients, with benefits seen as early as the first year of therapy.

### Summary statements

21. In postmenopausal women with osteoporosis,
  - a. alendronate<sup>85,117,118,127,133</sup> and risedronate<sup>38,136,137</sup> are efficacious in preventing vertebral and non-vertebral fractures [*Level 1*]
  - b. alendronate<sup>117</sup> and risedronate<sup>38</sup> prevent hip fractures in postmenopausal women with severe osteoporosis [*Level 1*]
  - c. alendronate<sup>84-86,114,117-120,122,123,125,127,128,130-133</sup> and risedronate<sup>38,83,136-138</sup> increase BMD at spine and hip [*Level 1*]
  - d. etidronate is efficacious in preventing vertebral fractures<sup>111,113</sup> [*Level 2*]
  - e. etidronate increases BMD at the spine and maintains BMD at the femoral neck<sup>111,113</sup> [*Level 1*].
22. In early postmenopausal women at risk of developing osteoporosis, alendronate,<sup>123,125</sup> risedronate<sup>135</sup> and etidronate<sup>103,107-109</sup> are efficacious in increasing or maintaining BMD at the spine and femoral neck [*Level 1*].
23. In men with osteoporosis,
  - a. alendronate is efficacious in preventing vertebral fractures<sup>142</sup> [*Level 1*]
  - b. alendronate<sup>142</sup> [*Level 1*] and etidronate<sup>164</sup> [*Level 3*]

increase BMD at the spine; alendronate<sup>142</sup> increases femoral neck BMD [*Level 1*] and etidronate<sup>164</sup> maintains it [*Level 3*].

24. For glucocorticoid-induced osteoporosis,
  - a. in postmenopausal women, alendronate, etidronate and risedronate are efficacious in preventing vertebral fractures<sup>144,156,158,161-163</sup> [*Level 1*]
  - b. in men, risedronate<sup>143</sup> is efficacious in preventing vertebral fractures [*Level 2*]
  - c. alendronate,<sup>158,159</sup> etidronate<sup>144,156</sup> and risedronate<sup>161,163</sup> increase BMD at the spine and maintain or increase BMD at the hip [*Level 1*].

### Recommendations

11. Bisphosphonates are a first-line preventive therapy in postmenopausal women with low bone density: alendronate [*Grade A*]; etidronate [*Grade A*]; risedronate [*approved in Canada for prevention, but data thus far only published in abstract form*].
12. Bisphosphonates are a first-line treatment for postmenopausal women with osteoporosis, especially those with pre-existing vertebral fractures: alendronate [*Grade A*]; risedronate [*Grade A*]; etidronate [*Grade B*].
13. Bisphosphonates are the first-line therapy for the prevention of glucocorticoid-induced osteoporosis: alendronate [*Grade A*]; risedronate [*Grade A*]; etidronate [*Grade A*].
14. Bisphosphonates are the first-line therapy for the treatment of glucocorticoid-induced osteoporosis in patients requiring prolonged glucocorticoid therapy: alendronate [*Grade A*]; risedronate [*Grade A*]; etidronate [*Grade B*].
15. Bisphosphonates are the first-line treatment for men with low bone mass or osteoporosis: alendronate [*Grade A*]; etidronate [*Grade B*].
16. In premenopausal women with osteopenia or osteoporosis, the use of bisphosphonates has not been examined and is not yet recommended in the absence of an identified secondary cause of osteoporosis. However, in certain circumstances, they may be considered. In the absence of evidence of safety of these drugs in pregnancy, contraception would be prudent and treatment should be stopped in the event of pregnancy [*Grade D*].

### Calcitonin

Calcitonin is a naturally occurring peptide hormone. Although its precise physiologic role in adult health is not well understood, at pharmacologic dose levels calcitonin inhibits osteoclast activity and, thus, acts as an anti-resorptive agent.

Because it is a polypeptide, calcitonin cannot be taken by mouth and was initially given by injection.<sup>165,166</sup> This route of administration was associated with a high rate of side

effects, which limited its use as a long-term osteoporosis treatment. A nasal spray vehicle that allows calcitonin to pass through the nasal mucosa was found to cause fewer side effects.<sup>167</sup>

Because fish forms of calcitonin are more potent in humans than the human form, recombinant salmon calcitonin has become the standard chemical form of the drug.<sup>165-167</sup>

**Calcitonin treatment of postmenopausal women with osteoporosis:** We found 25 reports of RCTs of calcitonin in postmenopausal women with osteoporosis.<sup>116,119,168-191</sup> Most used salmon calcitonin delivered by nasal spray. Results based on surrogate endpoint parameters of bone biochemical markers or bone densitometry were generally consistent across studies: calcitonin treatment produced modest, but reproducible, reductions in bone resorption (5-20% greater than placebo) and increases in BMD (1-8% greater than placebo) over 1-5 years.

Only one study — Prevent Recurrence of Osteoporotic Fractures (PROOF) Study<sup>168</sup> — had sufficient power and was designed to detect a change in fracture rates. In that investigation, a daily dose of 200 IU of nasal salmon calcitonin significantly reduced vertebral fractures by 33-36%. Although this study was a prospective RCT, its results are classified as Level 2 evidence because of concerns about the absence of a dose response (no significant fracture reduction with the daily dose of 400 IU) and a high drop-out rate. The study was not powered to detect a reduction in non-vertebral fractures.

Several other studies,<sup>172,174,175</sup> produced data showing reduced vertebral fracture rates in calcitonin-treated groups, but either the nature of the studies or the data analysis did not meet the criteria for a Level 1 RCT.

**Calcitonin in the prevention of postmenopausal osteoporosis:** Most calcitonin studies do not provide sufficient information to determine how the study population would fall into current diagnostic categories. As no studies were found that definitively addressed osteoporosis prevention in postmenopausal women, calcitonin cannot be recommended for use in this setting.

**Calcitonin use in premenopausal women:** One RCT<sup>191</sup> investigated calcitonin efficacy in premenopausal women. No benefit was found, but the dose of nasal salmon calcitonin was less than the accepted effective dose. Thus although evidence is absent, calcitonin may be considered a treatment option in premenopausal women because of its safety profile and the lack of therapeutic alternatives for this group.

**Calcitonin and glucocorticoid-induced osteoporosis:** Calcitonin has been studied for both prevention and treatment of glucocorticoid-induced osteoporosis. Four reports used nasal salmon calcitonin; 3 others investigated injectable calcitonin.<sup>192-198</sup> In prevention studies, calcitonin reduced bone loss caused by glucocorticoids but did not lead to a net gain in BMD.<sup>193,194,198</sup> In osteoporotic patients or those on long-term glucocorticoids, calcitonin produced a net gain in BMD.<sup>192,195-197</sup> No data on fractures are

available for either group. Therefore, although injectable or nasal calcitonin may be used in the prevention or treatment of glucocorticoid-induced osteoporosis, it is not a drug of first choice, as fracture-outcome data are available for other drugs.

**Calcitonin in vertebral fracture pain:** Four RCTs<sup>199-202</sup> have shown that calcitonin reduces the pain associated with acute vertebral fractures. Both injectable (2 studies) and nasal salmon calcitonin (2 studies) have been investigated. Patients were studied 3-14 days following fracture. Within 3 days, pain was significantly less in the calcitonin-treated group than in the placebo group; in 7-10 days, these patients showed marked improvement; and benefit was maintained for 28 days (the limits of the longest study). The daily dose of injected calcitonin was 100 IU, whereas 200 IU/day was given in the nasal delivery studies. A head-to-head comparison has shown the equivalence of these doses.<sup>203</sup> There are no substantial data on pain relief in other types of fractures or in chronic vertebral fractures.

**Side effects:** The only absolute contraindication to the use of nasal or injectable salmon calcitonin is known hypersensitivity to calcitonin or the drug vehicle.<sup>165-167</sup> In animal tests, calcitonin caused lower birthweight when given during pregnancy and reduced milk production when given during lactation.<sup>165-167</sup> In the absence of human data, calcitonin should be avoided in pregnancy and breastfeeding.

Anaphylaxis and other severe allergic reactions have been reported, but they are rare for both formulations. Skin testing using a diluted sample can be performed before administering the full dosage, although this is not standard clinical practice for the nasal formulation.<sup>165-167</sup>

Up to 30% of nasal salmon calcitonin users will experience nasal irritation over a 5-year period. Minor nosebleeds (< 15%), assorted nose symptoms (< 15%) and nasal ulceration (< 5%) also occur.<sup>167</sup> Most of these side effects are mild or moderate and do not lead to drug discontinuation. Serious side effects are rare (< 1%).<sup>167</sup>

Adverse effects are more frequent with injectable calcitonin than nasal. The most common are nausea or vomiting (< 40%), flushing (< 35%) and skin rash at the injection site (< 10%).<sup>165,166</sup> Although not serious, these manifestations can lead to discontinuation. Serious side effects are rare (< 1%).<sup>165,166</sup>

Antibodies to calcitonin develop in people treated with either formulation in a dose-related manner. However, they do not appear to influence drug efficacy or to be related to side effects and do not need to be monitored.<sup>165-168</sup>

## Summary statements

25. Nasal calcitonin is efficacious in preventing vertebral fractures in postmenopausal women with severe osteoporosis<sup>168</sup> [Level 2]. BMD at the hip and the spine is maintained or minimally increased<sup>116,119,168,170-191</sup> [Level 1]. Nasal calcitonin has not been shown to be efficacious in preventing non-vertebral fractures<sup>168</sup> [Level 2].

26. In those recently started on glucocorticoid therapy, calcitonin slows bone loss at all sites and prevents loss at some sites<sup>193,194,198</sup> [Level 2].
27. In those with established glucocorticoid-induced osteoporosis, calcitonin maintains or increases BMD<sup>192,195–197</sup> [Level 2].
28. Calcitonin is efficacious in reducing the pain associated with acute vertebral fractures<sup>199–202</sup> [Level 1].

### Recommendations

17. Nasal calcitonin is a second-line treatment for postmenopausal women with osteoporosis [Grade B].
18. Due to its safety profile, nasal calcitonin can be considered for use in nonpregnant premenopausal women with osteoporosis [Grade D].
19. Nasal calcitonin can be considered for use in men with osteoporosis [Grade D].
20. Nasal or parenteral calcitonin is a first-line treatment for pain associated with acute vertebral fractures [Grade A].

### Hormone replacement therapy for postmenopausal women

Hormone replacement therapy (HRT) and ovarian hormone therapy (OHT) are terms that the OSC has used synonymously. Postmenopausal women are not hormonally deficient, as low estrogen and progesterone levels are the norm; therefore “replacement” is not an appropriate term. However, to conform with current international usage, the OSC adopted “HRT” as the acronym for combined estrogen and progestin/progesterone therapy.

One of the most common uses for HRT (or estrogen or progesterone alone) is to treat hot flashes and night sweats (vasomotor symptoms) occurring as a result of reduced levels of estrogen and progesterone. All doses, delivery methods and kinds of HRT are efficacious in reducing vasomotor symptoms.<sup>204</sup>

The accelerated phase of bone loss that begins with irregular flow in perimenopause<sup>205</sup> continues for 4–5 years and sometimes up to 10 years after menopause.<sup>206</sup> HRT in postmenopausal women is efficacious in halting this bone loss and increasing BMD at all measured sites.

The average age for menopause (defined by 1 year without flow) is about 51 years. Women who experience an early (before age 40) or relatively early (before age 45) menopause are at increased risk for osteoporosis.<sup>207</sup> For this reason, HRT is important in women whose menopause occurs before age 45.

Although HRT has been used for over 60 years to treat osteoporosis and, until recently, has been the primary treatment, the clinical trial evidence for its efficacy has been suboptimal. The first bisphosphonate trials were published in the 1990s; however, until the last decade, the designs of osteoporosis therapy trials have been cohort, case-control or epidemiology studies in postmenopausal women who asked

for or whose physicians prescribed HRT. Women who reported taking HRT were also those who were adherent to therapy. We now know that studies with such designs are predisposed to healthy-cohort and compliance biases that make therapy appear more effective than it actually is.<sup>208</sup>

Until recently, only a single, small, 1-year randomized double-blind placebo-controlled trial<sup>209</sup> of transdermal estrogen has shown vertebral fracture prevention, although there are some methodologic problems with this study. There have been no RCTs designed to show hip fracture prevention. An ongoing, large prospective randomized double-blind placebo-controlled therapy trial (Women’s Health Initiative)<sup>210</sup> in the United States was terminated early because of an unfavourable risk-benefit ratio with estrogen-progesterone combination therapy (Premarin and Provera); there was a significant increase in relative risk for coronary artery disease (hazard ratio [HR] 1.29; 95% nominal CI 1.02–1.63), invasive breast cancer (HR 1.26; CI 1.00–1.59), stroke (HR 1.41; CI 1.07–1.85) and venous thromboembolism (HR 2.11; CI 1.58–2.82) although the absolute risk, while still significant, was small. On the positive side, it was finally demonstrated that a continuous estrogen-progesterone regimen significantly decreases the risk of fractures at all sites including the hip (HR 0.66; CI 0.45–0.98) and significantly decreases colorectal cancer (HR 0.63; CI 0.43–0.92). Only the combined estrogen-progesterone arm of the study has been discontinued. The estrogen-only arm<sup>210</sup> is still being followed and will yield additional information.

Important risks with estrogen and progestin/progesterone therapy include venous thromboembolism<sup>210,211</sup> and cancers of the breast and endometrium.<sup>212–216</sup> In current users this therapy, if taken for more than 5 years following menopause, increases the risk for breast cancer. Irregular vaginal bleeding as well as the risk of endometrial cancer is increased with the use of estrogen without progestin/progesterone or with insufficient doses of progestin/progesterone. Absolute risk of pulmonary embolism per 10,000 person-years attributable to HRT increased by 8 events and risk of all venous thromboembolic disease increased by 18 events.<sup>210</sup>

### Summary statements

29. In postmenopausal women with osteoporosis, HRT is efficacious in preventing clinical vertebral fractures<sup>209,210</sup> and in preventing non-vertebral fractures, including hip fractures<sup>210</sup> [Level 1].
30. In postmenopausal women, HRT is efficacious in increasing BMD at all sites<sup>88,217–220</sup> [Level 1].
31. In current users, HRT taken for more than 5 years after menopause increases the risk of invasive breast cancer by 26%, the risk of coronary heart disease by 29% and the risk of stroke by 41%<sup>210</sup> [Level 1].
32. The use of estrogen without progestin/progesterone increases irregular vaginal bleeding and the risk of endometrial cancer<sup>210,212–216</sup> [Level 1].



33. HRT increases the risk of venous thromboembolism from 16 with placebo to 34 with HRT per 10,000 person-years over 5 years<sup>210</sup> [Level 1].
34. HRT is efficacious in the treatment of vasomotor symptoms<sup>204</sup> [Level 1].

### Recommendations

21. HRT is a first-line preventive therapy in postmenopausal women with low bone density. However, when used only for the prevention of postmenopausal osteoporosis, the risks of HRT may outweigh the benefits [Grade A].
22. HRT is a first-line preventive therapy for women who experience menopause before age 45 [Grade D].
23. HRT is a second-line treatment for postmenopausal women with osteoporosis [Grade B]. With prolonged use of HRT taken only for the treatment of postmenopausal osteoporosis, the substantial risks of cardiovascular disease, stroke and invasive breast cancer may lead to an unfavorable risk-benefit ratio.

### Selective estrogen-receptor modulators

Selective estrogen-receptor modulators (SERMs) are nonhormonal agents that bind to estrogen receptors with an affinity equivalent to that of estradiol, but they have estrogen agonist effects in some tissues and antagonist effects in others. The structure of any ligand is an important factor in determining the conformational changes that occur in the estrogen receptor when the ligand binds to it. Each ligand seems to produce a different final shape in the estrogen receptor and this shape determines interactions with protein cofactors and DNA response elements that ultimately translate into tissue-specific estrogen agonist or antagonist effects.<sup>221</sup>

Raloxifene is the only SERM that has been approved for the prevention and treatment of osteoporosis. It is taken as a single tablet (60 mg/day) without regard to meals, calcium and vitamin D supplements or time of day. Raloxifene has estrogen-agonistic effects on bone and lipid metabolism and estrogen antagonistic effects in the breast and uterus.

**Skeletal effects:** A large RCT, the Multiple Outcomes of Raloxifene Evaluation (MORE),<sup>35</sup> examined the anti-fracture efficacy of raloxifene in late postmenopausal women with osteoporosis (T-score below -2.5 at lumbar spine or femoral neck). Raloxifene significantly reduced the incidence of new vertebral fracture in those with (30% reduction) and without (50% reduction) prior vertebral fracture. Furthermore, raloxifene significantly reduced the incidence of 2 or more new vertebral fractures in both groups. However, the risk of non-vertebral fracture was not significantly reduced. Compared with placebo, raloxifene significantly increased BMD at the lumbar spine and femoral neck and significantly reduced the bone turnover markers.

In a post-hoc analysis<sup>222</sup> involving a small proportion of the study population, raloxifene was found to decrease the risk of new clinical vertebral fractures at 1 year by 68% compared with placebo. Moreover data from the 4th year of the MORE trial suggest a sustained vertebral anti-fracture efficacy.<sup>223</sup>

**Extra-skeletal effects:** Compared with placebo, raloxifene treatment for 2 years resulted in significant reductions in total and low-density lipoprotein (LDL) cholesterol.<sup>224</sup> There were no significant differences in high-density lipoprotein (HDL) cholesterol and triglyceride levels. Four-year results from the MORE trial showed similar effects on lipids.<sup>225</sup> Raloxifene therapy for 4 years did not significantly affect the overall risk of cardiovascular events in the total population, but did significantly reduce the risk of such events among women at high risk and among those with established cardiovascular disease. In contrast to HRT,<sup>226</sup> there was no evidence that raloxifene caused an early increase in risk of cardiovascular events although there were too few events during the first year to draw definitive conclusions. Adequately powered randomized prospective trials with cardiovascular events as predefined outcomes are needed before raloxifene is used for the prevention of such events.

Raloxifene significantly reduced (84%) the incidence of estrogen-receptor-positive invasive breast cancer after 4 years in postmenopausal women with osteoporosis who were at low risk of breast cancer.<sup>227</sup> Additional observation confirms this protective effect and indicates that 93 women would need to be treated with raloxifene for 4 years to prevent one case of invasive breast cancer.<sup>227</sup> Again, a prospective RCT in women at high risk of breast cancer is needed before raloxifene is used for the prevention of breast cancer. The compound has not been studied in women with a history of breast cancer, nor in menstruating women.

**Side effects:** Raloxifene appears to be generally safe and well tolerated. Although patients taking raloxifene experienced an increase in hot flashes and leg cramps compared with placebo,<sup>228,229</sup> these symptoms were usually mild to moderate and did not cause women to discontinue the drug. There was no association between leg cramps and the risk of venous thromboembolism. In contrast to estrogen and tamoxifen, raloxifene did not cause more vaginal bleeding or endometrial cancer than placebo.<sup>228-231</sup>

Venous thromboembolism is a serious side effect associated with raloxifene, although it is reported infrequently: 1.44 and 3.32 events per 1000 person-years for placebo and raloxifene at 60 mg/day, respectively.<sup>227</sup> The magnitude of the relative risk is similar to that observed with both HRT<sup>210,211</sup> and tamoxifen.<sup>232</sup> Raloxifene is contraindicated in patients with past history of venous thromboembolism. It would be prudent to stop this medication 3 days before any prolonged immobilization.

Raloxifene is a first-line therapy in postmenopausal

women for the prevention and treatment of osteoporosis. If additional studies confirm the positive extraskeletal effects, raloxifene could improve the overall benefits of a therapeutic intervention in postmenopausal women with low short-term risk of fracture.

### Summary statements

35. Raloxifene is efficacious in preventing vertebral fractures in postmenopausal women with osteoporosis<sup>35,223</sup> [Level 1]. It increases BMD at the spine and femoral neck<sup>35,223</sup> [Level 1]. Raloxifene has not yet been shown to be efficacious in preventing non-vertebral fractures<sup>35</sup> [Level 2].
36. In postmenopausal women with osteoporosis, raloxifene decreases the incidence of estrogen-receptor-positive invasive breast cancer<sup>227,228</sup> [Level 1]. However, it is not yet recommended for the prevention or treatment of breast cancer.
37. Raloxifene does not increase the risk of endometrial hyperplasia or endometrial cancer<sup>228,230,231</sup> [Level 1].
38. Raloxifene increases the risk of venous thromboembolism from 1.44 to 3.32 events per 1000 person-years<sup>227</sup> [Level 1].
39. Raloxifene has no beneficial effect on vasomotor symptoms and may increase their incidence<sup>228,229</sup> [Level 1].

### Recommendations

24. Raloxifene is a first-line therapy in the prevention of further bone loss in postmenopausal women with low bone density [Grade A].
25. Raloxifene is a first-line treatment for postmenopausal women with osteoporosis [Grade A].

### Alternative or adjunct therapies

Alternative therapies are those that are not currently an integral part of conventional medicine.<sup>233</sup> At this time, vitamin K and ipriflavone are the only alternative therapies for which there are sufficient data on BMD and fracture outcomes to warrant inclusion in clinical guidelines for osteoporosis.

**Ipriflavone — a synthetic phytoestrogen:** Phytoestrogens are weak estrogen-like chemicals produced by plants; they have estrogen agonist and antagonist effects. There are 3 major groups of naturally occurring phytoestrogens: the isoflavones (found principally in soybeans and other legumes), the lignans (found principally in flax seed, fruits and vegetables) and the coumestans (found in bean sprouts and fodder crops). Epidemiologic studies suggest that populations with high phytoestrogen intakes (such as Asians living in Asia) have lower rates of hip fracture than North Americans.<sup>234</sup> However, direct evidence for a protective effect of natural phytoestrogens in humans is extremely sparse.

There is considerably more data on the synthetic phytoestrogen, ipriflavone.<sup>235-249</sup> Trials of ipriflavone are difficult to

compare because of differences in BMD measurement techniques and sites measured. Interpretation of these studies is also limited by the fact that RCTs of ipriflavone have not consistently ensured adequate intake of calcium and vitamin D in either the treatment or placebo arms. Further, data on the long-term effects of ipriflavone on other estrogen-sensitive tissues (breast and uterus) are lacking, and the largest study to date<sup>247</sup> suggests that ipriflavone use was associated with significant lymphopenia in 29 of the 237 treated women. Only one study<sup>247</sup> reported fracture outcomes. Although this study did not demonstrate any difference in the occurrence of vertebral fractures among women taking ipriflavone compared with women taking placebo, only a small number of women had vertebral fractures during the 36-month follow-up. Larger studies are needed to determine whether ipriflavone protects against vertebral fractures.

### Summary statements

40. Due to differences in techniques for measuring BMD and sites measured, trials of ipriflavone for the prevention of bone loss and fractures in postmenopausal women are difficult to compare.<sup>235-249</sup>
41. Ipriflavone (200 mg, 3 times daily) is efficacious in maintaining BMD in the spine in postmenopausal women<sup>235,239</sup> [Level 1].
42. Ipriflavone is not efficacious in preventing fractures in postmenopausal women with osteoporosis<sup>247</sup> [Level 2].
43. Ipriflavone has not been studied in men or premenopausal women.

### Recommendations

26. Ipriflavone may be considered as a second-line preventive therapy in postmenopausal women [Grade B].
27. Ipriflavone is not recommended for treatment of postmenopausal women with osteoporosis [Grade B].
28. Because there is inconclusive evidence regarding the long-term safety of ipriflavone, patients taking it should be monitored closely [Grade B].
29. Ipriflavone is not recommended for use in men or premenopausal women [Grade D].

**Vitamin K:** Two types of vitamin K occur naturally: vitamin K1, which is found in plants (such as lettuce) and vitamin K2, which is found in meat, cheese and fermented products. Vitamin K is important in the function of bone proteins. Circulating levels of vitamin K are lower in patients with hip fractures compared with controls and observational studies suggest that high levels of dietary vitamin K are associated with lower risk of hip fracture.<sup>250,251</sup> These findings have led to the development of RCTs examining the effects of vitamin K treatment on BMD or fracture.<sup>252-256</sup> The studies are limited by the fact that RCTs of vitamin K (typically menatetrenone, 45 mg/day) did not examine calcium or vitamin D intake in either the treatment or placebo arms.

## Summary statements

44. Vitamin K is not efficacious in preventing bone loss associated with medication-induced ovarian failure<sup>252</sup> [Level 2].
45. Vitamin K may be efficacious in slowing bone loss in postmenopausal women with osteoporosis, but has not been shown to be superior to calcium and vitamin D<sup>255,256</sup> [Level 1].
46. Vitamin K may be efficacious in the treatment of postmenopausal women with severe osteoporosis, but has not been shown to be superior to calcium and vitamin D<sup>254</sup> [Level 2].
47. Vitamin K has not been studied in men or premenopausal women.

## Recommendations

30. Vitamin K is not currently recommended for the prevention of postmenopausal osteoporosis [Grade B].
31. Vitamin K is not currently recommended for the treatment of postmenopausal women with osteoporosis [Grade B].
32. Vitamin K is not recommended for use in men or premenopausal women [Grade D].

## Fluoride

Sodium fluoride is a potent stimulator of bone formation. It was initially investigated as a therapy for osteoporosis in 1964<sup>257</sup> and gained popularity through the 1970s and 1980s.<sup>258</sup> It was the first agent to be reported as capable of increasing axial BMD in patients with osteoporosis<sup>259</sup> — mainly in uncontrolled studies. In 1989, a consensus report<sup>260</sup> expressed cautious optimism about the efficacy of fluoride therapy, but recognized the high incidence of side effects, particularly with some formulations.

The 1990s marked the introduction of RCTs into osteoporosis research and the use of precise vertebral fracture morphometry. However, fluoride compounds have not been adequately investigated using modern, evidence-based standards; almost all of the studies have been small and have had limited power. Furthermore, the clinical profile of fluoride treatment varies greatly with different pharmacologic compounds and formulations in terms of bioavailability and side effects. Thus, the studies that do exist are not, for the most part, comparable.

**Fluoride in the treatment of postmenopausal women:** Five RCTs examined fluoride therapy and the prevention of vertebral fractures in postmenopausal women.<sup>261–265</sup> They varied in duration (from 2 to 4 years) and used different pharmacologic preparations of fluoride (plain NaF, enteric-coated NaF, Na-monofluorophosphate and slow-release fluoride) and different fluoride doses and are, thus, not comparable. However, no study demonstrated a significant reduction in vertebral fractures, despite consistent and significant increases in spinal BMD of as much as 6–8% a

year. One small randomized study<sup>263</sup> of therapy with slow-release fluoride claimed to show a reduction in vertebral fractures, but quoted the data only as grouped fracture rates and did not indicate a significant reduction in the number of women with newly fractured vertebrae. With fluoride therapy, even a major increase in BMD cannot be considered as a surrogate marker for fracture prevention. Sodium fluoride therapy has not been shown to be effective in preventing fractures in postmenopausal osteoporosis, and there have been no studies in premenopausal women.

**Fluoride therapy in men:** In one small RCT,<sup>266</sup> 60 men with a mean age of 52 years and a mean lumbar spine T-score of  $-2.74$  were divided equally into treatment and control groups. The treatment group received 114 mg of Na-monofluorophosphate (15 mg fluoride ion) daily in cycles of 3 months of treatment and 1 month without fluoride. After 36 months the number of patients with vertebral fractures was reduced by 75% (12 patients experienced vertebral fractures in the control group; 4 in the treatment group). Among those in the treatment group, 10 patients experienced adverse effects. This single RCT demonstrating an effect on fractures in men stands in contrast to the negative results for women. It is not likely that the effects of fluoride would be different in men and women, nor is there any direct evidence for this. Thus, it must be concluded that anti-fracture efficacy of fluoride therapy for osteoporosis has not yet been demonstrated.

**Fluoride and glucocorticoid-induced osteoporosis:** Four RCTs of fluoride therapy in glucocorticoid-induced osteoporosis<sup>267–270</sup> demonstrated 2- to 10-fold increases in spinal BMD over 1–2 years of fluoride treatment, but were too small to show a significant anti-fracture effect.

**Toxicity:** The toxic effects of fluoride are dose-related and the prevalence of adverse effects differs with different pharmacologic preparations. In 5 of the studies mentioned above,<sup>261,262,264,265,271</sup> patients showed significant gastrointestinal toxicity (gastric pain and nausea) and skeletal toxicity (lower extremity pain, and stress fractures). Toxicity was particularly associated with plain fluoride and monofluorophosphate<sup>264,265</sup>; both these formulations can cause gastrointestinal as well as skeletal side effects. Far fewer gastrointestinal side effects were associated with enteric-coated preparations<sup>262</sup> and even fewer with the slow-release fluoride preparation.<sup>263</sup>

## Summary statements

48. Fluoride preparations have not been shown to reduce vertebral or non-vertebral fractures in postmenopausal women with osteoporosis<sup>261,262,264,265</sup> despite consistent and sustained increases in spinal BMD.<sup>261–265</sup> Fluoride preparations maintain or marginally increase BMD at the femoral neck<sup>262–265</sup> [Level 1].

## Recommendations

33. Fluoride is not recommended for treatment of postmenopausal women with osteoporosis [Grade A].

34. Fluoride is not recommended for use in premenopausal women or in men [Grade D].

### Parathyroid hormone

Parathyroid hormone (PTH) was reported as a clinical treatment for osteoporosis in 1980,<sup>272</sup> but its commercial development was delayed until the advent of central DXA densitometry, which allowed rapid assessment of the hormone's efficacy in increasing bone mass. The synthetic N-terminal fragment, hPTH(1-34), has been used almost exclusively in published reports, culminating in the pharmaceutical trials of teriparatide rhPTH(1-34). At the time of writing, teriparatide was expected to receive regulatory approval in the United States to be followed shortly in other countries including Canada. Another PTH hormone containing the amino-acid sequence rhPTH(1-84) is currently undergoing phase III evaluation.

**PTH in the treatment of postmenopausal osteoporosis:** The pivotal RCT of teriparatide<sup>273</sup> evaluated its efficacy in reducing vertebral and non-vertebral fractures in 1637 postmenopausal women with at least one vertebral fracture at enrolment. This trial was terminated prematurely at a median period of 21 months because of the occurrence of osteosarcomas in a long-term toxicology study in rats treated with large doses of teriparatide from infancy to senescence (see below).

Fracture reduction depended on the type of fracture analysed. For new vertebral fractures, the relative risk was approximately 0.35 compared with placebo. The risk of new vertebral fractures (radiographic deformities) for women with moderate to severe vertebral fractures was reduced by up to 90%. For non-vertebral fractures, the relative risk was 0.47 with no evidence that either dose (20 or 40 µg/day injected subcutaneously) was more effective.<sup>273</sup> Compared with placebo treatment, teriparatide resulted in dose-dependent increases in BMD at both the lumbar spine (10–14%) and total hip or femoral neck (3–4%).<sup>273</sup> Although, other small RCTs of hPTH(1-34) have not been powered to evaluate anti-fracture efficacy, similar and consistent increases in spine and hip BMD were observed over periods of 1–3 years of therapy.<sup>274–276</sup>

**PTH in male osteoporosis:** There are few data from which to evaluate the effects of PTH in male osteoporosis. In a small uncontrolled cohort study of 8 men with severe osteoporosis, Slovik and colleagues<sup>277</sup> reported a large gain in lumbar spine BMD (measured by quantitated computed tomography) with no significant change in forearm BMD following 12 months of PTH(1-34) treatment. In a small RCT<sup>278</sup> lasting 18 months, PTH(1-34) resulted in a 13.5% increase in lumbar spine BMD among 10 men with severe osteoporosis compared with a control group of 13 men treated only with placebo injections together with calcium and vitamin D. BMD was measured by DXA. Preliminary data have also been presented on the use of teriparatide in an RCT conducted in 437 men as part of its regulatory trials.<sup>279</sup>

Dose-dependent increases in BMD of 6–9% measured by DXA in the lumbar spine and 2–3% in the femoral neck were observed over 12 months; insignificant changes were observed in the placebo-treated patients. In the teriparatide trial, the increase in lumbar spine BMD mirrored the changes seen in a larger trial in postmenopausal women.<sup>273</sup> These studies were of 18 months duration or less and were not powered to detect anti-fracture efficacy; however, the comparable increases in BMD in men and postmenopausal women leads us to expect similar anti-fracture efficacy.

**PTH and glucocorticoid-induced osteoporosis:** To date, the only study of PTH in secondary osteoporosis is a 12-month RCT in 51 postmenopausal women with glucocorticoid-induced osteoporosis.<sup>280</sup> All women had been on chronic estrogen therapy; nearly a third had vertebral fractures at baseline and were receiving clinically significant doses of prednisone for an average of 12–15 years before enrolment. Compared with the control group on estrogen therapy, treatment with PTH(1-34) resulted in a significant (11.1%) gain in BMD in the lumbar spine and an insignificant average gain of 2.9% in the femoral neck. The trial cohort was followed for an additional 12 months while they continued estrogen therapy and further small increments in BMD were observed in the group previously treated with PTH(1-34).<sup>281</sup> Despite the apparent high risk of incident fractures in this trial cohort, very few vertebral or clinical fractures were observed; in any event, the trial was too small to detect anti-fracture efficacy for PTH.

Side effects during PTH therapy have been relatively scarce. Pain and induration at the injection sites were likely due to the vehicle used to reconstitute the peptide<sup>274,275</sup> and were not seen with teriparatide.<sup>273</sup> Nausea, headaches, dizziness and leg cramps were observed infrequently as dose-dependent side effects during the teriparatide trials.<sup>273</sup> Not surprisingly the pharmacologic properties of PTH resulted in occasional episodes of hypercalcemia or hypercalciuria during the teriparatide trials, which were obviated by either cessation of concurrent calcium supplementation or minor dose reductions.<sup>273</sup> To date the toxicology data from teriparatide, documenting late-onset osteosarcomas in rats treated with large doses of rhPTH(1-34) from infancy to senescence, has not been seen in human studies. Currently, the consensus is that limited exposure (1–2 years) to PTH therapy in older people with osteoporosis does not expose this population to the risk of osteosarcoma or any other neoplasm.

### Summary statements

49. hPTH(1-34) is efficacious in preventing both vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis.<sup>273</sup> hPTH(1-34) increases BMD at all skeletal sites with the exception of the radius<sup>273</sup> [Level 1].
50. In men with severe osteoporosis, hPTH(1-34) increases BMD at the spine<sup>277–279</sup> [Level 2].
51. In postmenopausal women with glucocorticoid-in-

duced osteoporosis, hPTH(1-34) increases BMD at the spine<sup>280</sup> [Level 2].

**Recommendations**

- 35. Although hPTH(1-34) is not yet approved for use in Canada, it is expected to become a first-line treatment for postmenopausal women with severe osteoporosis [Grade A].
- 36. hPTH(1-34) is also expected to become a recommended treatment for men and people with severe osteoporosis who are receiving prolonged glucocorticoid therapy [Grade D].

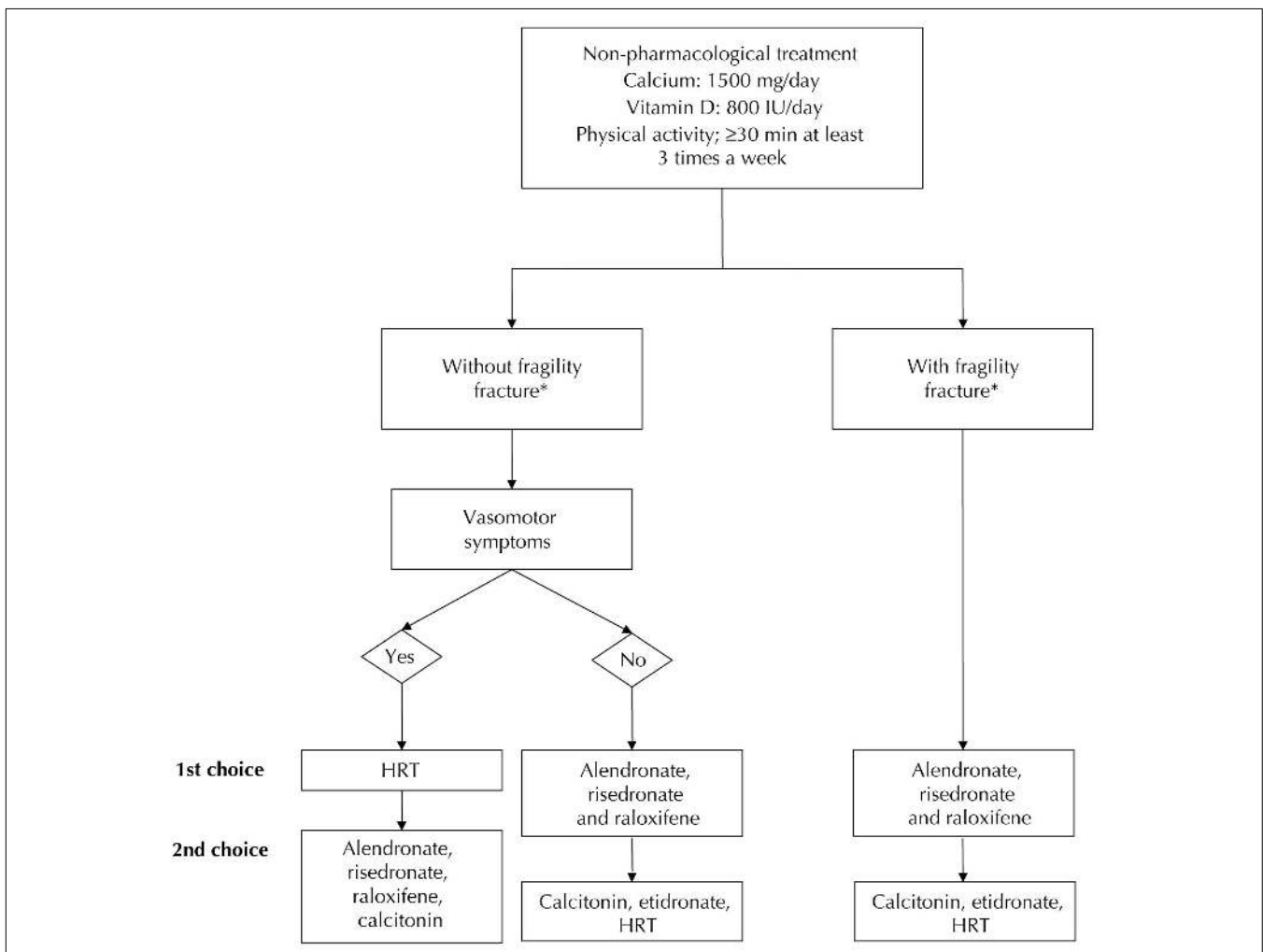
**Non-pharmacologic interventions**

**Nutrition**

The nutrition section committee’s mandate was to determine whether calcium, vitamin D or selected nutritional variables could be used in osteoporosis prevention

and treatment (Figure 3). The questions addressed concerned the effect of the intake of nutrients and other food components on subsequent attainment of peak bone mass, as well as prevention of bone loss and fractures. The initial scan of the literature revealed 16 058 abstracts from which 996 studies were reviewed. The resulting evidence-based database included 56 studies on vitamin D, calcium or both, and 26 on other nutrients and food-related components.

The nutrient intake recommendations have been evaluated with respect to the effect of the nutrient on bone health; other functions of the nutrients have not been examined. If an essential nutrient had no apparent effect on bone, it is recommended that no *additional* intake of nutrient is needed, recognizing that bone is a complex tissue that would require the presence of all essential nutrients for synthesis and maintenance. As data on dietary levels needed for bone growth of infants and children are lacking, the recommendations apply only to adults unless stated otherwise. Intake recommendations represent di-



**Fig. 3: Optimal treatment for osteoporosis in postmenopausal women. (Note: \*Mainly vertebral fracture. Only alendronate and risedronate and recently continuous estrogen-progesterone have been shown to decrease hip fracture risk.)**

etary goals for an individual. The recommended values are the lowest or most consistently reported effective amounts that were tested, plus background levels of the nutrient. Thus, recommendations are for the total dietary intake.

## Summary statements

### Calcium and vitamin D

52. Adequate calcium and vitamin D through diet or supplements are essential for the prevention of osteoporosis and, taken together, are essential adjuncts to preventative therapy<sup>107–109,123,125,230,282</sup> [Level 1].
53. Calcium and vitamin D should not be used as the sole treatment of osteoporosis; however, calcium and vitamin D through diet or supplements are essential adjuncts to osteoporosis treatment<sup>35,38,85,106,113,117,118,136,137,283–285</sup> [Level 1].
54. The recommended calcium intake from all sources (where “all sources” means total diet and supplement) is as follows:
  - a. prepubertal children (ages 4–8 years) — 800 mg/day<sup>286–289</sup> [Level 1]
  - b. adolescents (ages 9–18 years) — 1300 mg/day<sup>287,290–292</sup> [Level 1]
  - c. premenopausal women — 1000 mg/day<sup>293–295</sup> [Level 1]
  - d. men after adolescence and until the age of 50 years — 1000 mg/day<sup>296,297</sup> [Level 3]
  - e. menopausal women — 1500 mg/day<sup>282–285,298–305</sup> [Level 1]
  - f. men over the age of 50 years — 1500 mg/day<sup>285,296,297</sup> [Level 1]
  - g. women 18 years and over who are pregnant or lactating — same as nonpregnant adult, i.e., 1000 mg/day<sup>306–309</sup> [Level 1].
55. Vitamin D3 (cholecalciferol) is preferred over vitamin D2 (ergocalciferol)<sup>310</sup> [Level 2].
56. For Canadians, sun exposure does not appear to be sufficient to replace ingested forms of vitamin D<sup>311</sup> [Level 3].
57. The recommended vitamin D intakes from all sources (where “all sources” means total diet and supplement) are as follows:
  - a. men and women aged 19–50 years — 400 IU (10 µg)/day<sup>311–313</sup> [Level 4]
  - b. men and women > 50 years — 800 IU (20 µg)/day<sup>282–285,314</sup> [Level 1].

### Macronutrients — protein, fatty acids, dietary fibre

58. Increasing protein intake among those who have inadequate dietary protein has a positive effect on the risk of hip fracture in men and women<sup>315,316</sup> [Level 3].
59. There is no good-quality evidence to support or refute the benefits of essential fatty acids or dietary fibre on BMD or fracture risk.

### Diet-related lifestyle factors — caffeine, salt

60. Heavy caffeine ingestion (> 4 cups coffee/day) is significantly associated with hip fracture in men and women<sup>317,318</sup> [Level 2].
61. The effects of sodium on BMD are equivocal; however, in studies in which sodium intake is measured properly, there is a significant negative effect for women<sup>319</sup> [Level 3] and men<sup>320</sup> [Level 5] when daily intake exceeds 2100 mg (90 mmol).

### Other micronutrients

62. In both men and women who have normal digestion, providing additional dietary magnesium has no significant effect on the risk of hip fracture<sup>296,321–323</sup> [Level 3].
63. In men and menopausal women, providing additional dietary copper has no significant effect on the risk of hip fracture<sup>296,324</sup> [Level 3].
64. There is no significant association between fracture risk and zinc intake in men<sup>325</sup> [Level 3] and additional dietary zinc intake has no significant effect on BMD in women<sup>322</sup> [Level 5].
65. There is no good-quality evidence to support or refute the benefits of iron on BMD or fracture risk; however, in women over 39 years, high intake of iron (> 30 mg/day) may be associated with an increased risk of hip fracture<sup>326</sup> [Level 4].
66. Few studies have adequately addressed dietary phosphorus. In the normal range of daily intake, assessed without consideration of phosphate additives in processed foods, there does not appear to be any significant relation between phosphorus intake and hip fractures in men<sup>325</sup> [Level 3] or BMD in women<sup>320</sup> [Level 5].
67. There is no good-quality evidence to support or refute the effect of providing dietary silica, boron or strontium, or additional manganese, on BMD or fracture risk.

### Recommendations

37. The following daily intake levels are recommended for calcium:
  - a. prepubertal children (ages 4–8 years) — 800 mg/day [Grade B]
  - b. adolescents (ages 9–18 years) — 1300 mg/day [Grade B]
  - c. women (ages 19–50 years) — 1000 mg/day [Grade A]
  - d. women over 50 years — 1500 mg/day [Grade A]
  - e. pregnant or lactating women (≥ 18 years) — 1000 mg/day [Grade A]
  - f. men (ages 19–50 years) — 1000 mg/day [Grade C]
  - g. men over 50 years — 1500 mg/day [Grade C].
38. The following daily intake levels are recommended for Vitamin D<sub>3</sub>:
  - a. women (ages 19–50 years) — 400 IU (10 µg)/day [Grade D]

- b. women over 50 years — 800 IU (20 µg)/day [Grade A]
- c. pregnant or lactating women (≥ 18 years) — 400 IU (10 µg)/day [Grade D]
- d. men (ages 19–50 years) — 400 IU (10 µg)/day [Grade D]
- e. men over 50 years — 800 IU (20 µg)/day [Grade A].

Vitamin D<sub>3</sub> is specified as it shows greater potency than Vitamin D<sub>2</sub>; therefore more of the latter may be required to meet these recommendations.

- 39. Maintaining adequate protein intake is important [Grade C].
- 40. Excess caffeine (> 4 cups coffee/day) should be avoided [Grade B].
- 41. Excess dietary sodium (> 2100 mg/day or > 90 mmol/day) should be avoided as it reduces BMD in adult men and women [Grade C].
- 42. No evidence exists to recommend additional intakes of the following nutrients for the prevention or treatment of osteoporosis: magnesium, copper, zinc, phosphorus, manganese, iron, essential fatty acids [Grade D].

### Physical activity and falls prevention

Physical activity will benefit skeletal structure and strength; and the detrimental effects of immobilization are well known. Physical activity varies in type, frequency, duration, intensity and age of onset. It affects different parts of the skeleton differently, according to the pattern of stress produced. An additional complication is that overactivity, by affecting hormonal status, especially in premenopausal women, and perhaps because of associated undernutrition, can be detrimental to the skeleton.

Sports are the most extreme form of physical activity normally undertaken, but by their nature are not amenable to RCTs. They also fall mainly into the 2 categories of physical activity — aerobic or impact type (jogging, field and racquet sports, gymnastics) and endurance and strength type (weightlifting, body building, swimming, cycling and use of static exercise machines) — and so can offer insight into the type of physical activity most likely to be valuable.

### Physical activity and BMD

**Children, before and during puberty:** The question of greatest importance is probably whether a permanent change in the skeleton can be induced by physical activity, such that it will bring benefit throughout the rest of life. Clearly the time of growth would represent the best chance of achieving this. In children, interpretation of BMD changes is difficult, as the usual method for measuring BMD (by DXA) is size sensitive; the density of small bones tends to be underestimated and that of large bones overes-

timated. Thus it is important to match control and study groups for stage of growth and puberty and take into account any effect of the physical activity on growth, which could occur, for example, through a delay in puberty.

An RCT large enough and long enough to provide a definite answer to our question is not available and likely never will be. We must piece together the answer as best we can from the available evidence.

Two RCTs, one in boys and one in girls aged 9–12 years have shown that an exercise program of 7 months' duration, entailing jumping, will produce changes in BMD and some measures of skeletal size. In girls, the impact was greater for those entering puberty than for younger children<sup>327,328</sup>; however, benefit is not confined to the time of puberty, but also occurs at younger ages.<sup>329–331</sup> Most of the sports that children participate in are impact types, such as baseball, basketball and soccer, and are associated with improved BMD. Gymnastics is particularly effective. Non-impact exercises, such as swimming and resistance strength training are of little benefit.<sup>332,333</sup>

**Young adults after puberty:** Benefits from impact-type exercises are seen in young adults after puberty,<sup>334–337</sup> with the best results in those who have exercised throughout childhood.<sup>338</sup> Running produces variable results in both men (see below) and women depending on nutrition and hormone changes. This effect in young women is reviewed by Khan and colleagues.<sup>339</sup>

Weight training in young adulthood also gives inconsistent results.<sup>340,341</sup> Young male olympic weight lifters had greater BMD, although potential use of anabolic steroids in such competitors has been reported.<sup>342,343</sup>

**Older adults — men, premenopausal and postmenopausal women:** Case-control studies<sup>344–348</sup> have shown varying degrees of BMD increase in men who participate in sports. However, many of these studies included adults who had been active in sports since childhood.<sup>349–351</sup> In a study of adult male tennis players, BMD was found to be 15% greater at the lumbar spine and 11% at the proximal femur.<sup>349</sup> For long-distance running, benefit appears to occur among those who run up to 15–20 miles a week; longer distances, for whatever reason, result in little benefit or actual reduction in bone density.<sup>352–354</sup> Most intervention studies of men are case-control and not randomized. There is a great need for large-scale randomized long-term trials.

A meta-analysis<sup>355</sup> of 8 RCTs (6–36 months duration) in premenopausal women (16–44 years old) reviewed whether impact exercise versus non-impact exercise reduced age-related bone loss. Impact exercises included high-impact aerobics, running and jump training. Non-impact exercises included stretching, resistance training and weight-lifting. The studies were limited by small sample sizes and high dropout rates. Bone loss in the lumbar spine was 1.5% lower in the group participating in impact exercises (95% CI 0.6%–2.4%) and 1.2% lower in those in the non-impact exercise group (95% CI 0.7%–1.7%). One study in female college students found that running (im-



pect) and weight-training (non-impact) were equally effective in reducing bone loss.<sup>356</sup> Overall, studies with high compliance had a greater impact on maintaining or improving BMD.

Studies in postmenopausal women similarly tend to be small and short term, although there are many more RCTs. As these studies involve trying to change an activity pattern, compliance becomes an issue, although under study conditions it tends to be relatively high (50–100%). Most investigators have studied the impact of physical activity in those who have chosen to participate fully compared with lower compliers and a control group. Therefore, the studies explore efficacy rather than effectiveness and do not carry out intention-to-treat analyses.

Brisk walking, dancing and jumping appear to slow or prevent bone loss in postmenopausal women, although the results are not entirely consistent.<sup>300,357–366</sup> Physical activities designed to improve strength and endurance or the strength of specific muscles that act on the bone in question (mostly weight training or the use of stationary equipment) produce inconsistent results.<sup>367–374</sup> The potential benefits of physical activity in synergy with HRT are unclear, as results are inconsistent.<sup>365,375,376</sup>

Several meta-analyses have been conducted on the effect of physical activity on bone loss in postmenopausal women. Wolff and co-workers<sup>377</sup> concluded that physical activity prevented or reversed almost 1% of bone loss per year in both the lumbar spine and femoral neck. Several other meta-analyses<sup>355,378</sup> have also found a greater benefit of physical activity, particularly impact exercise, at the spine. BMD at the hip may also benefit from impact exercise but the effect of non-impact exercises on hip BMD remains unproven.<sup>355</sup>

**Physical activity and fracture prevention:** Case-control studies<sup>379,380</sup> of older adults with hip fractures have shown that these people had lower activity levels through adult life. A large prospective, observational study<sup>381</sup> found faster rates of BMD loss from the hip in those most inactive (bed or chair bound). A prospective study<sup>382</sup> of 9012 men over 7 years found fewer fragility fractures in men who did more weight-bearing activity. Intense activity (defined as activity beyond walking) was associated with a reduction in hip fracture occurrence in the most active group (HR 0.38; 95% CI 0.16–0.91) in a 21-year cohort study.<sup>383</sup>

There are no long-term prospective RCTs of physical activity exploring fracture outcomes.

**Physical activity and falls prevention:** In adults over the age of 65 years living independently, physical activity has been shown to reduce falls.<sup>384</sup> Physical activity included individually tailored programs of progressive muscle strengthening, balance retraining exercises and a walking plan which reduced the number of people sustaining falls and the number of people with fall-related injuries over 1 year (RR 0.80, 95% CI 0.66–0.98). A reduced rate of falls was also found in those who continued the activity for a second year.<sup>385–387</sup>

Tai chi has also been shown to reduce falls.<sup>388</sup> One of the limitations of this study was that when “falls” were redefined to discount minor events, such as stumbling, the study results were no longer statistically significant.

Group-delivered exercise programs that have not been individually prescribed appear to be not as effective in reducing falls, and further study is needed in this area.

**Other programs to reduce falls:** Home hazard assessment and modification prescribed by an occupational therapist for older adults with a history of falling have been shown to reduce the risk of falling both inside and outside the home (RR 0.64, 95% CI 0.49–0.84).<sup>389</sup> Those without a history of falls did not receive benefit from this program.

Withdrawal of psychotropic medication is also effective in reducing falls among the elderly living in the community.<sup>386</sup>

Educational preventive home visits (evaluation of medical, functional, psychosocial and environmental factors followed by recommendations) have not been found to be effective in reducing falls in community-dwelling elderly.<sup>390</sup>

Multi-faceted programs in community-dwelling elderly people are effective in reducing falls (pooled RR 0.79, 95% CI 0.67–0.94) in those with a history of falling or known risk factors for falls.<sup>384,391,392</sup> Also, Tinetti and colleagues<sup>393</sup> showed a reduction in the number of falls using a multifactorial intervention (adjusted incidence rate ratio 0.69, 95% CI 0.52–0.90). Such interventions include screening of health and environment risk factors, assessment of physical activity and home hazards and modification and withdrawal of psychotropic medications. These programs have only been found to be positive in North America, which may be due to differences in health care systems and differences in the types of multifactorial and multidisciplinary interventions.

## Summary statements

68. Children who exercise habitually have stronger bones than those who do not.<sup>329,331,338,394</sup> [Level 3].
69. Exercising throughout puberty may be particularly efficacious in producing a stronger skeleton.<sup>327,328</sup> [Level 1].
70. Impact exercises lead to an improvement in BMD in both boys and girls.<sup>327,328</sup> [Level 1].
71. Impact exercises and sports that include them as a component are more efficacious at all ages than strength, endurance or non-weight-bearing activities.<sup>332,333,359</sup> [Level 4].
72. Physical activity in men, particularly of the impact type, is associated with greater BMD.<sup>344–348</sup> [Level 4].
73. In premenopausal women, both impact and non-impact exercise prevent bone loss in the lumbar spine, with impact exercise somewhat more beneficial.<sup>355,356</sup> [Level 2+].
74. In postmenopausal women, impact exercise may reduce the rate of bone loss or lead to some bone gain, at least in the short term. Response to non-impact or endurance exercises is lower and more inconsistent.<sup>300,357–360,364,365,367,368,371–373</sup> [Level 1].
75. In both men and women, excessive physical activity,

such as that associated with long-distance running, can be detrimental<sup>352-354</sup> [Level 4].

76. A higher level of activity throughout middle life is associated with a reduced risk of hip fracture in old age [consensus].
77. Exercise programs that are individually tailored and include muscle strengthening, balance training and walking over 1 year are effective in reducing falls<sup>384-387</sup> [Level 1+] and injuries<sup>384</sup> [Level 2+]. General group-delivered exercise programs have not been shown to be effective in reducing falls.
78. Multifactorial programs that combine interventions are effective in reducing falls in both unselected people and those with a history of falling or with known risk factors for falls<sup>384,391-393</sup> [Level 1+].

### Recommendations

43. Children, particularly those entering and passing through puberty, should be encouraged to participate in impact exercises or sports (mainly field and court sports) [Grade B].
44. Throughout life, both men and women should be encouraged to participate in exercise, particularly in weight-bearing exercises, which include impact as a component [Grade C for men; Grade B for pre- and menopausal women].
45. For older men and women at risk of falling or who have fallen, tailored programs that are based on individual assessment, contain exercises to improve strength and balance and, where necessary, are multidisciplinary in nature should be made available [Grade A].

### Conclusion

These clinical practice guidelines are intended to provide family practitioners with the current best evidence from clinical research to help them make health care decisions about osteoporosis. For each section in this document, we have followed the steps necessary to develop recommendations based on evidence-based medicine: defining a question, gathering and summarizing the evidence and making a judgment on that evidence. As in many other fields of medicine, the evidence in the literature on osteoporosis is rapidly growing and we expect these guidelines to be a work in progress that will need to be updated to integrate new evidence.

Health care decisions should, as far as possible, be evidence-based and adapted to patient needs to ensure appropriate resource utilization, good adherence to therapy and optimal outcomes. That is what makes medicine an art as well as a science.

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**Scientific Advisory Council chair:** Jacques P. Brown, MD.  
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**Correspondence to:** Dr. Jacques P. Brown, Centre de recherche du CHUL, Room S-784, 2705, boul. Laurier, Ste-Foy QC G1V 4G2; fax: 418-654-2142; email: jacques.brown@crchul.ulaval.ca

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**Reprint requests:** Osteoporosis Society of Canada, 33 Laird Dr., Toronto ON M4G 3S9; fax: 416-696-2673; email: osc@osteoporosis.ca

# Hip Fracture in Women without Osteoporosis

Stacey A. Wainwright, Lynn M. Marshall, Kristine E. Ensrud, Jane A. Cauley, Dennis M. Black, Teresa A. Hillier, Marc C. Hochberg, Molly T. Vogt, and Eric S. Orwoll, for the Study of Osteoporotic Fractures Research Group

*Bone and Mineral Research Unit, Department of Medicine (S.A.W., L.M.M., E.S.O) and Department of Public Health and Preventive Medicine (L.M.M.), Oregon Health and Science University, Portland, Oregon 97239; Department of Medicine and Division of Epidemiology, University of Minnesota (K.E.E.), Minneapolis, Minnesota 55454; Section of General Internal Medicine, Minneapolis Veterans Affairs Medical Center (K.E.E.), Minneapolis, Minnesota 55417; Departments of Epidemiology (J.A.C.) and Orthopedic Surgery (M.T.V.), University of Pittsburgh, Pittsburgh, Pennsylvania 15260; Department of Epidemiology and Biostatistics; University of California at San Francisco (D.M.B.), San Francisco, California 94105; Kaiser Permanente Center for Health Research Northwest/Hawaii Division (T.A.H.), Portland, Oregon 97227; and Departments of Medicine and Epidemiology and Preventive Medicine, University of Maryland School of Medicine, and Medical Service, Maryland VA Health Care System (M.C.H.), Baltimore, Maryland 21201*

The proportion of fractures that occur in women without osteoporosis has not been fully described, and the characteristics of nonosteoporotic women who fracture are not well understood. We measured total hip bone mineral density (BMD) and baseline characteristics including physical activity, falls, and strength for 8065 women aged 65 yr or older participating in the Study of Osteoporotic Fractures and then followed these women for hip fracture for up to 5 yr after BMD measurement.

Among all participants, 17% had osteoporosis (total hip BMD T-score  $\leq -2.5$ ). Of the 243 women with incident hip fracture, 54% were not osteoporotic at start of follow-up. Nonosteoporotic women who fractured were less likely

than osteoporotic women with fracture to have baseline characteristics associated with frailty. Nevertheless, among nonosteoporotic participants, several characteristics increased fracture risk, including advancing age, lack of exercise in the last year, reduced visual contrast sensitivity, falls in the last year, prevalent vertebral fracture, and lower total hip BMD.

These findings call attention to the many older women who suffer hip fracture but do not have particularly low antecedent BMD measures and help begin to identify risk factors associated with higher bone density levels. (*J Clin Endocrinol Metab* 90: 2787–2793, 2005)

LOW BONE MINERAL density (BMD) is one of the most consistent predictors of fracture risk in older women. Moreover, clinical trials have demonstrated the effectiveness of pharmacological therapies in subjects with low BMD (1–3). Hence, clinical approaches to fracture prevention have focused on BMD measurements for risk stratification and decisions concerning therapy. This emphasis on BMD is highlighted by the attention paid to prevention, identification, and treatment of osteoporosis [defined by the World Health Organization as a BMD T-score at any measurement site  $\leq -2.5$  (4)] in fracture prevention efforts. However, a growing number of reports suggest that many women who fracture have BMD higher than that usually associated with osteoporosis (5–11).

Better understanding the characteristics of these women with fracture could lead to improved interventions to reduce fracture risk. Recently Miller *et al.* (10) described an approach to identifying the risk of fracture in postmenopausal women with peripheral BMD T-scores  $-2.5$  to  $-1.0$ , and Robbins *et al.* (12) described hip fracture risk factors for women with

high hip BMD among women older than 74 yr. In this investigation, we focused on the hypotheses that women without very low hip BMD who subsequently suffer hip fracture might be especially frail, physically active, or may have a genetic predisposition to fracture, putting them at increased risk for fracture.

In the Study of Osteoporotic Fractures (SOF) (13), a large cohort of postmenopausal women, we identified incident hip fracture cases during a period of up to 5 yr of follow-up and determined which proportion of these fractures occurred in women with total hip BMD at the start of observation above that usually associated with hip osteoporosis. Then, to learn more about the characteristics of these nonosteoporotic women with fracture, we compared baseline participant characteristics and potential risk factors for hip fracture among hip fracture cases with and without hip osteoporosis, as well as identified hip fracture risk factors for women without hip osteoporosis among potential risk factors previously described in this population.

## Participants and Methods

### Study population

Participants in SOF were women aged 65 yr or older recruited from population-based listings and health maintenance membership lists at four sites in the United States: Baltimore, MD; Minneapolis, MN; the Monongahela Valley near Pittsburgh, PA; and Portland, OR. Black women were excluded due to their lower incidence of hip fracture, as

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, 95% confidence interval; OR, odds ratio; SOF, Study of Osteoporotic Fractures.

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were women who were unable to walk without the assistance of another person, had bilateral hip replacements, or were institutionalized. Written informed consent was obtained from all participants after the appropriate institutional review boards approved the study protocol.

Between October 1986 and October 1988, 9704 women attended the first study examination. Examinations were conducted approximately every 2 yr. The second study examination was attended by 9339 women (98% of survivors) from January 1989 through December 1990 and was the first study examination at which hip BMD was measured. Follow-up for hip fracture began at this second examination among the 8065 participants who had adequate total hip BMD measurements. Circumstances resulting in inadequate BMD data were varied; primarily these women completed the study examination questionnaire only.

### Ascertainment of fracture cases

Participants were contacted every 4 months by telephone or mail to determine whether any fractures had occurred in the preceding 4-month period. In addition, participants were asked to notify the clinical center as soon as possible after any fracture. All hip fractures were radiographically confirmed. Fractures due to severe trauma (mainly as a result of motor vehicle accident) were excluded. After 5 yr, hip fracture follow-up remained over 98% complete for surviving participants. Details of fracture ascertainment methods have been published (14). Cases for this study were women who experienced a new hip fracture during the 5 yr of follow-up after total hip BMD measurement at the second SOF study examination.

Because a disproportionate loss to follow-up, particularly loss to death, might bias the proportion of hip fracture cases with and without osteoporosis as a competing risk for fracture, we assessed the number of confirmed deaths during follow-up among participants at risk for fracture. Deaths were documented by review of official death certificates and hospital records, if available. In 5 yr of follow-up, there were 191 confirmed deaths (14%) among women with osteoporosis and 511 (8%) among women without osteoporosis at the start of follow-up. Among participants who died during the observation period and had not experienced a hip fracture, 173 had osteoporosis, whereas 490 did not have osteoporosis. The proportion that terminated their participation in the study was approximately 1% and did not differ among those with and without osteoporosis.

### Definition of osteoporosis

Total hip BMD was quantified at the second SOF examination using dual-energy x-ray absorptiometry (QDR-1000, Hologic, Inc., Bedford, MA). Interscanner precision was good for measurement of block phantom (coefficient of variation 0.25–0.77%) and anthropomorphic femoral neck phantom (coefficient of variation 0.93%) (15). Details of bone density measurement methods have been published (14–16).

To categorize total hip BMD in familiar terms, we used the World Health Organization BMD-based osteoporosis classification (4) to define osteoporosis. Total hip BMD T-scores were calculated using the third National Health and Nutrition Examination Survey Caucasian female mean BMD aged 20–29 yr as reference peak BMD (17) [T-score = (BMD – peak BMD)/peak BMD SD]. We then divided participants by BMD T-score into two groups, one with osteoporosis (total hip BMD T-score  $\leq -2.5$ ) and one without osteoporosis (total hip BMD T-score  $> -2.5$ ). In additional analyses, we identified participants with total hip BMD T-score greater than  $-2.0$  and greater than  $-1.0$  because these are cut points referred to in some diagnostic and treatment guidelines.

We focus on total hip BMD measurements in these investigations because BMD measurement at this site has been described as the best predictor of all types of hip fracture, is associated with low precision error, and represents an assessment of both cortical and trabecular bone (18, 19). However, to determine which proportion of hip fracture cases had osteoporosis at the femoral neck or lumbar spine, we also measured BMD at these sites using dual-energy x-ray absorptiometry at the second study examination. Femoral neck BMD T-scores were calculated as described for the total hip BMD T-scores. Lumbar BMD T-scores were calculated using the manufacturer's Caucasian female reference mean for age 25 yr as peak BMD. For both the femoral neck and lumbar spine measurements, osteoporosis was defined as BMD T-score  $-2.5$  or less.

### Other measurements

We assessed baseline demographics, potential risk factors for hip fracture previously described in the SOF cohort (7, 20, 21) and several measures of strength and fall propensity. Participants completed a questionnaire and were interviewed for self-assessment of health, exercise, physical activity, falls, medical history, habits, and medication use. Current and past activity levels were assessed using a modified Paffenbarger survey (22, 23). Weekly caloric expenditure was determined by converting values for type, frequency, and duration of weight-bearing activities for the preceding 12 months. Intensity-weighted lifetime activity was derived from designating activities as low intensity (walking or gardening), medium intensity (dancing or tennis), or high intensity (jogging or skiing) and multiplying the reported frequency of the activity by 2.5, 5.0, and 7.5, respectively, for several time periods (past week, past 12 months, at about 50 yr of age, at about 30 yr of age, and as a teenager). Caffeine intake was tabulated assuming caffeine content of 95 mg per cup of coffee, 55 mg per cup of tea, and 45 mg per cola drink. Weight was measured using a balance beam scale. Height was assessed using a standard held-expiration technique with a wall-mounted Harpenden stadiometer. Resting heart rate was measured in the supine position. Neuromuscular function was tested by determining whether participants could rise from a chair five times without using their arms for support. Grip strength was measured using an adjustable handgrip dynamometer. Knee extension strength was tested using a hand-held isometric dynamometer. Distance depth perception was measured using a Howard-Dolman apparatus and reported as the SD of four trials (20, 24). Contrast sensitivity was measured using a VCTS 6500 wall chart and light meter (Vistech Consultants, Inc., Dayton, OH) and the average score calculated separately for high and low spatial frequencies (25). Mental status was assessed using a modified version of the Mini-Mental State Examination with a maximum score of 26 (26, 27). Prevalent vertebral fracture was defined using radiographs, as lateral, cross-sectional height of a measured thoracic or lumbar vertebra exceeding 3 SD below the mean at that vertebra for normal women (21).

Because many of the potential characteristics of interest were measured at only the first study examination, baseline information for all case characteristics and risk factors was collected from this examination, with the exception of age, which was updated at the time of hip BMD measurement during the second study examination.

Main risk factors for hip fracture were derived from 16 previously described BMD-independent risk factors for hip fracture in the SOF cohort (20, 21): a low self-rated health score; no walking for exercise; being on one's feet no more than 4 h each day; previous hyperthyroidism; previous fracture after age 50 yr; maternal history of hip fracture; caffeine intake of greater than 190 mg each day; current use of long-acting benzodiazepines; current weight less than that at age 25 yr; height at age 25 yr at least 168 cm; inability to rise from chair without the use of one's arms; being in the lowest quartile of the cohort for distance depth perception or for low-frequency contrast sensitivity; resting pulse rate greater than 80 beats/min; being at least 80 yr of age; and prevalent vertebral fracture.

### Statistical analysis

We first conducted a case-case analysis restricted to hip fracture cases grouped by osteoporosis status at the start of observation, comparing baseline characteristics and hip fracture risk factors. To examine these relationships in a different way, we made similar comparisons after dividing cases by total hip BMD tertile and quartile at the start of observation. The resulting inferences were similar to those for comparisons between cases grouped by hip osteoporosis classification. Therefore, for the remainder of this report, we refer to the two fracture case groups defined as having osteoporosis or not at the start of observation.

To control for a number of potential confounders in this case-case analysis, we additionally used multivariable logistic regression to quantify the association between baseline characteristics and risk factors and prevalence of total hip BMD T-score greater than  $-2.5$  (no osteoporosis), compared with prevalence of total hip BMD T-score  $-2.5$  or less (osteoporosis) at the start of observation. Here the odds ratios (ORs) from logistic regression estimate the magnitude of the difference in the frequency of fracture risk factors and distribution of the characteristics among cases without osteoporosis, compared with cases with osteopo-



rosis. For risk factors previously identified in the SOF cohort (20, 21), we modeled variables as they had been categorized in those analyses. For additional characteristics considered, we modeled variables as continuous if there was evidence for a linear trend in the log OR for that variable. When there was not a trend in OR, we examined the OR in categories of the continuous variable (by creating quartiles or equal increments). To express the OR and 95% confidence intervals (CIs) for continuous variables, units of change were chosen to be approximately 1 SD in the distribution of that variable for all participants. The multivariable model was generated by first examining groups of related variables in the main areas of interest in our investigation of participant characteristics (physical activity, family history of fracture, and fall propensity) for associations with total hip BMD T-score greater than  $-2.5$  (no osteoporosis). When more than one variable within a group was associated with total hip BMD T-score greater than  $-2.5$ , we examined these variables for multicollinearity and determined which parsimoniously explained the association of variables in these groups with total hip BMD T-score greater than  $-2.5$ . These selected variables were then included in the full multivariable analysis. Other variables from Table 1 were examined and included in the model if they were associated with total hip BMD T-score greater than  $-2.5$  independent of the selected variables in the main areas of interest, or behaved as confounders to the relationship between the variables in the main areas of interest and total hip BMD T-score greater than  $-2.5$ .

Although height was independently associated with total hip BMD T-score greater than  $-2.5$  on addition to the multivariable model, it was excluded from the final model; height and grip strength were correlated and excluding height from the final model allowed us to more clearly examine the association between grip strength, a variable in one of the main areas of interest, and total hip BMD T-score greater than  $-2.5$ . And, after adding covariates, the association between distance depth perception and total hip BMD T-score greater than  $-2.5$  was no longer statistically significant, and it was removed from the final model. We further addressed potential confounding by computing the time of observation from total hip BMD measurement at the second SOF study examination to hip fracture and including this variable in the logistic regression models.

After completing the case-case comparison, we used univariate and multivariable Cox proportional hazards regression analyses to quantify the relationship between baseline characteristics and hip fracture risk among women with and without osteoporosis. We approached the classification of variables and the modeling strategy as we had for the logistic regression analyses described above. To improve the proportional hazards regression models, a variable for total hip BMD was added to address potential confounding by BMD.

All statistical analyses used SAS (version 8.1, SAS Institute Inc., Cary, NC).

## Results

At the start of observation, the median age of the 8065 participants was 72 yr (range 67–99) (Table 1). The mean total hip BMD and BMD T-score were  $0.76 \text{ g/cm}^2$  (SD 0.13) and  $-1.51$  (SD 1.07), respectively; 6667 (83%) of the participants were without hip osteoporosis.

### BMD in hip fracture cases

During 5 yr of observation, 243 participants experienced a new hip fracture. Among the women with incident hip fracture, median age at the start of follow-up was 77 yr (range 67–95) and mean baseline weight was 63.0 kg (SD 12.5). Mean time of observation from BMD measurement to fracture was 2.8 yr (SD 1.4). Crude incidence rates of hip fracture were 17.7 per 1000 person-years among women with hip osteoporosis and 4.1 per 1000 person-years among those without osteoporosis.

Although the average BMD in the hip fracture cases was lower than that among all participants, of the 243 incident hip

fracture cases, 54% (131) did not have hip osteoporosis (Fig. 1), 32% had total hip BMD T-scores greater than  $-2.0$ , and 6% had total hip BMD T-scores greater than  $-1$ . To examine whether the length of follow-up influenced these results, we restricted the analysis to the hip fracture cases identified during the first 2 yr of follow-up. These results were similar; in 2 yr of follow-up, 49% of 76 hip fracture cases did not have hip osteoporosis and 28% had total hip BMD T-scores greater than  $-2.0$  at start of observation. With the exception of the oldest women, after 5 yr of follow-up, the majority of hip fracture cases was without hip osteoporosis regardless of age; hip osteoporosis at start of observation was absent in 58% of the 26 fracture cases aged 65–69 yr at the time of BMD measurement, 55% of the 65 women aged 70–74 yr, 66% of the 74 women aged 75–79 yr, 44% of the 22 women aged 80–84 yr, and 32% of the 28 women aged 85 and older (Fig. 2).

When lumbar spine and a combination of BMD sites were assessed, a similar pattern for proportion without osteoporosis across age groups was observed (Fig. 2); of those with incident hip fracture in 5 yr of follow-up, 54% were without osteoporosis at the lumbar spine, and 42% did not have osteoporosis at the lumbar spine or for the total hip. Osteoporosis at the femoral neck BMD measurement site was not present for 37% of hip fracture cases.

### Osteoporotic vs. nonosteoporotic hip fracture cases

Compared with cases with osteoporosis at the total hip at start of observation, those without osteoporosis were younger, heavier, and taller; had better distance depth perception, grip strength, and knee extension force; and less frequently had weight loss since age 25 yr, previous hyperthyroidism, or prevalent vertebral fracture (Table 1) at baseline. Hip fracture cases with and without osteoporosis did not differ with regard to self-rated health, time on feet less than 4 h each day, weighted lifetime activity, weekly activity in the last year, mental status score, ability to stand without using one's arms, any falls in the last year, or maternal history of hip fracture.

The results of the final multivariable logistic regression model (Table 2) indicated that independent of other variables in this model, hip fracture cases without hip osteoporosis were significantly less likely than fracture cases with hip osteoporosis to have had a history of hyperthyroidism or prevalent vertebral fracture and had greater body mass index (BMI) and grip strength. In addition, these data suggest that hip fracture cases without osteoporosis may have been less likely to be age 80 yr or older than cases with osteoporosis.

Although we had hypothesized that the total number of risk factors might be higher among cases without hip osteoporosis, the median number of risk factors for hip fracture [of 16 previously identified in this cohort (20, 21)] among cases without osteoporosis was less (median 4.0) than for cases with osteoporosis (median 5.0) ( $P < 0.0001$ ). Similarly, the proportion of cases with at least five risk factors was significantly lower among those without osteoporosis (35%) than among cases with osteoporosis (64%) ( $P < 0.0001$ ) (Fig. 3). We note, however, that all fracture cases with osteoporosis and most fracture cases without osteoporosis (96%) had at least one non-BMD risk factor and that a greater proportion of

**TABLE 1.** Baseline characteristics of all women and those with and without incident hip fracture subdivided by hip osteoporosis status at start of observation<sup>a</sup>

	All women (n = 8065)	Without hip fracture, Osteoporosis at hip		Hip fracture cases, Osteoporosis at hip		P value <sup>b</sup>
		No (n = 6536)	Yes (n = 1286)	No (n = 131)	Yes (n = 112)	
<b>General</b>						
Age (yr) <sup>c</sup>	72 (67–99)	72 (67–98)	75 (67–99)	76 (67–92)	78 (67–95)	0.05
Age ≥ 80 yr <sup>c</sup>	13%	10%	25%	24%	42%	0.002
<b>Body size</b>						
Weight (kg)	67.2 (12.4)	69.0 (12.2)	58.7 (9.1)	67.3 (12.9)	58.0 (10.0)	<0.0001
Current weight < at age 25 yr	13%	9%	29%	17%	36%	0.0007
Height (cm)	159.1 (6.0)	159.6 (5.9)	157.3 (6.1)	159.5 (6.6)	155.7 (6.8)	<0.0001
Height at age 25 yr ≥168 cm	15%	15%	11%	18%	13%	0.20
BMI (kg/m <sup>2</sup> )	26.5 (4.6)	27.1 (4.6)	23.7 (3.5)	26.5 (4.7)	23.9 (3.9)	<0.0001
Resting pulse rate > 80 beats/min	11%	10%	13%	13%	21%	0.08
Previous hyperthyroidism	10%	9%	11%	10%	21%	0.02
Fair to very poor self-rated health	15%	15%	17%	19%	23%	0.43
Caffeine intake >190 mg/d	47%	47%	48%	39%	50%	0.08
<b>Physical activity</b>						
Exercise activity in last yr						
Walking; no other activity	30%	31%	30%	30%	20%	0.07
Other activity: ± walking	37%	39%	33%	24%	33%	0.10
On feet ≤4 hrs/day	9%	8%	10%	15%	19%	0.37
Weighted lifetime activity: above median <sup>d</sup>	3665 (0–32115)	51%	46%	47%	46%	0.89
Total kcal/wk burned last yr: above median <sup>d</sup>	1171 (0–18282)	52%	44%	39%	41%	0.80
<b>Propensity for falling</b>						
Mental status score: above median <sup>d</sup>	25.0 (10.0–26.0)	44%	38%	31%	28%	0.63
Distance depth perception: lowest quartile <sup>d</sup>	1.4 (0–23.1)	23%	31%	31%	47%	0.01
Contrast sensitivity, low-frequency: lowest quartile <sup>d</sup>	1.2 (0–3.7)	23%	35%	43%	52%	0.16
<b>Neuromuscular function</b>						
Requires use of arms to stand	3%	2%	6%	9%	11%	0.55
Grip strength (kg)	21.1 (4.3)	21.4 (4.2)	19.5 (4.0)	20.0 (4.4)	17.9 (4.6)	0.0004
Knee extension force (kg)	18.0 (5.1)	18.3 (5.1)	16.6 (4.7)	17.1 (5.5)	15.5 (4.5)	0.02
Current long-acting benzodiazepine use	9%	8%	10%	9%	15%	0.18
Any falls in last yr	30%	29%	29%	41%	37%	0.46
<b>Personal fracture history</b>						
Any fracture after age 50 yr	36%	33%	50%	49%	59%	0.12
Prevalent vertebral fracture	19%	15%	35%	33%	51%	0.005
<b>Family fracture history</b>						
Maternal history of hip fracture	11%	10%	13%	16%	14%	0.71
Total hip bone mineral density (g/cm <sup>2</sup> )	0.76 (0.13)	0.80 (0.11)	0.58 (0.05)	0.73 (0.07)	0.56 (0.06)	<0.0001

<sup>a</sup> Continuous variables presented as mean (SD) or median (range). Hip osteoporosis criteria: total hip bone mineral density T-score ≤ -2.5.

<sup>b</sup> For tests comparing hip fracture cases with and without hip osteoporosis.

<sup>c</sup> Age assessed at visit 2.

<sup>d</sup> For all women, continuous variables presented; where participants grouped by hip osteoporosis/fracture classification, categorical data presented.

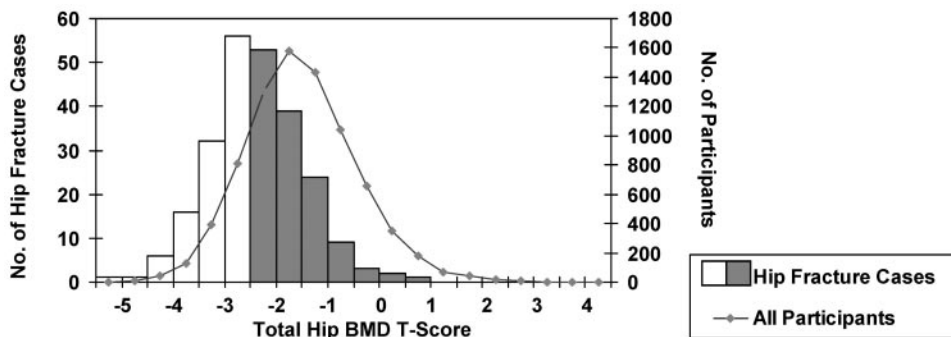
fracture cases without osteoporosis had at least five fracture risk factors than for all participants without osteoporosis.

#### Risk factors for hip fracture in nonosteoporotic women

A number of previously identified risk factors for hip fracture (20, 21) were associated with increased fracture risk

when multivariable analysis was restricted to women without hip osteoporosis (Table 3) or with hip osteoporosis (Table 4). Independent of other variables in the model, risk factors for hip fracture among women without osteoporosis included advancing age, reduced visual contrast sensitivity, falls in the last year, prevalent vertebral fracture, and lower

**FIG. 1.** Total hip BMD T-scores at the start of observation among incident hip fracture cases (n = 243) and all participants (n = 8065). Open bars represent cases with hip osteoporosis (total hip BMD T-scores ≤ -2.5); gray bars represent cases without hip osteoporosis.





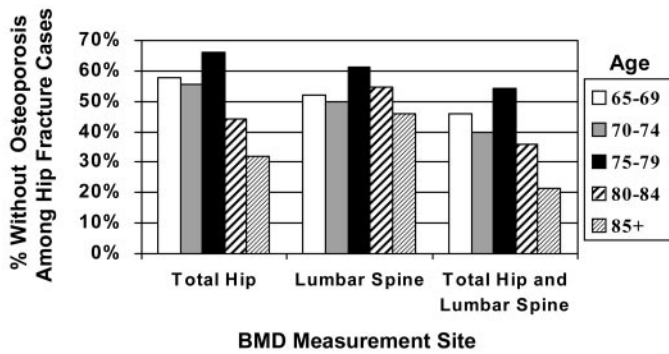


FIG. 2. Proportion of hip fracture cases (n = 243) without osteoporosis at total hip, lumbar spine, and both total hip and lumbar spine BMD measurement sites at start of observation, by age group. Osteoporosis criteria: BMD T-score  $\leq -2.5$  or less. Lumbar spine BMD measurements were unavailable for 14 cases with hip fracture.

total hip BMD. Furthermore, there was a tendency toward decreased risk associated with walking for exercise *vs.* no exercise activity in the past year and significantly decreased risk for other exercise activity alone or in addition to walking in the previous year.

Discussion

In this observational study of a large cohort of older women, many (54%) hip fracture cases that occurred in 5 yr of follow-up did not have osteoporosis at the total hip at the start of observation. Furthermore, many did not have osteoporosis at the lumbar spine or a combination of axial BMD measurement sites. These findings are important because they call attention to the number of women with hip fracture but without particularly low antecedent BMD. Moreover, current therapies for reducing fracture risk have been evaluated primarily in women with low BMD levels, but in postmenopausal women without osteoporosis it has been difficult to demonstrate the antifracture efficacy of antiresorptive treatment (1, 2). Even if effective, widespread therapy of large populations with a low absolute risk of fracture would be prohibitively expensive. Thus, an important segment of women who will experience fractures does not have hip osteoporosis, and therapies for the prevention of fracture are not proven for these women with higher BMD.

The finding that fractures occur in older women without osteoporosis at the start of follow-up is not inconsistent with the well-documented relationship between BMD and fracture risk. It is clear that those with low total hip BMD are at

TABLE 2. Multivariable logistic regression model of baseline characteristics associated with total hip bone mineral density T-score  $> -2.5$  (no hip osteoporosis) at start of observation, among 243 incident hip fracture cases

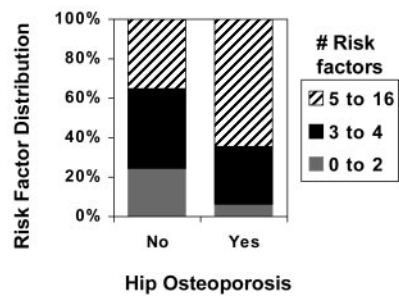
Characteristics	Multivariable OR (95% CI) <sup>a</sup>
Age $\geq 80$ yr <sup>b</sup>	0.54 (0.29–1.01)
BMI (per 5 kg/m <sup>2</sup> )	2.11 (1.46–3.04)
Previous hyperthyroidism	0.39 (0.17–0.89)
Grip strength (per 5 kg)	1.44 (1.03–2.00)
Prevalent vertebral fracture	0.46 (0.25–0.82)

<sup>a</sup> Reference group is cases with osteoporosis at hip.

<sup>b</sup> Assessed at visit 2.



A. All Participants



B. Hip Fracture Cases

FIG. 3. Hip fracture risk factors (20, 21) among study participants without (n = 6667) or with (n = 1398) hip osteoporosis (total hip BMD T-score  $\leq -2.5$ ) at start of observation (A) and incident hip fracture cases without (n = 131) or with (n = 112) hip osteoporosis at start of observation (B).

higher risk. Indeed, in our study the hip fracture incidence rate was more than 3 times higher among women with osteoporosis. Similarly, hypertension is strongly associated with the risk of stroke, but strokes also occur in normotensive individuals (28, 29).

A negative association between hip BMD and age and positive associations between hip BMD and weight and strength have been described previously in the SOF cohort (30). Therefore, our similar findings in analyses restricted to fracture cases might be expected. However, we hypothesized that on average women without osteoporosis who suffer hip fracture might have a greater propensity for falling, might be more active (and hence more likely to fall), or might have a

TABLE 3. Multivariable proportional hazards model of baseline characteristics associated with incident hip fracture risk among women without hip osteoporosis (total hip bone mineral density  $> -2.5$ ) at start of observation

Characteristics	Multivariable HR (95% CI)
Age (per yr) <sup>a</sup>	1.08 (1.05–1.12)
Walking for exercise: no other activity	0.73 (0.48–1.09)
Other activity: alone or in addition to walking	0.50 (0.32–0.78)
Contrast sensitivity, low frequency: lowest quartile	1.54 (1.06–2.25)
Any falls in last year	1.64 (1.15–2.34)
Prevalent vertebral fracture	1.86 (1.28–2.71)
Total hip bone mineral density (per SD decrease)	1.95 (1.53–2.46)

HR, Hazards ratio.

<sup>a</sup> Assessed at visit 2.

**TABLE 4.** Multivariable proportional hazards model of baseline characteristics associated with incident hip fracture risk among women with hip osteoporosis (total hip bone mineral density  $\leq -2.5$ ) at start of observation

Characteristics	Multivariable HR (95% CI)
Previous hyperthyroidism	1.86 (1.11–3.10)
Distance depth perception: lowest quartile	1.67 (1.11–2.53)
Contrast sensitivity, low frequency: lowest quartile	1.56 (1.03–2.37)
Grip strength (per 5 kg)	0.74 (0.59–0.94)
Prevalent vertebral fracture	1.52 (1.00–2.29)
Total hip bone mineral density (per SD decrease)	1.52 (1.09–2.10)

HR, Hazards ratio.

genetic predisposition to fracture and as a result, an increased fracture risk despite higher levels of BMD. Instead, baseline fall frequency, family history of fracture, and activity were similar in fracture cases with and without osteoporosis at the start of observation, and we were not able to demonstrate increased risk associated with activity among women without osteoporosis. Furthermore, we considered that cases without osteoporosis might have more risk factors for fracture than those who fracture with lower BMD at the start of follow-up. On the contrary, although most cases had at least one non-BMD risk factor for fracture, cases without osteoporosis at start of follow-up had fewer baseline risk factors, and those with osteoporosis who fractured appeared generally frailer at baseline.

It is important to note that whereas women without hip osteoporosis who experience hip fracture are not as frail as might be anticipated, several factors are associated with an increased risk of fracture in this group, including advancing age, lack of exercise activity in the last year, reduced visual contrast sensitivity, falls in the last year, prevalent vertebral fracture, and lower total hip BMD. These results are consistent with previous reports from this population that emphasized that these factors were associated with fracture risk independent of BMD and point to the potential clinical usefulness of assessing information concerning these factors even in the absence of osteoporosis.

Although in these initial analyses we focused on previously established hip fracture risk factors for all women (with and without osteoporosis), through further study it will be important to identify possible new hip fracture risk factors specific to nonosteoporotic women. Candidates for such investigations include geometric, structural, or material properties of bone.

This study has important strengths. It is based on a large, community-based, well-characterized population of postmenopausal women followed prospectively, with follow-up after 5 yr of observation remaining more than 98% complete for surviving participants. A large number of validated fractures are available for analysis. The results reported here should be applicable to a large segment of the population of women at risk for fracture. On the other hand, the study also has several limitations. First, a disproportionate loss to follow-up, specifically loss as a result of death, may have affected the proportion of hip fracture cases with and without osteoporosis. This disproportionate loss to death is not unexpected because an inverse relationship between mortality

and BMD has been described (31–33). However, even if we assume that all women with osteoporosis at start of observation who died before completing fracture follow-up in the 5 yr after BMD measurement would have experienced a hip fracture and that none of the women without osteoporosis who died in the same follow-up would have fractured, we would still observe that 32% of those with hip fracture did not have osteoporosis at the start of observation. Therefore, the large proportion of hip fractures without osteoporosis is not explained completely by loss to death.

Because many of the characteristics of interest were assessed at only the first study examination, we analyzed baseline characteristics and risk factors from the first examination but BMD from the second examination. Some risk factors, such as activity, health status, vision, and fracture history, may have changed during that 2-yr interval. However, it seems unlikely that major changes in health status occurred in a large number of women in this short period.

Finally, women enrolled in this study were primarily Caucasian, community-dwelling volunteers in the United States, and our findings may not be generalizable to populations of older women.

In summary, a large proportion of older women who experience hip fracture has antecedent total hip BMD measurements, and other axial BMD measurements, which are not dramatically low, suggesting that the health care burden represented by hip fractures in women without osteoporosis may be large. And, interestingly, whereas it might be assumed that the group with fracture but without hip osteoporosis would be older and frailer than those with fracture and osteoporosis, our results suggest that on average just the opposite is true. Fracture cases without hip osteoporosis at start of observation were younger and seemed to be less frail at baseline than women with hip osteoporosis who suffered a fracture. Still, several factors, including advancing age, lack of exercise in the last year, reduced visual contrast sensitivity, falls in the last year, prevalent vertebral fracture, and lower total hip BMD, were found to be associated with increased fracture risk in women without hip osteoporosis. Together, these findings highlight the complex etiology of hip fracture and help begin to identify risk factors associated with higher bone density levels.

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Address all correspondence and requests for reprints to: Stacey Wainwright, M.D., Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Mail Code CR113, Portland, Oregon 97239. E-mail: s\_wainwright@comcast.net.

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### Appendix

Investigators in the Study of Osteoporotic Fractures Research Group: University of California, San Francisco (Coordinating Center): S. R.

Cummings (principal investigator), M. C. Nevitt (coinvestigator), D. C. Bauer (coinvestigator), K. L. Stone (coinvestigator), D. M. Black (study statistician), H. K. Genant (director, central radiology laboratory), T. Blackwell, B. Blunt, M. Dockrell, S. Ewing, C. Fox, M. Jaime-Chavez, S. Litwack, L.Y. Lui, P. Mannen, L. Nusgarten, L. Palermo, M. Rahorst, C. Schambach, J. Schneider, R. Scott.

University of Maryland: M. Hochberg (principal investigator), L. Makell (project director), C. Boehm, L. Finazzo, R. Nichols, T. Page, S. Trusty, B. Whitkop.

University of Minnesota: K. Ensrud (principal investigator), M. Homan (coinvestigator), P. Bowman (project coordinator), S. Love (clinical research director), E. Mitson (clinic coordinator), C. Bird, D. Blanks, C. Burchhardt, M. Cardenas, J. Holmes, F. Imker-Witte, K. Jacobson, K. Moen, N. Nelson, H. Peterson, M. Slindee.

University of Pittsburgh: J. A. Cauley (principal investigator), L. H. Kuller (co-principal investigator), M. Vogt (coinvestigator), L. Harper (project director), L. Buck (clinic coordinator), C. Bashada, N. Chiarvalle, A. Githens, M. Gorecki, D. Lee, D. Medve, C. Newman, D. Stewart, N. Watson.

The Kaiser Permanente Center for Health Research, Portland, Oregon: T. Hillier (principal investigator), E. Harris (co-principal investigator), E. Orwoll (coinvestigator), H. Nelson (coinvestigator), M. Aicken (coinvestigator), J. Van Marter (project administrator), M. Rix (clinic coordinator), K. Canova, T. Constantin-Suvalcu, R. Garza, P. Legarda, K. Pedula, K. Redden, J. Rehinhardt, J. Rizzo, K. Snider, J. Wallace.

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## The Use of Biochemical Markers of Bone Turnover in Osteoporosis

P. D. Delmas<sup>1</sup>, R. Eastell<sup>2</sup>, P. Garnero<sup>3</sup>, M. J. Seibel<sup>4</sup> and J. Stepan<sup>5</sup>, for the Committee of Scientific Advisors of the International Osteoporosis Foundation\*

<sup>1</sup>Inserm Research Unit 403 and Claude Bernard University of Lyon, France; <sup>2</sup>Bone Metabolism Group, University of Sheffield, UK; <sup>3</sup>Inserm Research Unit 403 and Synarc, France; <sup>4</sup>Department of Medicine, University of Heidelberg, Germany; <sup>5</sup>Department of Internal Medicine 3, Charles University Faculty of Medicine, Czech Republic

### Introduction

Biochemical markers of bone turnover have been developed over the past 20 years that are more specific for bone tissue than conventional ones. As a result, several studies have shown that these new markers are more sensitive than conventional ones for detecting abnormalities of bone turnover rate. They have been widely used in clinical research and in clinical trials of new therapies as secondary endpoints of treatment efficacy. Most of the interest has been devoted to their use in postmenopausal osteoporosis, a condition characterized by subtle modifications of bone metabolism

that cannot readily be detected by conventional markers of bone turnover. However, their clinical use in the management of the individual patient has not been clearly defined and is a matter of debate.

Because of the crucial importance of clarifying this issue, the Committee of Scientific Advisors of the International Osteoporosis Foundation commissioned an expert committee to summarize the available data and to make recommendations. The following paper includes:

- A synthesis of the literature divided into five section summaries, based on five resource documents included in this issue of *Osteoporosis International*. For detailed information, the reader is invited to refer to these resource documents
- Recommendations for nomenclature and abbreviations, for clinical use and for future research of biochemical markers of bone turnover.

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Correspondence and offprint requests to: Prof. Pierre D. Delmas, Hôpital Edouard Herriot, Pavillon F, F-69437 Lyon Cedex 03, France. Tel: +33 4 72 11 74 84. Fax: +33 4 72 11 74 83. e-mail: delmas@lyon15inserm.fr

\*Members of the Committee of Scientific Advisors: Jonathan Adachi (Canada), Silvano Adami (Italy), Roberto Arinovic (Chile), John Bilezikian (USA), Jean-Philippe Bonjour (Switzerland), Steven Boonen (Belgium), Aurelio Borelli (Brazil), Maria Luisa Brandi (Italy), Narong Bunyaratavej (Thailand), Daniel Chappard (France), Claus Christiansen (Denmark), Juliet Compston (UK), Cyrus Cooper (UK), Marie-Christine de Vernejoul (France), Pierre D. Delmas (France), Jean Pierre Devogelaer (Belgium), Martina Dören (UK), John Eisman (Australia), Erik Fink Eriksen (Denmark), Dieter Felsenberg (Germany), Jose Luis Ferretti (Argentina), Herbert Fleisch (Switzerland), Carlo Gennari (Italy), Piet Geusens (Belgium), Claus Glüer (Germany), Shi-fu Guo (China), Stephen Hough (South Africa), Olof Johnell (Sweden), John A. Kanis (UK), Jean Marc Kaufman (Belgium), Sundeep Khosla (USA), Edith Lau (China), Uri Liberman (Israel), Paul Lips (The Netherlands), Sverker Ljunghall (Sweden), Roman Lorenc (Poland), George P. Lyritis (Greece), Frank Luyten (Belgium), Michael McClung (USA), Daniel Messina (Argentina), Pierre J. Meunier (France), Paul D. Miller (USA), Jorge Morales Torres (Mexico), Hajime Orimo (Japan), Sergio Ortolani (Italy), Socrates Papapoulos (The Netherlands), Mario Passeri (Italy), Gyula Poor (Hungary), Christine Pouliart (Belgium), Jonathan Reeve (UK), Jean-Yves Reginster (Belgium), Ian R. Reid (New Zealand), Johann Ringe (Germany), René Rizzoli (Switzerland) (chair), Christian Roux (France), Graham Russell (UK), Ego Seeman (Australia), Markus J. Seibel (Germany), Alan Silman (UK), Jan Stepan (Czech Republic), Nelson B. Watts (USA), Christian Wüster (Germany).

### Biochemical, Technical and Analytical Aspects

The development of new markers of bone metabolism has greatly enriched the spectrum of serum and urine analytes used in the assessment of skeletal pathologies. For clinical purposes, markers of bone formation are distinguished from markers of bone resorption. It should be borne in mind, however, that some of these markers may reflect, at least to a certain degree, both bone formation and bone resorption. Furthermore, most if not all of these markers are present in tissues other than bone and may therefore be influenced by nonskeletal processes as well. Thirdly, changes in biochemical markers of bone turnover are usually not disease-specific, but reflect alterations in skeletal metabolism independently of the underlying cause.



### *Bone Formation Markers*

Bone formation markers are direct or indirect products of active osteoblasts expressed during different phases of osteoblast development and reflecting different aspects of osteoblast function and bone formation. All markers of bone formation are measured in serum or plasma.

Alkaline phosphatase (ALP) is a ubiquitous enzyme that plays an important role in osteoid formation and mineralization. The total ALP serum pool consists of several dimeric isoforms which originate from various tissues such as liver, bone, intestine, spleen, kidney and placenta. In adults with normal liver function, approximately 50% of the total ALP activity in serum is derived from the liver, whereas 50% arises from bone [1]. Many techniques have been developed to differentiate between the two main isoforms of circulating ALP, including heat denaturation, electrophoresis, precipitation, selective inhibition and, more recently, immunoassays. The last allow the quantitation of either enzyme activity or enzyme mass. However, even these assays show some cross-reactivity between bone and liver ALP (15–20%), and in subjects with high liver ALP the results of bone ALP measurements may be artificially high. From a clinical perspective, however, detection of the bone-specific ALP (bone ALP) isoenzyme is increasingly preferred because of its higher specificity.

Osteocalcin (OC) is a small, hydroxyapatite-binding protein synthesized by osteoblasts, odontoblasts and to a lesser extent by hypertrophic chondrocytes. It contains three gamma-carboxyglutamic acid (Gla) residues, which are responsible for the calcium binding properties of the protein. The precise function of OC has yet to be determined, but recent studies suggest that OC is involved in bone remodeling via a negative feedback mechanism. Serum OC is considered as a specific marker of osteoblast function, as its levels correlate with bone formation rates. However, the peptide is rapidly degraded in serum and both intact peptides and OC fragments of various sizes coexist in the circulation [2]. The resulting heterogeneity of OC fragments in serum results in limitations in the clinical application of this a priori specific marker. In practice, different immunoassays have routinely yielded such varying results that values in one assay cannot readily be compared with those obtained with another assay [3]. Assays that measure both the intact molecule and the large N-mid fragment of OC appear to be more stable and reproducible.

Procollagen type I propeptides (PINP) are derived from collagen type I, in which they form amino- (N-) and carboxy- (C-) terminal extension peptides. Since both the carboxy- and the amino-terminal propeptides of type I collagen (PICP, PINP) are generated in a stoichiometric fashion, the propeptides are considered quantitative measures of newly formed type I collagen. Both propeptides may be measured by specific, polyclonal-based immunoassays. Moderate correlations between serum PICP levels and the rate of bone

formation have been reported [4]. Measurement of the trimer of PINP appears to be a more sensitive marker of bone formation rate in osteoporosis.

### *Bone Resorption Markers*

Most biochemical markers of bone resorption are degradation products of bone collagen, but noncollagenous proteins such as bone sialoprotein or tartrate-resistant acid phosphatase are being investigated.

Hydroxyproline (Hyp) constitutes 12–14% of the total amino acid content of mature collagens, but only 10% of Hyp released during bone resorption reaches the urine in free or peptide-bound forms. Urinary Hyp has long served as the only marker of bone resorption, despite the fact that significant amounts of urinary Hyp are derived from the degradation of newly synthesized collagens, from collagens of tissues other than bone, and from the diet. Today, Hyp is considered a nonspecific index of collagen turnover and has been largely replaced by more specific techniques. The hydroxylysine-glycosides are integral parts of bone collagen and occur in two forms: glycosyl-galactosyl-hydroxylysine (Glc-Gal-Hyl) and galactosyl-hydroxylysine (Gal-Hyl). Both components are released into the circulation during collagen degradation and may be measured in urine by high-performance liquid chromatography (HPLC). The ratio of the two glycosides may allow for the recognition of tissue specificity. Although the hydroxylysines have potential as markers of bone resorption, their major disadvantage is presently the absence of a convenient immunoassay format.

The hydroxyproline crosslinks of collagen, pyridinoline (PYD) and deoxypyridinoline (DPD), are formed during the extracellular maturation of fibrillar collagens and are released upon the degradation of mature collagens. The measurement of PYD and DPD is not influenced by the degradation of newly synthesized collagens and independent of dietary sources. In addition, the two components show a high specificity for skeletal tissues. While PYD is found in cartilage, bone, ligaments and vessels, DPD is found in bone and dentin only.

Both crosslink components may be measured by a reverse-phase ion-paired HPLC technique. In urine PYD and DPD are present both as free moieties (about 40%) and peptide-bound (about 60%). In addition, The free (non-peptide-bound) forms can be detected by direct immunoassays (free DPD, 'Pyrilinks-D') [5]. Sensitive immunoassays are available for the measurement of type I collagen telopeptides in urine (U) and serum (S). Currently, these include a serum radioimmunoassay (RIA) for the carboxy-terminal type I collagen telopeptide generated by matrix metalloproteases (CTX-MMP, also called 'ICTP') in serum [6], several immunoassays involving a synthetic octapeptide from the C telopeptide of type I collagen containing the crosslinking site (CTX-I, 'Crosslaps') [7] and an

enzyme-linked immunosorbent assay (ELISA) for the crosslinked N-terminal telopeptide of type I collagen (NTX-I, 'Osteomark') [8]. The pyridinium crosslinks and the collagen telopeptides involving the crosslinking site are currently considered the best indices for the assessment of bone resorption [9]. Their urinary levels need to be corrected by creatinine excretion.

Bone sialoprotein (BSP) accounts for 5–10% of the non-collagenous matrix of bone. The protein has been shown to be a major synthetic product of active osteoblasts and odontoblasts. BSP may play an important role in cell–matrix adhesion processes and in the supramolecular organization of the extracellular matrix of mineralized tissues. Immunoassays have been developed for the measurement of the immunoreactive form of BSP in serum. Based upon clinical data and the rapid reduction of serum BSP levels following intravenous bisphosphonate treatment, it is assumed that serum BSP reflects processes mainly related to bone resorption, but data are lacking to assess the utility of this new marker in osteoporosis [10].

Tartrate-resistant acid phosphatase (TRACP) exists in two sub-isoforms named 5a and 5b, of which only TRACP-5b has been shown to be characteristic for osteoclasts [11]. Recently, immunoassays for TRACP-5b have been described and preliminary clinical results indicate that this marker may be useful to assess osteoclast activity.

Like all chemical analytes, markers of bone turnover have their specific technical and analytical limitations. As pointed out before, some markers are sensitive to thermodegradation, to UV radiation, to hemolysis and other ambient influences. In order to obtain meaningful results, sample handling should be strictly standardized to keep the components stable and to provide reproducible conditions for their measurement. Furthermore, the various assays used for the measurement of biochemical bone markers need to be standardized and included in routine proficiency testing programs [12].

## Preanalytical Variability

Clinical interpretation of biochemical markers of bone turnover must take into account the preanalytical variability of these markers. Numerous sources of biological variability contribute to preanalytical variability and they can be broadly divided into two categories: (1) uncontrollable factors such as age, gender, menopausal status, disease or recent fracture, which can be accounted for in the interpretation of levels of bone markers by using appropriate reference ranges or by making suitable individual adjustments to a given reference range; and (2) controllable factors such as circadian, menstrual or exercise effects, which can be minimized by standardizing the timing and conditions under which samples are taken. However,

despite being able to identify and minimize some sources of preanalytical variability there will remain some endogenous day-to-day variability that cannot be reduced. The preanalytical variability is larger than the analytical variability. For example, the preanalytical variability estimates for bone ALP, OC, DPD and NTX in one study were 3%, 4%, 4% and 10% and the analytical variability estimates were 9%, 7%, 9% and 24%, respectively [13].

### *Uncontrollable Sources of Biological Variability*

*Age and Renal Function.* Biochemical markers are significantly higher in children than adults, particularly in the first year of life and at puberty when they increase to levels 2–10 times the levels found in adults. After mid-puberty levels decrease toward adult levels; however, they probably do not reach a nadir until the fourth decade or later. In men the majority of markers do not change with age in subsequent years [14]. In women there is a marked increase in markers of bone turnover at the menopause [15]. It is debatable whether there are any changes in bone turnover in the perimenopausal period; however, once markers have increased at the menopause they remain elevated and generally do not change with age. In the very elderly gradual renal impairment may lead to an increase in osteocalcin and in other markers metabolized and/or excreted by the kidney (pyridinoline crosslinks and related peptides); care should be taken in the interpretation of these bone markers when the creatinine clearance decreases below 30 ml/min.

*Gender.* Markers levels tend to be higher in young men in the third and fourth decades than in young women, but in older men the levels tend to be lower than in postmenopausal women.

*Ethnicity.* Comparative studies of black and white populations have found that in children and young adults markers of bone resorption are somewhat lower in black subjects than in white subjects. OC, but not bone ALP, may be lower (20%) in black subjects. However, in women this difference may not be apparent until the menopause.

*Fractures.* During the first 4 weeks of fracture healing markers of bone resorption and formation increase by 20–50% and remain elevated for at least 6 months and possibly for 1 year [16]. It is important to establish whether the subject has had a fracture of any kind in the year preceding a measurement and also to be aware that an asymptomatic vertebral fracture will also cause an increase in markers.

*Pregnancy and Lactation.* Pregnancy and lactation place a considerable burden on the maternal skeleton to provide calcium for the growing fetus and infant. The greatest demand from the fetus for calcium comes in the

third trimester, but an anticipatory mechanism results in a gradual increase in bone resorption from the sixteenth week of pregnancy onward, followed by an increase in bone formation [17]. Contrary to this overall pattern, serum levels of OC appear to decrease and may even be undetectable during pregnancy. It has been suggested that this is due to placental clearance of OC. However, it may also be due in part to the type of assay used and to the increase in renal function during pregnancy. A small increase in OC may be seen in the third trimester or after delivery. At term, markers of bone resorption such as NTX-I are increased by 200% and markers of bone formation such as PINP by 60% compared with prepregnancy levels. After delivery, urinary NTX-I and CTX-I decrease but there may be a continued increase in the less bone-specific markers such as PYD, possibly due to the involution of the uterus. During the first months of lactation, markers of bone resorption and formation are elevated, in some studies up to twice the level in aged-matched nonlactating controls. However, once lactation stops markers of bone turnover return to premenopausal levels.

*Drugs.* Antiresorptive treatments for osteoporosis and other metabolic bone diseases such as hormone replacement, selective estrogen receptor modulators and bisphosphonates, rapidly reduce markers of bone turnover by up to 70%. Other drugs prescribed for unrelated conditions can affect markers of bone turnover. Corticosteroid treatment significantly reduces serum OC levels but has less impact on other markers of bone turnover, although markers of bone resorption may be elevated. Anticonvulsant therapy and GnRH agonist treatment both result in significant increases in markers of bone turnover. In contrast thiazide diuretics decrease bone turnover.

*Diseases.* Changes in markers of bone turnover are found not only in metabolic bone diseases but in other conditions. In some metabolic bone diseases the changes in markers of bone turnover may not be concordant. An example is Paget's disease of bone where there is large increase in total and bone ALP but only a small increase in OC [18]. In nonskeletal diseases such as liver or kidney disease, levels of bone markers may reflect extraskeletal production and/or impaired metabolism.

*Oral Contraception.* The effect of oral contraception on bone turnover appears to be age-dependent. In women in the third decade results of studies on the effect of oral contraception give inconsistent results. In contrast, significant decreases of between 15% and 30% in specific markers of bone resorption and bone formation have been reported in women aged 35–49 years [19].

*Immobility.* Bed rest results in a very rapid increase in markers of bone resorption [20]. Urinary excretion of PYD and DPD are significantly increased after only 2 days and by 40% after a week. Markers of bone formation change little or remain unchanged during bed

rest or immobility. In elderly, partially immobile subjects, the increase in urinary HYP is related to the degree of immobility. Once remobilization occurs resorption markers gradually return to initial levels, although paradoxically PICP may increase.

### *Controllable Sources of Biological Variability*

*Circadian.* Circadian variability has more impact on markers of bone turnover than most other sources of variability [21]. Most markers of bone turnover are increased at night, reaching a peak between 0200 and 0800 hours, after which they decrease rapidly and reach a nadir between 1300 and 2300 hours. The amplitude of the rhythm is considerably greater for resorption markers than for formation markers. Serum level of CTX-I at the nocturnal peak may be twice that at the nadir. Due to the rate of decrease in these markers in the morning, the difference between a measurement of U-NTX at 0700 and 1500 hours could be as much as 50%, similar to the mean response of NTX to HRT; this variation is equivalent to a CV of 10%. Serum PICP and OC are increased by 20% at night compared with their nadir in the early afternoon. Bone ALP has a somewhat different circadian rhythm with a peak between 1100 and 1400 hours and possibly another peak at 2330 hours. The nocturnal peak in urinary DPD excretion may be greater and extend into the morning in postmenopausal women with osteoporosis. Calcium supplementation taken at night and bisphosphonate treatment can both suppress the circadian rhythm of markers of bone resorption. Fasting also greatly diminishes the rhythm of urinary and serum CTX-I, in particular the rapid decrease during the morning [22]. To reduce the effect of circadian rhythms on the clinical interpretation of markers of bone turnover it is essential that the timing of sample collection is tightly controlled.

*Menstrual.* The changes in markers of bone turnover across the menstrual cycle are small. Indeed, some studies have failed to identify any changes at all [23]. Markers of bone formation are 10–15% higher in the luteal phase than in the follicular period, with OC and bone ALP reaching maximal levels in the mid-luteal phase and PICP reaching maximal levels in the early luteal phase. The reported patterns of changes in resorption markers across the menstrual cycle are inconsistent. The amplitude of the changes is between 15% and 30%. These changes are so small that the effect of the menstrual cycle on levels of bone turnover may be regarded as insignificant.

*Seasonal.* Seasonal variation in markers of bone turnover is not a universal finding. It has been suggested that overall seasonal changes may be low, accounting for up to 12% of the variability of the markers [24], but some studies suggest that differences between summer and



winter may be greater. OC is elevated in the winter and spring whereas bone ALP shows an inverse rhythm and is decreased during the winter and spring. PICP does not appear to have a significant seasonal rhythm. Most markers of bone resorption are elevated during the winter although one study showed that urinary PYD excretion was elevated during the summer. The impact of seasonal changes of bone turnover may be important when monitoring the short-term response to treatment.

*Exercise.* Exercise may affect the variability of markers of bone turnover in two ways: the effect of persistent exercise and the acute effect of a bout of exercise within a day of the sample collection. In trained endurance athletes PICP and ICTP are 18–20% lower than in age-matched sedentary controls but other formation markers are unchanged. Sub-acute exercise results in an increase in bone formation markers and a decrease in bone resorption markers. In most studies the acute effect of exercise is to increase markers of collagen formation and degradation by 15–40%. These increases persist for 24 h and possibly for as long as 72 h [25]. It is therefore important to enquire about regular exercise and ask the subject to refrain from exercise for at least 24 h before samples are collected.

*Diet.* Serum and urinary levels of most markers of bone turnover are unaffected by diet, with the exception of HYP, a nonspecific marker of bone resorption. Before samples are collected for HYP measurements, subjects must have an overnight fast. The other markers of collagen degradation, PYD and DPD, have been shown to be unaffected by normal dietary collagen (gelatine) intake. Specific dietary restrictions are therefore only applicable to HYP measurements.

*Reference Ranges.* Each laboratory should establish its own reference ranges. Age, gender, menopausal status and race all affect levels of markers of bone turnover. Therefore separate reference ranges should be established for men, premenopausal women and postmenopausal women. Because markers are still elevated in the third decade the male and premenopausal reference ranges should only include subjects over the age of 30 years. Standardized time and conditions for sample collection must also be defined for each reference range.

*Long-Term Intra-individual Variability of Biochemical Markers.* The intra-individual reproducibility of bone markers remains a challenge, if treatment decisions have to be taken based on a single measurement. There are some differences between bone marker variability figures reported by the various studies which probably result from differences in the populations studied, the number of subjects, assay features, length of the study period or sample collection. Nevertheless, in general intra-individual variability expressed as coefficient of variation (CV%) is lower for serum bone formation markers than for urinary resorption markers. For example, in a cohort of 259 healthy untreated

postmenopausal women aged 51–89 years who had four sequential measurements over 3 years, the within-patient CV was 12% for serum OC, 14% for bone ALP and 24% for urinary CTX [26]. The intra-patient variability of bone markers can be improved in different ways. The technical features, especially of the antibodies used, are critical. For example, the long-term precision error of serum OC measured seven times over 18 months in untreated postmenopausal women was reduced from 28% to 12% by using an assay that measures both the intact and N-Mid fragment instead of using a conventional RIA recognizing mainly the intact molecule. Measuring a marker in serum rather than in urine results in better reproducibility as the variable ionic strength of urine samples and the need to correct for creatinine excretion may introduce some variability into the results. Variability of serum CTX over 12 months in 44 postmenopausal women (three samples) was recently reported to be 13%, i.e., about 2-fold lower than that of urinary CTX measurements [27]. In another 2 month study of 150 untreated postmenopausal women, the intra-patient CV% was of 7.2% for serum NTX and 14.2% for urinary NTX [28]. An extensive review of the within-subject variability of bone markers is included in the paper by Hannon and Eastell in this issue. As discussed below, intra-patient CV% can be used to calculate the least significant change of bone markers under treatment and to identify individual responders.

## Prediction of Bone Loss in Postmenopausal Women

Biochemical markers reflect the whole-body rates of bone resorption and bone formation and are likely to reflect changes in the number of bone remodeling sites [29]. Therefore, they may provide a more representative index of the overall skeletal bone loss than would be obtained by measuring the rates of change in bone mineral density (BMD) at specific skeletal sites containing different ratios of cancellous to cortical component with different metabolic rates.

Estrogen deficiency after spontaneous as well as after artificial menopause results in an increase in bone remodeling. A sustained increase in the bone turnover induces a faster bone loss and therefore an increased risk of osteoporosis. The increase in markers of bone resorption (of 50–150%) is rapid and precedes by a few months the increase (of 50–100%) in markers of bone formation [30–34]. During the first years after ovariectomy, the ratio between the markers of bone resorption and bone formation indicates an imbalance in bone remodeling, with an inappropriately high rate of bone resorption compared with formation [32]. This imbalance remains even in late postmenopausal women [30–33]. Thus, the negative correlation between BMD and the bone turnover becomes much stronger with advancing age, as documented in population-based

studies [31,32,35]. However, measurement of bone marker, even when combined with anthropometric measures, offers little practical information for estimating BMD level in individual women and cannot be used as a surrogate measure to predict bone mass and therefore to diagnose osteoporosis.

Relationships between the biochemical markers of bone turnover and the rate of bone loss in women after menopause have been investigated in prospective studies that avoid several confounding factors. However, these studies are limited by (i) the precision error of repeated measurements of BMD in a single individual, which is of the same order of magnitude as rate of bone loss over 2–4 years, i.e., 3–4%; (ii) the precision error of repeated measurements of the markers; (iii) by differential rates of bone loss between various skeletal sites; and (iv) because it is not clear whether bone loss at the various sites is consistent over time. A variable production of sex hormone precursors and individual response to estrogen deficiency is one of the possible causes for an increased inter-individual as well as long-term variability of the bone loss. Therefore, in this review, the association of the biochemical markers with the bone loss is considered separately at the different skeletal sites.

#### *Association of Biochemical Markers with Bone Loss at the Forearm*

Consistent associations have been found in prospective studies between bone markers and bone loss rate at the distal forearm. In some studies, the relationship between the markers and the rate of bone loss appears to be continuous [36,37], with greater probability of rapid bone loss with increasing levels of the markers. However, in some studies [38] estimated rates of bone loss were not stable over time, making it difficult to identify long-term 'fast-losers'. The best markers (OC, PINP, U-CTX, U-DPD) contributed 16–27% to the variance in 1-year percentage change of the forearm bone mineral content [30,33,34,37,39,40]. Women with marker values 2 SDs greater than the mean had a 75–80% probability of rapid bone loss compared with women with values 2 SDs below the mean, who had a 20–25% probability of rapid loss [30,37]. Recently [40], in a large population-based prospective cohort of 305 women aged 50–88 years (mean 64 years), 1–38 years postmenopausal, the baseline levels of a panel of specific and sensitive biochemical bone markers were found to be highly correlated ( $p < 0.001$ ) with the rate of change of forearm BMD assessed by four measurements over a 4-year period using dual-energy X-ray absorptiometry (DXA). In 51 untreated women within 5 years of menopause who had the highest rate of bone loss, the predictive value of bone markers was increased, with correlation coefficients reaching  $-0.53$  for S-OC and  $-0.47$  for S-CTX. Corrections of the observed correlation coefficients by errors on bone loss and bone marker estimations resulted in an increase in the  $r$  values

to  $-0.91$  for S-OC and  $-0.79$  for S-CTX. Women with levels of bone markers at baseline 2 SD above the mean of premenopausal women had a rate of forearm bone loss that was 2- to 6-fold higher than in women with a low turnover ( $p = 0.01$ – $0.0001$ ), according to the marker. In a logistic regression model, the odds ratio of fast bone loss, defined as the rate of bone loss in the upper tertile of the population, was increased by 1.8- to 3.2-fold for the levels of biochemical markers in the high turnover group compared with the levels within the premenopausal range; however, the value for identifying individual fast bone losers was limited. A strong association was also observed in a retrospective study between biochemical markers and bone loss measured at the calcaneus.

#### *Association of Biochemical Markers with Bone Loss at the Lumbar Spine*

Several studies have shown a deceleration or even a cessation of bone loss at the lumbar spine with advancing age – an unexpected finding that is probably related to the high prevalence of spinal osteoarthritis in the elderly. This might explain why only a slight though significant association was found in some [41] but not other [35,42] prospective studies between the rate of bone loss at the lumbar spine and some baseline biochemical markers of bone turnover. With the exception of a period of several months after estrogen withdrawal, a single marker accounted for no more than 10% of the variance of BMD change. Adding the single most robust resorption marker to age and BMI increased  $R^2$  to no more than 19% of the variance [35]. The maximum available information obtained by a panel of the markers explained 40% of the variance in the BMD change. In a study of 117 early postmenopausal women treated for 1-year with calcium (500 mg daily), women in the highest quartile of U-NTX values had a significantly greater decrease in the spine BMD than subjects in the lowest quartile of NTX values [43].

#### *Association of Biochemical Markers with Bone Loss at the Hip*

Bone loss from the femoral neck is approximately linear across life in postmenopausal women, although some studies have shown an apparent acceleration of bone loss with age and season. In one retrospective study, associations have been reported between the rate of bone loss at the hip and some markers (U-NTX, U-DPD), that contributed to about 27% of the variance of bone loss at the hip [44], whereas other studies have demonstrated more modest correlations [35,45] or failed to find a significant association [39,41,42,46]. From the available data, it is not evident whether there are subsets of the fast and slow losers of bone from the hip.

## Conclusion

The current evidence indicates that in postmenopausal women, biochemical markers of bone turnover are associated with bone loss measured at the forearm, calcaneus and hip, with a progressively greater risk of rapid bone loss with increasing levels of markers. The results of several studies of bone loss at the forearm support the view that 80% of patients having increased biochemical markers in the early postmenopausal years are confirmed 2–12 years later as ‘fast bone losers’ (bone loss >3%/year) based on BMD measurements. An increase above the upper normal limit in serum or urinary markers of bone resorption suggests that the patient is losing bone, in contrast to normal or low values of markers of bone resorption and of serum OC. However, adequate thresholds are lacking and the current data do not indicate that markers can predict the rate of bone loss at the spine and hip over a 3-year period in an individual with sufficient accuracy to be used in clinical practice. Combinations of demographic and biochemical variables predict some (30–40%) of the variance of bone loss rates at these skeletal sites in untreated postmenopausal women.

## Prediction of Fracture Risk

The major consequence of osteoporosis is an increase in the risk of fracture. Several prospective studies have shown that a 1 SD decrease in BMD measured by DXA is associated with an approximately 2-fold increase in the relative risk of fracture including the hip, spine and forearm. In this context the question arises as to what extent bone markers could add to BMD in order to improve the assessment of fracture risk. Relationships between biochemical markers of bone turnover and fracture risk have been investigated, first in retrospective studies comparing bone marker levels in patients with osteoporotic fractures and in controls and more recently in prospective studies in which biochemical markers were measured before the occurrence of fractures.

### *Association Between Markers of Bone Turnover and Fracture Risk in Retrospective Studies*

Several retrospective studies have compared bone marker levels in patients with osteoporotic fractures and in controls. When samples are taken within 48 h following the fracture event – which can easily be registered for hip fracture in elderly women – a 20–30% decreased level of serum OC was consistently reported in hip fracture cases compared with apparently healthy age-matched controls. Thus in patients with fracture bone formation may be decreased, although this finding has been consistently found only for serum OC [47,48]. For bone resorption, studies using the most specific

markers, i.e., urinary PYD crosslinks, suggest that hip and other fractures cases are associated with increased bone resorption [47,49]. For example, Akesson et al. [47] in a large case–control analysis including 174 patients who had sustained a hip fracture within 22 h before assessment found a significant 36% and 40% increase in total urinary PYD (U-total PYD) and urinary total DPD (U-total DPD), respectively. However, when biochemical markers are measured within the few hours after hip fracture one cannot exclude the possibility that part of these changes of bone turnover may be related to acute changes in body fluid and hormonal levels related to the trauma. If bone turnover is measured later after the fracture, it may be difficult to determine whether differences in bone turnover levels are related to the underlying rate of bone turnover leading to fracture, or to changes in bone turnover occurring after the fracture. Relating baseline bone turnover levels to the subsequent risk of osteoporotic fractures is the valid methodology to assess their clinical utility.

### *Association Between Markers of Bone Turnover and Fracture Risk in Prospective Studies*

**Markers of Bone Formation.** Prospective studies relating levels of bone formation markers to risk of fracture have yielded somewhat conflicting results. Indeed either a decrease, no difference or an increase [50–53] in bone formation markers has been reported to be associated with increased fracture risk. The difference between studies may be related to the type of fracture or the population studied, but more probably to the duration of follow-up. In the EPIDOS study with a follow-up of 2 years, no significant association between either OC or bone ALP and hip fracture risk was observed [51]. In contrast in the OFELY study including a large population of healthy postmenopausal women followed prospectively for 5 years, increased bone ALP was associated with increased fracture risk, independently of the level of BMD [52]. Because increased levels of these bone formation markers are associated with significantly greater rate of bone loss in postmenopausal women, if the increased risk of fracture is mediated in part through a more rapid rate of bone loss, a follow-up of several years may be necessary to detect it. In summary, whether bone formation marker levels are related to fracture risk remains unclear.

**Markers of Bone Resorption.** In contrast to bone formation markers, data on the relationship between bone resorption markers and fracture risk are consistent. Riis et al. [54] reported that women within 3 years of menopause women classified as ‘fast bone losers’ had a 2-fold higher risk of sustaining vertebral and peripheral fractures during a 15-year follow-up than women classified as ‘normal’ or ‘slow’ losers. Interestingly, a low BMD and a high rate of bone loss at the radius predispose to the same extent to fractures with an odds

ratio of about 2. Women with both a low BMD and a fast rate of bone loss after the menopause had a higher risk of subsequently sustaining fractures than women with only one of the two risk factors. Concordant results have been obtained in four prospective studies (EPIDOS, Rotterdam, OFELY and the Hawaii Osteoporosis Study), indicating that increased levels of bone resorption markers are associated with increased risk of hip, vertebral and non-hip and non-vertebral fractures over follow-up periods ranging from 1.8 to 5 years [50–53,55]. This predictive value is consistently in the order of a 2-fold increase in the risk of fracture for levels above the upper limit of the premenopausal range. Both increased levels of S-CTX [52,55] and of U-CTX C-terminal crosslinking telopeptide of type I collagen and free deoxypyridinoline (U-f-DPD) [50,52,55] have been shown to be associated with a higher risk of hip, vertebral and other nonvertebral fractures. Increased bone resorption is associated with increased risk of fracture only for values above a threshold, suggesting that bone resorption rate becomes deleterious for bone strength only when it exceeds the normal physiologic range. As bone resorption rate predicts fracture independently of BMD, these data suggest that increased bone resorption can lead to increased skeletal fragility by two factors. First, a prolonged increase in bone turnover will lead after several years to a lower BMD, which is a major determinant of reduced bone strength. Second, increased bone resorption above the upper limit of the normal range may induce microarchitectural deterioration of bone tissue such as perforation of trabeculae, a major component of bone strength.

*Undercarboxylated Osteocalcin.* OC contains three residues of  $\gamma$ -carboxyglutamic acid (Gla), a vitamin-K-dependent amino acid. It was postulated that impaired  $\gamma$ -carboxylation of OC could be an index of both vitamin D and vitamin K deficiency in elderly populations. In two

prospective studies performed in a cohort of elderly institutionalized women followed for 3 years [56,57] and in a population of healthy elderly women (EPIDOS study) [58], levels of serum undercarboxylated OC (ucOC) over the premenopausal range were associated with a 2- to 3-fold increase in the risk of hip fracture. Like markers of bone resorption, the prediction was still significant after adjusting for hip BMD.

#### *Clinical Use of Bone Markers in the Assessment of Fracture Risk*

Increased levels of bone resorption markers and of ucOC have been shown to predict the risk of fracture independently of the level of BMD. Thus, combination of these two diagnostic tests could be useful to improve the identification of women at high risk for fracture. Using the database of the EPIDOS study, it was shown that combining a bone resorption marker (or ucOC) and hip BMD measurement can detect women at very high risk of fracture. Indeed women with both low hip BMD (according to the WHO definition of osteoporosis) and high bone resorption had a 4- to 5-fold higher risk compared with the general population [51]. This has been confirmed for vertebral, nonvertebral and non-hip fractures in two other cohorts of postmenopausal women [52,59]. By using such a combination the specificity of hip fracture prediction is increased without a loss of sensitivity [60]. The practical outcome of such a strategy is that the number of women who need to be treated to avoid one hip fracture is significantly reduced, which could result in a more cost-effective approach of treatment strategy. In the OFELY study, those women with both low hip BMD ( $T$ -score  $\leq -2.5$ ) and high S-CTX had a probability of fracture over 5 years of 55%, i.e., higher than the probability of fracture associated with low BMD alone (39%) or high CTX alone (25%)

**Table 1.** Combination of bone mineral density (BMD) and bone turnover markers to predict the risk of fractures in postmenopausal women: the OFELY study

	Odds ratio (95% CI)	Likelihood ratio	Probability of fracture over 5 years
All women	–	–	12.6%
Low femoral neck BMD ( $T$ -score $\leq -2.5$ )	2.8 (1.4–5.6)	2.80	39%
High S-CTX ( $T$ -score $\geq 2$ )	2.1 (1.2–3.8)	1.70	25%
High U-free DPD ( $T$ -score $\geq 2$ )	1.8 (1.0–3.4)	1.68	24%
Low BMD + high CTX	3.8 (1.9–7.3)	3.70	54%
Low BMD + high free DPD	2.1 (0.7–6.2)	3.04	45%

Modified from Garnero et al. [52].

Four hundred and thirty-five healthy untreated postmenopausal women (mean age 64 years, range 50–89 years) were followed prospectively for an average of 5 years. During this follow-up period, 58 incident fractures (21 vertebral, 37 peripheral fractures) occurred in 55 women. The table shows the odds -ratio (adjusted for age, prevalent fractures and physical activity), the likelihood ratio of fracture and the 5-year probability of fractures associated with low BMD, high bone resorption assessed by serum C-terminal crosslinking telopeptide of type I collagen (S-CTX) or urinary free deoxypyridinoline (U-free DPD) and the combination of BMD and bone resorption. The  $T$ -scores of BMD, S-CTX and free DPD were calculated from the mean and standard deviation of premenopausal women from the same cohort.

(Table 1). These probabilities of fracture should then be compared with the treatment intervention threshold. Because of economic constraints in health care, it appears that effective (but somewhat expensive) treatments that have shown a marked reduction in incident fractures should be targeted to those women who are at higher risk. Clearly, bone markers are not surrogates for BMD measurements, but instead the two diagnostic tools could be combined to improve the risk assessment in an individual, when BMD measurement alone is not sufficient to assess the risk of fracture. In that strategy, bone markers can be used as risk factors of skeletal fragility independent of BMD, in the same way as history of fractures and low body weight are used.

In summary, large prospective studies have shown that increased bone turnover – more consistently markers of bone resorption – is associated with increased vertebral and nonvertebral fractures independently of BMD on a group basis. The upper limit of the premenopausal range appears to be an adequate cutoff. The main issue that remains to be explored is the practical use of these markers in identifying individual women at risk of osteoporotic fractures, i.e., to determine which postmenopausal women could benefit from these measurements. The place of biochemical markers of bone resorption in the assessment of fracture risk is likely to be in combination with other important risk factors including low BMD, personal and maternal history of fracture and low body weight.

### Monitoring Treatment of Osteoporosis with Antiresorptive Drugs

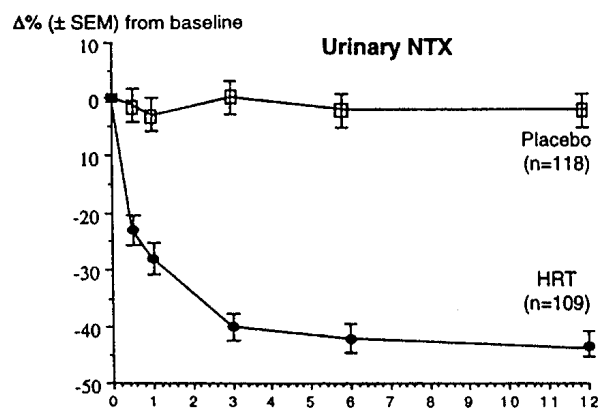
Similar to most chronic diseases, monitoring the efficacy of treatment of osteoporosis is a challenge. The goal of treatment is to reduce the occurrence of fragility fractures, but their incidence is low, and the absence of events during the first year(s) of therapy does not imply necessarily that treatment is effective. Measurement of BMD by DXA is a surrogate marker of treatment efficacy that has been widely used in clinical trials. Its use in the monitoring of treatment efficacy in the individual patient, however, has not been validated. Given a short-term precision error of 1–1.5% of BMD measurement at the spine and hip, the individual change must be greater than 3–5% to be seen as significant. With potent bisphosphonates such as alendronate or risedronate, repeating BMD measurement 2 years after initiating therapy will show whether a patient is responding to therapy, i.e., has a significant increase in BMD, at least at the lumbar spine which is the most responsive site. With treatments such as raloxifene or nasal calcitonin that induce much smaller increases in BMD, DXA is not appropriate to monitor therapy, and with any treatment DXA does not identify all responders within the first year of therapy. Failure to respond may be due to noncompliance (probably the most important single factor), to poor intestinal absorption of drug (i.e., bisphosphonates), to other factors contributing to bone

loss, or to other unidentified factors. Monitoring treatment of osteoporosis with bone markers may have the added advantage of improving compliance, although this needs to be proven. We will review the evidence suggesting that markers of bone turnover may be used for monitoring antiresorption therapy and discuss their clinical utility in the management of the individual patient. Given the paucity of data, we will not review studies looking at bone marker changes under bone-forming agents.

### Effects of Antiresorptive Therapy on Bone Markers

Estrogen deficiency induces a rapid and sustained increase in skeletal remodeling that is reflected by a 50–100% mean increase in formation and resorption markers. Hormone replacement therapy (HRT) induces a rapid decrease in bone resorption markers that can be seen as early as 2 weeks with a plateau reached within 3–6 months. The decrease in bone formation markers under HRT is delayed, reflecting the physiologic coupling of formation to resorption and a plateau is usually achieved within 6–12 months [34]. The magnitude of the decrease in bone markers depends both on the sensitivity of the marker and on the dose of estrogen, but in most studies using an adequate dose of estrogen bone markers fall within  $\pm 1$  SD of the premenopausal mean normal value [34,61,62]. The plateau is maintained as long as HRT is continued (Fig. 1). Resorption markers rise toward untreated values within a few weeks after HRT cessation, and formation markers rise within a few months [63].

Oral daily treatment of osteoporotic patients with bisphosphonates (alendronate, clodronate, ibandronate, pamidronate, risedronate) induces changes in bone markers that follow a pattern comparable to that with



**Fig. 1.** Effect of HRT on bone resorption in early postmenopausal women. The figure represents the percentage change from baseline of urinary N-telopeptide of type I collagen (NTX) for HRT (0.625 mg conjugated equine estrogen) and placebo groups. In the placebo group, the sustained increased NTX levels during the 1-year study period was associated with bone loss. HRT decreased NTX within 2 weeks of treatment and levels reached a plateau after 3 months. This rapid decrease in NTX was associated with an increase in spinal BMD. Adapted from Chesnut et al. [62], reproduced with permission.

HRT. These changes have been extensively studied with alendronate treatment. Alendronate induces a dose-dependent decrease in bone turnover markers with levels around 20% of baseline values (i.e., 80% suppression) at the daily dose of 10 mg for the most sensitive markers of resorption (i.e., U-NTX and U-CTX) with stable values throughout treatment [64]. Intermittent bisphosphonates, either cyclical oral etidronate and risedronate, or intravenous ibandronate and pamidronate, produce a different pattern of bone marker changes, with a rapid decrease in resorption markers followed within a few weeks by a slow increase that usually does not reach the baseline value at the time of the second course of bisphosphonate [65,66]. This cyclical pattern of change depends on the potency and dose of the bisphosphonate.

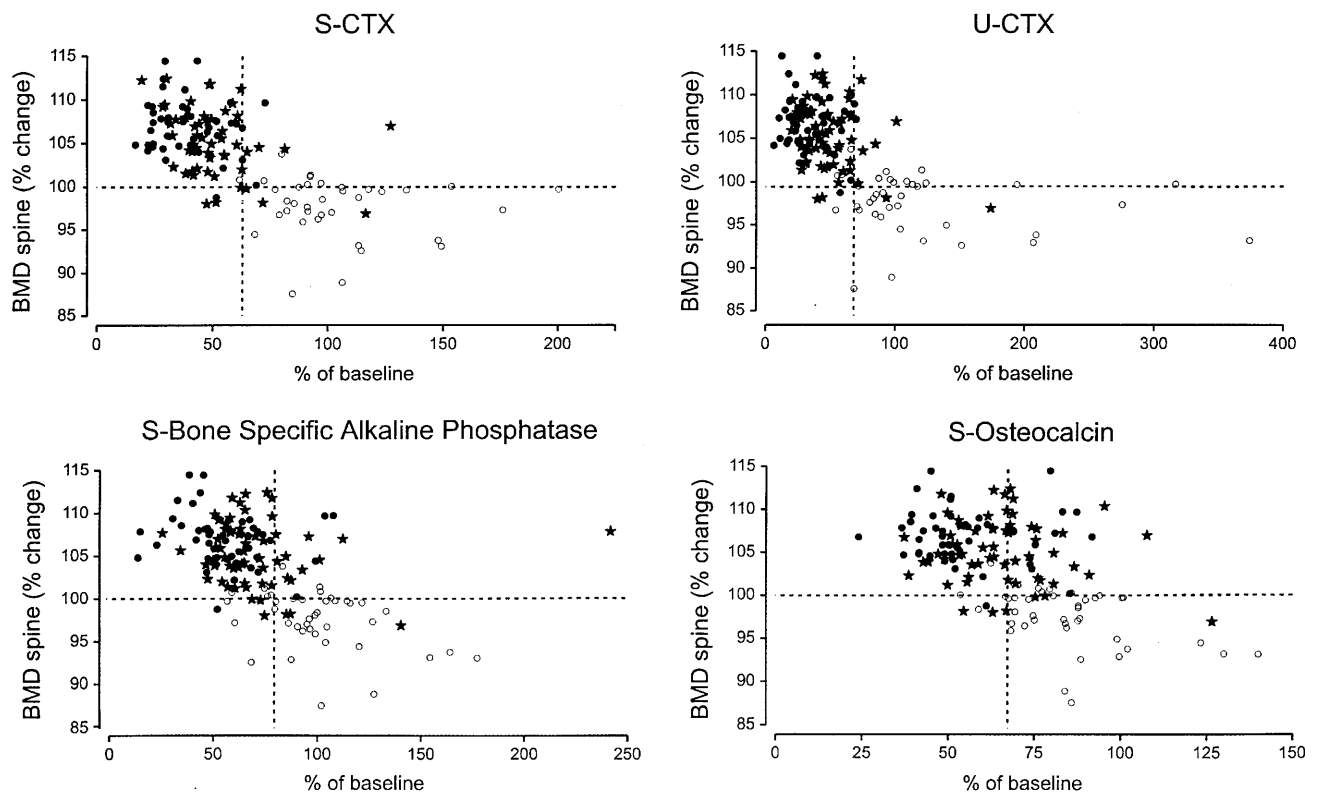
Oral daily raloxifene produces a sustained decrease in bone turnover of smaller magnitude than most HRT regimens, with a 30–40% reduction in U-CTX and a 20–30% reduction in bone formation markers [67]. The reduction in bone turnover is even smaller with nasal calcitonin.

In summary, most effective antiresorptive treatments induce a decrease in bone turnover that reaches a plateau within a few weeks or months, depending on

the potency and route of administration of the drug and on the marker. These early changes might be used, as discussed below, as a surrogate marker for treatment efficacy.

#### *Prediction of BMD Changes by Bone Markers Under Antiresorptive Therapy*

It has been suggested that baseline bone turnover is a determinant of BMD response, i.e., that patients with high-turnover osteoporosis show a higher increase in BMD than patients with low-turnover osteoporosis. Patients with high bone turnover have a significantly greater increase in spinal BMD with injectable or nasal calcitonin than those with low turnover [68]. A similar trend has been observed in patients treated with HRT and with alendronate [69]. There is, however, a large overlap in the BMD response between the two groups, so that baseline bone turnover does not appear to be a useful parameter to predict the individual response to therapy. In contrast, the decrease in bone turnover markers under antiresorptive therapy, usually expressed as a percentage of the initial value, is strongly correlated



**Fig. 2.** Serum and urinary CTX, serum OC and serum bone ALP at 6 months of treatment expressed as a percentage of baseline, versus spinal BMD change at 3 years. Patients were treated daily with 2 mg estradiol (*filled circles*), 1 mg estradiol (*stars*) or placebo (*open circles*). The optimum cut-offs of bone markers, i.e., the best trade-off between sensitivity and specificity, were derived from ROC analyses and were used to estimate the accuracy of the marker changes after 6 months of treatment to predict the long-term changes of BMD at the spine. For example, a –37% cutoff for serum CTX provided a sensitivity of 86.9%, a specificity of 88.6%, a positive predictive value of 95.6% and a negative predictive value of 70.5%. From Bjarnason and Christiansen [71]; reproduced with permission.

with the increase in BMD. Several studies of HRT in the past 10 years [34,43,63,70,71], with one exception [35], have shown that the short-term (3–6 months) decrease in bone turnover markers is significantly correlated with the long-term (1–2 years) increase in BMD at the spine and radius. A marked decrease in markers is associated with a subsequent positive BMD response, while nonresponders show little or no changes in bone markers, suggesting that bone markers, especially new sensitive and specific ones, can be used to monitor HRT. Similarly, studies with alendronate suggest that the magnitude of the short-term decrease in bone turnover is correlated with the magnitude of the increase of BMD [64,72–74], especially when placebo-treated patients are included in the analysis. Few studies, however, have addressed the clinical use of these markers, i.e., how they should be used in the monitoring of the individual patient.

For the clinician, the primary concern is the identification of nonresponders, i.e., of patients who will fail to demonstrate a significant increase in BMD after 2 years of treatment. A BMD response has been defined either as a positive BMD change or as a positive change greater than the precision error in a single individual, also called the least significant change. Several methods have been suggested to identify responders and nonresponders according to the bone marker response to therapy. One approach is to consider the least significant change of a bone marker (based on the short-term or long-term within-subject variability), regardless of the BMD response [13]. Another approach is to search for the minimum marker change associated with a positive BMD response, as previously defined. The optimal threshold of bone marker change can be defined using receiver operating characteristics analysis, or by using logistic regression models [70–73]. The percentage change and/or the absolute value of the marker under treatment can be used [74], and cut-off values can be obtained with a prespecified sensitivity or specificity [70]. These retrospective analyses of several clinical trials using HRT or alendronate suggest that, for a given marker of resorption or formation, a cut-off value under treatment can be defined that provides adequate predictive value of the subsequent 2–3 year BMD response in a single patient. Figure 2 shows the results from one of these studies. For resorption markers, the decrease is usually largest with U-CTX and U-NTX, and slightly less with S-CTX. The decrease in U-free DPD is consistent under HRT, not under bisphosphonates. In terms of formation markers, the decrease is of similar magnitude for serum OC, bone ALP and probably for PINP. For a given marker, the decrease with alendronate treatment is more pronounced than with HRT, leading to cut-off values, expressed as the percentage change from baseline, that are approximately 20% lower for alendronate than for HRT. If the goal is to identify responders with a high specificity (i.e., 90%, with  $\leq 10\%$  false positive cases), a low threshold (i.e., a large decrease in the marker) should be chosen. Conversely, a higher threshold, corresponding to a

smaller decrease in the markers should be chosen to identify most responders (i.e., with a high sensitivity). The same approach can be applied to the identification of nonresponders. When the decrease in a bone marker is equivocal, a third measurement 3 months later is likely to correctly identify 50% of misclassified patients [70]. The recommended cut-offs listed below are derived from the available data [64,70–74]. These cut-off values should be tested in other cohorts using the same therapeutic regimens in order to strengthen their clinical utility.

#### *Prediction of Fracture Risk under Antiresorptive Therapy by Bone Markers*

The value of BMD changes to predict the risk of fracture with treatment is debated, especially because treatments, such as raloxifene, can induce a 30–50% reduction in vertebral fracture rate despite a small 2–3% increase of BMD at all skeletal sites. Thus, BMD changes may not be an adequate surrogate endpoint to analyze the ability of bone markers to predict fracture risk. Unfortunately, there have been few attempts to correlate bone marker changes with fracture risk. In a retrospective analysis of a small placebo-controlled trial of HRT, Riggs et al. [75] suggested that changes in bone turnover (assessed by histomorphometry) predict change in vertebral fracture risk as well as change in BMD in osteoporotic women. More recently, it was found that the short-term changes in serum OC with raloxifene treatment were associated with the subsequent risk of vertebral fractures in a large subgroup of osteoporotic women enrolled in the MORE study, while changes in BMD were not predictive [76]. Clearly, such analyses should be performed in current and recently completed large clinical trials performed in postmenopausal women with osteoporosis treated with bisphosphonates, HRT or SERMs. Ultimately, recommended cut-off values of bone marker changes with treatment should be based on prospective studies with incident fractures as an endpoint.

In summary, changes in new markers of formation and resorption during treatment with HRT, bisphosphonates and raloxifene have been adequately documented in many clinical trials. The fact that they decrease rapidly and reach a drug- and dose-dependent plateau within a few months suggests that they could be used to predict the longer-term response to therapy. Statistical models have recently been developed, indicating that the percentage decrease in some bone markers after 3–6 months of HRT or alendronate can be used to predict the 2-year response in BMD with adequate sensitivity and specificity. These studies provide cut-offs values to predict responders and nonresponders to therapy that should be tested in other cohorts. Importantly, the same approach should be applied to large trials with incident fracture as an endpoint.



## Recommendation for Bone Marker Nomenclature and Abbreviations [77,78]

Marker	Abbreviation	Comments about what the assay measures	Marker	Abbreviation	Comments about what the assay measures
<b>Formation markers</b>					
<i>Osteocalcin</i>					
Osteocalcin (or bone gla-protein)	OC		Pyridinoline	PYD	Can be qualified by total, free moieties or peptide-bound (pb), and in serum (S) and urine (U)
Undercarboxylated osteocalcin	OC		Deoxypyridinoline	DPD	
Total osteocalcin	total OC	Intact + N-mid fragment	<i>Type I collagen telopeptides</i>		
Intact osteocalcin	OC [1-49]		N-terminal crosslinking telopeptide of type I collagen	NTX-I	In publications concerning bone, the I can be omitted
N-mid fragment of osteocalcin	OC [1-43]		C-terminal crosslinking telopeptide of type I collagen	CTX-I	$\beta$ (beta) isomerized unless otherwise specified. In publications concerning bone, the I can be omitted
<i>Alkaline phosphatase</i>			C-terminal crosslinking telopeptide of type I collagen generated by MMPs	CTX-MMP	Also called ICTP
Total alkaline phosphatase	total ALP	Bone + liver + other sources	Bone sialoprotein	BSP	Formerly BSP-2; gene name is IBSP = integrin binding sialoprotein
Bone alkaline phosphatase	bone ALP		Acid phosphatase Tartrate-resistant acid phosphatase	ACP TRACP	Includes two isoforms: type 5a (platelets and other sources) and type 5b (osteoclasts)
<i>Type I collagen propeptides</i>					
Procollagen type I N propeptide	PINP	Also called extension peptides of type I collagen Refers to the trimer			
Monomer of Procollagen type I N propeptide	mon PINP				
Intact procollagen type I N propeptide	intact PINP				
Total procollagen type I N propeptide	total PINP	Monomer + trimer			
Procollagen type I C propeptide	PICP				
<b>Resorption markers</b>			<b>Prefix</b>		
Hydroxyproline	Hyp	Total (i.e., free + peptide-bound) urinary excretion unless otherwise specified	Serum	S	
Hydroxylysine	Hyl		Urine	U	
Galactosyl hydroxylysine	Gal-Hyl	Urinary excretion of free moieties unless otherwise specified	Immunoreactive	i	
Glucosyl galactosyl hydroxylysine	Glc-Gal-Hyl		Peptide-bound	pb	
			Non-isomerized (alpha) aspartic acid	$\alpha$	
			Isomerized (beta) aspartic acid	$\beta$	

(Continued)

## Recommendations for the Use of Bone Markers in Postmenopausal Osteoporosis

### Monitoring of Antiresorptive Agents

a) Which marker to choose preferentially and when to measure?

- Type of marker
  - Bone resorption: U-NTX, or U-CTX or S-CTX for monitoring bisphosphonate therapy; the same markers or free U-DPD for monitoring HRT
  - Bone formation: Bone ALP, OC, PINP
  - Use one marker or one resorption and one formation marker
- Timing of sample:
  - Serum: morning (before 0900 hours) after an overnight fast
  - Urine: either first or second morning void, with creatinine correction, after an overnight fast
- Intervals of measurement:
  - Resorption markers: before starting treatment, and 3 or 6 months after treatment has been initiated
  - Formation markers: before starting treatment and 6 months after treatment has been initiated
  - More than one measurement before starting treatment will reduce the variability of the measurement (not mandatory)

b) Which cut-off to use?

- Ideally cut-off values should be based on fracture probability, but data are not yet available. Currently cut-offs are based on BMD changes during treatment with HRT and alendronate. These cut-offs are consistent with least significant changes of bone markers (see Appendix)
- For a given marker, the decrease with alendronate treatment is more pronounced than with HRT. Thus, the lowest values of ranges of the following cut-offs apply to alendronate, the upper values to HRT.
- For a 90% specificity to predict a positive BMD response (+3%), cut-offs, expressed as a percentage decrease from baseline, are:
  - -45% to -65% for U-NTX and U-CTX
  - -35% to -55% for S-CTX
  - -20% to -30% for total or free U-DPD
  - -20% to -40% for OC and bone ALP
- For a 90% sensitivity, cut-offs are higher by approximately 20%, i.e., -25% to -45% for U-NTX and U-CTX
- In case of an equivocal change in bone markers, a third measurement should be performed 3 months later

### Prediction of Fragility Fractures

- High levels of bone resorption markers (above the premenopausal range, i.e., mean +2 SD,  $T \geq 2$ ) are associated with an approximately 2-fold increased risk of osteoporotic fractures
- Resorption markers can be used in the assessment of fracture risk in selected patients in whom BMD and clinical risk factors are not sufficient to take a treatment decision
- In patients with osteoporosis, a very high level of bone turnover markers ( $T \geq +3$ ) is suggestive of other metabolic bone disease, including malignancy
- Normal values are reference values established in healthy premenopausal women 30–45 years of age

### Prediction of Bone Loss

- Currently, bone markers cannot be recommended for the prediction of spontaneous bone loss
- It is not clear whether the lack of reliability of markers to predict bone loss in untreated individuals is related to the precision error of markers, to the precision error of DXA to assess individual rates of bone loss, or to both

## Recommendations for Research

- Normal values should be established for all bone markers in large samples (150–200 women) of healthy premenopausal women, 30–45 years old, with normal BMD at the spine and hip measured by DXA; potential differences in normal values across geographic areas and races should be searched.
- Available data were obtained in research centers with bone markers measured under controlled conditions. Quality control programs of bone marker measurements should be established and widely implemented, as already done for other biological tests in clinical chemistry.
- The association between baseline bone marker levels and the subsequent rate of bone loss measured by DXA at various skeletal sites over the long term (>5 years, ideally 10 years) should be further explored.
- The association between bone markers (baseline values, 3–6 month percentage decrease and absolute value under treatment) and the probability of fractures should be explored in large clinical trials of anti-osteoporotic drugs.
- Cut-offs of markers established for defining responders and nonresponders should be validated in other cohorts using the same therapeutic regimens.
- The ability to monitor treatment with bone markers to improve compliance and treatment efficacy should be tested prospectively.

## Appendix

Response to treatment based on BMD/fractures	Bone marker response to treatment	
	+	-
Responders	A	B
Nonresponders	C	D

A, true positives; C, false positives; D, true negatives; B, false negatives.

Sensitivity =  $A/A+B$

= proportion of true responders correctly identified by the bone marker

Specificity =  $D/C+D$

= proportion of true nonresponders correctly identified by the bone marker

Positive predictive value =  $A/A+C$

Negative predictive value =  $D/B+D$

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