

Lebanese Guidelines for Osteoporosis Assessment and Treatment

Who to test?

What measures to use?

When to treat?

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ABSTRACT

With the demographic explosion of the population worldwide, the human, social and economic costs of osteoporosis will continue to rise. It is estimated that the magnitude of the problem may be even larger in developing countries, including those in the Middle East. Although several organizations and countries have developed or adapted guidelines to their local needs, as of today there are no guidelines for osteoporosis assessment in the Middle East. In April 2002, a panel of osteoporosis experts met and discussed practice guidelines for osteoporosis assessment and treatment in Lebanon. The process, which involved an overview of International guidelines as well as local data on osteoporosis, resulted in a draft for Lebanese guidelines that addressed three main questions: “who to test, what measures to use, and when to treat?” Representatives from five major Lebanese societies, Endocrinology, Rheumatology, Orthopedics, Obstetrics and Gynecology and Radiology subsequently reviewed, discussed and officially endorsed the guidelines after revisions. The Lebanese guidelines were also endorsed by the Eastern Mediterranean branch of the World Health Organization (WHO).

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INTRODUCTION

Osteoporosis is a major public health problem projected to generate an increasingly heavier social and economic toll in view of the demographic explosion of the aging population worldwide, in general, and in developing countries (including those in the Middle East), in particular.

International guidelines on osteoporosis have been put forth and further refined over the years, in light of the substantial body of evidence that has accumulated from prospective studies evaluating fracture and other risk factors, and from large randomized and controlled trials evaluating the safety and efficacy of various osteoporosis treatment strategies. In the Eastern Mediterranean region, the high prevalence of osteoporosis risk factors and the expected further increase in life expectancy underscore the need to act now to prevent a foreseeable epidemic of the disease in the next fifteen to twenty years.

In an effort to optimize the quality of care of osteoporosis in Lebanon, an initiative was launched in Beirut in the spring of 2002, which ultimately led to the development of Lebanese guidelines for the assessment and treatment of osteoporosis. These guidelines were reviewed and ultimately endorsed by five Lebanese societies and the Eastern Mediterranean branch of the World Health Organization (WHO). The societies were the Lebanese Societies of Endocrinology, Obstetrics and Gynecology, Orthopedics, Radiology and Rheumatology (1). The active participation of local experts in the process of guideline development, following a standardized protocol, was a critical step towards an effective implementation of those guidelines nationally and regionally.

The Lebanese guidelines provide a structural framework—based on the evidence available up to July 2003—on which to build sound clinical decision-making in the management of the patient at risk or with osteoporosis. They are not meant to be considered as rigid yardsticks to measure standard of care, and

will undoubtedly continue to be refined and revised as our knowledge base on this challenging silent disease keeps evolving globally, regionally and, last but not least, nationally. The Lebanese guidelines have also been evaluated through the Appraisal of Guidelines for Research and Evaluation instrument (AGREE) and as of fall 2004, is posted on the International Osteoporosis Foundation (IOF) webpage as part of its guideline documents (www.IOF.osteofound.org).

METHODS

On April 20, 2002, a group of experts convened and presented national and regional data on osteoporosis, with the aim of preparing a draft for Lebanese guidelines based on local considerations and on a review of the evidence provided by currently published international guidelines. The experts were leaders in the field of osteoporosis, associated with the two major university-based medical centers in Beirut: the American University of Beirut and the University of St. Joseph. The evidence used was obtained through a Medline internet search, current to July 2003, by entering the two key words “guidelines” and “osteoporosis”. Position statements and guidelines issued by the following major organizations were retained: National Osteoporosis Foundation (NOF), European Foundation for Osteoporosis (EFFO) now known as the International Osteoporosis Foundation (IOF), International Society of Clinical Densitometry (ISCD), American Association of Clinical Endocrinologists (AACE), National Institutes of Health (NIH), North American Menopause Society (NAMS) and the American College of Rheumatologists (ACR). Also considered were randomized controlled trials on osteoporosis, as well as major review articles relevant to the topic, as put forth by the group of experts who launched the initiative.

The guidelines addressed three main questions having to do with the use of

densitometry in the management of the patient at risk or with osteoporosis. The questions were: “Who to test?”, “What measures to use?” and “When to treat?” The guidelines for “who to test” and “when to treat” were stratified into three categories, based on the strength of the evidence available at the time the guidelines were drafted.

Guidelines were considered under “definite indications” based on the following:

- a. For “who to test”: if there was solid data on high prevalence of osteoporosis and fractures.
- b. For “who to treat”: if there was solid data on efficacy of therapies in reducing fractures.

Guidelines were considered under “less definite indications” based on the following:

- c. For “who to test”: if there was data on the prevalence of low BMD but not of osteoporosis or fractures.
- d. For “who to treat”: if there was data on efficacy of therapies in maintaining BMD but not in reducing fractures.

Guidelines were considered under “not indicated” based on the following:

- e. For “who to test”: if the prevalence of low BMD was rare and fracture risk was very low, even in the case of low BMD.
- f. For “who to treat”: if the safety, efficacy and duration of pharmacological intervention were not established.

Subsequent to the April 2002 meeting, an extensive scientific document detailing the guidelines and the evidence upon which they were based was submitted by the experts to the five Lebanese medical societies. During the following year (2002–2003), a committee within each of those societies was appointed by the society president to review and debate the guidelines in consideration of their final endorsement. Individual meetings were then scheduled,

during which the society committees had the opportunity to discuss the guidelines in the presence of at least one of the experts involved in their development and arrive at suggestions for possible modifications. Ultimately, agreement on the guidelines was reached by consensus, resulting in the revised scientific document that was subsequently unanimously endorsed by the five Lebanese scientific societies mentioned above.

“Lebanese Guidelines for Osteoporosis Assessment and Treatment” was published in September 2003 in a separate supplement of the *Lebanese Medical Journal*, which contained the proceedings of the original workshop, the scientific document, and a summary of the guidelines presented in a slide format in English and French (1). The manuscript presented herein consists only of the scientific document of the “Lebanese Guidelines for Osteoporosis Assessment and Treatment”; it includes some editorial changes and incorporates an Introduction and a section on Methodology as background information.

“WHO TO TEST?”

When the question is “to test or not to test” using bone mineral density (BMD), one can anticipate that the answer will not be straightforward. As with any diagnostic procedure, indications should be linked to clinical decision-making; and this has to do with issues of sensitivity, specificity, predictive value, and balance between the health and economic consequences of false positive and false negative results. Moreover, targeting osteoporosis lends some peculiarities to the analytical process. The outcome is a probability; i.e., the risk of fracture as indicated by the test is a quantitative measure with an arbitrary cut-point threshold (2-4). Clinical decision-making (5) can occur in the setting of either initiating or monitoring therapy. In the first situation, two approaches are identified: mass screening or targeting high-risk population (6, 7). The latter is currently the main policy, driven by considerations of

cost-effectiveness and using the evidence-based knowledge about osteoporosis. Therefore, the question of “who to test” can first be approached through identifying subjects at high risk of fracture. The difficulty, however, comes from the very objective of BMD testing itself, which is to estimate the risk of fracture (8).

Regarding the risk of fracture, epidemiological evidence supports the role of multiple risk factors for fracture, commonly classified into bone and non-bone-related determinants (see Table I). The former are related to bone strength determinants, including bone density and bone quality, and the latter are related to the risk of falls, namely loco-motor problems and environmental characteristics (9-15). So far, bone density remains the most important determinant of fracture in terms of relative risk that we can estimate with enough confidence, using DXA technology, and that is amenable to modification through pharmacological interventions (16–20).

In practice, however, we are dealing with two different estimations of the risk of fracture: the absolute risk of fracture at any point in time, or during the remaining lifetime (21) and the relative risk (22). The lifetime risk is the probability of sustaining a fracture over life expectancy, and it is higher for early postmenopausal than for late postmenopausal women. The relative risk is the ratio of the probability of sustaining a fracture when the risk factor is present, compared to the probability of sustaining a fracture when the risk factor is absent in an age-matched cohort. At any discrete BMD value, relative risk is higher for late postmenopausal than for early postmenopausal women (23, 24).

Besides BMD values, simple clinical risk factors could be identified as determinants of fracture risk based on epidemiological data (25). These include age, gender, body mass index, history of fractures and smoking. However, these risk factors poorly predict BMD (26). Therefore, BMD testing

remains the cornerstone in the evaluation of the risk of fracture. Guidelines have been developed to select people at high risk of fracture based on those simple clinical risk factors (27–30).

Since guidelines necessarily reflect health system patterns, one might anticipate the publication of several guidelines. A literature review yields guideline reports from the American National Osteoporosis Foundation (28), the American Association of Clinical Endocrinologists (31), the American College of Rheumatology (32), the North American Menopause Society (33), the US Preventive Services Task Force (34), the International Society of Clinical Densitometry (29), the Osteoporosis Society of Canada (30), the European Foundation for Osteoporosis, now known as IOF (35-37), the Australian National Consensus Conference (38) and WHO (2).

Despite the apparent diversity of recommendations, common and simple clinical risk factors associated with increased fracture risk constitute the core set of the clinical decision-making rule of proposed guidelines, although their diagnostic value might be different. This issue was recently addressed in an original contribution (39), in which the diagnostic value of the NOF guidelines was compared to four other clinical decision rules (40–43) derived from simple clinical criteria identified through the MEDLINE search, excluding decision aids based on regression models or involving detailed questionnaires. The study found superiority of the Simple Calculated Osteoporosis Risk Estimation (SCORE) and the Osteoporosis Risk Assessment Instrument (ORAI) methods superior, as compared to the NOF recommendations in terms of sensitivity and specificity (40). The strength of the study arises from the database on which the comparison was made; that is, the population-based community sample from the Canadian Multicenter Osteoporosis Study (43). However, this might not apply to other populations nor address the issue of a cost-effectiveness that reflects health system

priorities and practices. BMD testing costs and reimbursements differ widely across national health systems. As a consequence, access to BMD testing may be dependent on patterns of health care provision (2).

Until further progress can be made in the validation of widely applicable rules (43–44), we recommend the use of a core set of accepted clinical risk factors to select individuals at high risk of fracture, whereby BMD testing will help clinical decision-making and universally add value to health outcomes. These are in large part driven by societal financial constraints in health care delivery, thus necessitating the identification of high risk individuals for treatment.

For women, the core set of clinical risk factors includes menopausal status, age, weight, past history of fragility fracture and previous steroid therapy (28, 37).

For men, although epidemiological data is less abundant, recent evidence suggests a similar BMD fracture relationship and BMD response to anti-resorptive agents in men as in women (45–50). However, the evidence is less definite. We suggest consideration of the following set of clinical risk factors for fracture in men: past history of fragility fracture, chronic steroid therapy, hypogonadism, alcohol abuse, demineralization, low weight and medical conditions associated with bone loss. The main difference is that the efficacy of osteoporosis therapies is less established in men and the incidence rate of fracture is lower in men compared to women. Therefore, testing in men would be recommended on less definitive grounds at present.

RECOMMENDATIONS FOR “WHO TO TEST”

*As recommended by the panel of experts:
FOR WOMEN*

Definite indications for BMD testing

- *In postmenopausal women, regardless of age, BMD testing (or measurement) is indicated if:*

- *There is evidence of radiological demineralization.*
- *Vertebral deformity or fragility fracture is present.*
- *Corticosteroid therapy for >3 months is contemplated.*
- *In late postmenopausal women (aged 65 years and above), BMD testing (measurement) is indicated in making a decision about pharmacological intervention, regardless of clinical risk factors.*

Less definite indications for BMD testing

- *In early postmenopausal women (age less than 65 years).*
 - *Clinical risk factors for fractures: maternal history of fragility fractures, low body weight ($Wt < 50$ kg or $BMI < 20$ kg/m²).*
 - *Presence of medical conditions associated with secondary causes of bone loss, which include premature menopause <45 years, chronic corticosteroid therapy, asymptomatic primary hyperparathyroidism, hyperthyroidism, chronic renal failure, chronic liver disease, malabsorption, use of anticonvulsants, etc.*
- *In premenopausal women:*
 - *Presence of medical conditions associated with secondary causes of bone loss, which include anorexia nervosa, chronic corticosteroid therapy, asymptomatic primary hyperparathyroidism, hyperthyroidism, chronic renal failure, chronic liver disease, malabsorption, use of anticonvulsants, etc.*

BMD testing is not indicated

In apparently healthy premenopausal women.

*FOR MEN****Definite indications for BMD testing**

- Presence of vertebral deformity or fragility fracture.
- Hypogonadism.
- Chronic steroid therapy.

Less Definite indications for BMD testing

- Alcohol abuse.
- Low body weight.
- Radiological evidence of demineralization.
- Medical conditions associated with bone loss, such as hyperparathyroidism, renal insufficiency, chronic liver disease and anticonvulsant use.

BMD testing is not indicated

Healthy men in the absence of clinical risk factors.

** Testing in men to date is recommended on less definitive grounds.*

The above recommendations represent general guidelines. For difficult and unusual cases, referral to a specialist is strongly recommended. The decision on who to test and how to treat, is ultimately left to the discretion of the expert.

“WHAT MEASURES TO USE?”

This question involves decisions regarding methods to use to evaluate fracture risk; and, in those individuals found at high risk and needing to be treated, what measures to use in monitoring response to therapy, if any. In order to adequately address that question, the following four issues need to be covered:

- A. Which methods for measuring BMD can predict fracture risk?
- B. Which technique and device to use?
- C. Which parameter—BMD versus T-Score—and which database?
- D. Which skeletal sites to measure?

A. Which methods for measuring BMD can predict fracture risk?

Bone mineral density as a strong predictor of fracture:

Before we discuss which methods to use to assess the risk of fracture, let us review two

widely recognized definitions of osteoporosis:

1. “A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.” International Consensus Definition, 1993 (50).
2. “A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality.” NIH Consensus Development Panel, 2001 (51).

The WHO working group operational definition of osteoporosis is based on BMD. Bone mass and BMD, the recurrent terms in the above two definitions, were coined almost a decade apart. This was owing to the fact that over the last twenty years abundant data had accumulated establishing BMD as one of the strongest, if not the strongest, predictor of fractures. As a matter of fact, it is a stronger predictor of fracture than cholesterol is a predictor of coronary artery disease (CAD) and is at least as good as hypertension is as a predictor of stroke (52). This was the main reason why the WHO working group developed an operational definition for osteoporosis based on BMD.

Although the relationship between BMD and fracture risk is a continuous one, a specific BMD-based cut-points was chosen for osteoporosis diagnosis; i.e., a BMD that is 2.5 S.D or more below (peak bone mineral density T-Score < -2.5) (2). “Such a cut-point value identifies approximately 30% of postmenopausal women as having osteoporosis, using measurements made at the spine, hip or forearm. This percent change is approximately equivalent to the lifetime risk of fracture at those sites” (2). Indeed, Melton et al recently demonstrated that the proportion of postmenopausal women who have a BMD T-Score of <-2.5 at the femoral neck, spine, forearm or at any of those three sites corresponds to the same

proportion of women with a lifetime fracture risk at hip, spine, wrist or any of those three sites respectively (53, 54). This -2.5 T-Score cut-point applies to postmenopausal Caucasian women and to DXA densitometry measurements (2, 52).

Measures validating the use of BMD to predict fractures:

The rationale for the use of BMD in fracture prediction is validated by biomechanical as well as epidemiologic and clinical trial data. Indeed, biomechanical testing in the laboratory supports a strong relationship between BMD and bone strength as assessed by failure load (55).

Ample epidemiologic data from longitudinal studies—such as the Study of Osteoporotic Fractures (SOF), the EPIdemiologie de l’Osteoporose (EPIDOS) study, the Rochester study, the Rotterdam study, and the Hawaii Osteoporosis study—document BMD to be a strong predictor of fractures. Indeed, for each SD decrease in BMD, the RR of fracture is 1.7-3, depending on the fracture type, the skeletal site and the device being used (56–65). An evaluation of the large randomized controlled trials using pharmacologic treatment reveals that BMD increments account for a significant proportion of the variance in vertebral fracture risk (66–71). However, the proportion of variance in fracture reduction explained by BMD changes has varied widely, depending on the study (66–71). Although measurement of BMD only captures one aspect of bone strength, since there is no additional readily available measure of bone quality to date, BMD remains a pivotal tool in the diagnosis of patients at risk for fracture.

B. Which device and technique to use?

There are multiple devices on the market to measure bone mineral density in the central or the peripheral skeleton. The techniques used in these devices also differ. The main techniques available today are dual energy x-ray absorptiometry (DXA), single energy x-ray absorptiometry (SXA), quantitative

computerized tomography (QCT) and ultrasonometry (QUS).

X-ray technology as DXA or SXA:

These techniques utilize ionizing radiation, and measures of areal density (bone mineral content/area) can be affected by size, growth, etc. DXA can be used to measure BMD at the central as well as the peripheral skeleton. Central DXA is the yardstick with which all measures are compared (see section on validation of techniques used below). Central devices measure BMD at the spine, hip, forearm and total body. Peripheral devices are based on single energy (SXA) or dual energy (pDXA) technology and measure BMD at the forearm or calcaneus (SXA) or at the finger, toe, heel, forearm (pDXA) (72).

Quantitative computerized tomography:

QCT uses ionizing radiation and measures true volumetric as opposed to areal density, such as measured by SXA and DXA. The method can be used for central measurements at the spine, and a special QCT is available to measure volumetric density at the forearm (pQCT). Recent advances in spiral CT and recent automated software make hip measurement also feasible. A major drawback of central QCT is its use of higher radiation exposure. Although QCT does offer high sensitivity in detecting osteoporosis and excellent fracture discrimination in cross-sectional studies, there are no longitudinal studies relating QCT BMD measures to fracture risk. Furthermore, since the WHO operational definition of osteoporosis was based on BMD measures using DXA, this definition does not apply to QCT technology. Therefore, caution must be exercised in the interpretation of QCT-derived T-Scores.

Quantitative ultrasonometry:

QUS technology uses sound waves to measure speed of sound and broadband ultrasound attenuation that can yield calculated parameters (e.g., stiffness, etc.) (73). Both the directly measured and the derived parameters are lower in the patient

with osteoporosis. As with QCT, T-Scores also do not apply to QUS.

Validation of the technique used:

DXA:

By far the most widely accepted technology and the one best validated by all three criteria listed above. It is the technique about which we have the most information and is regarded as the gold standard today. It offers very good accuracy and excellent precision in expert hands (see below), and incurs low radiation exposure. DXA is approved by the Food and Drug Administration (FDA) for the diagnosis of osteoporosis. Indeed, the biomechanical data was mostly obtained using DXA; most epidemiologic studies establishing the close relationship between fracture risk and BMD used DXA (59, 60, 63, 74). Similarly, the data from the randomized controlled trials linking treatment efficacy to fracture outcome exclusively used DXA (as opposed to pDXA or SXA) as an intermediary measure for efficacy, as required by the FDA.

pDXA, SXA:

Data from the National Osteoporosis Risk Assessment (NORA) study of over 200,000 women screened across the United States (using a wide variety of devices) demonstrates a significant relationship between BMD and fracture risk, as assessed by any of the SXA, pDXA and DXA techniques/devices, with variations in the risk measure depending on the device (64, 75).

QUS:

Several studies, among them the SOF, EPIDOS and NORA studies, have demonstrated a direct correlation between QUS measured and derived parameters and fracture risk (61, 62, 64). However, the calculated QUS parameters and not the directly measured ones are used to calculate T-Scores and, therefore, fracture risk by inference.

QCT:

Two studies have recently demonstrated the capability of QCT and pQCT to predict risk of vertebral fracture for the former, and spine, hip and global fracture for the latter (76, 77). However, QCT is considered of experimental value compared to DXA. QCT also incurs the highest radiation exposure, around 40 times that of a DXA.

Accuracy and Precision:

These are key characteristics to be considered in the choice of a device to be used to diagnose and monitor a clinical condition. In this regard, the main critical characteristic to be considered is accuracy: how close the measure is to what the device is supposed to measure. In this instance, this can be evaluated by measuring the BMD and BMC of a bone specimen using the different techniques and devices and comparing that to the actually measured bone mineral content by ashing the specimen afterwards. Upon careful study, the accuracy for various devices/techniques listed above was found to vary between 3–6 %, although it may be slightly poorer for both QCT and pQCT, with a range of 8–15% (78, 79). Precision (reproducibility), on the other hand, is the most important variable to consider when using a technique to monitor therapy (80–83). See section below: “Which skeletal sites to use to monitor the patient?”

Central DXA technology is the most established technology, in which the BMD-fracture relationship has been validated in longitudinal studies including the one with which WHO T-Score-based cut-points have been established. FDA-approved central DXA-based densitometry devices, when available, are therefore the preferred method for evaluating fracture risk. Alternative measures that could be used are QUS, PDXA, QCT or other validated devices. However, non-validated non-FDA-approved DXA-like devices are to be avoided, in view of their poor accuracy and their probable poor precision.

C. Which parameter—BMD versus T-score and which database

It is generally agreed that the relationship between BMD and fracture risk is an inversely exponential one. As BMD decreases, fracture risk increases; expressed differently, for each SD decrease in BMD, fracture risk almost doubles. This assessment was derived from several large epidemiologic studies conducted mostly on Caucasian populations: SOF in the United States (83), the Rotterdam study in the Netherlands (74), EPIDOS in France (63) and the osteoporosis study in Hawaii (56), although scarcer data on other races are available

At present, fracture risk can be expressed in one of two ways:

1. As an absolute risk, either a lifetime or 5-year risk, for a specific BMD at a certain age (since age is another independent predictor of fractures), such as provided in the Rotterdam study (74).
2. More commonly, but in less practical terms, as a relative risk expressed as relative risk per standard deviation decrease in BMD (RR/SD). Therefore, an individual with a T-Score (or Z-Score) of -3 has a fracture risk that is twice that of an individual with a T-Score (or Z-Score) of -2 . This assessment is less useful in the clinical setting, as it expresses risk in relative rather than in absolute terms, the latter being more clinically applicable and relevant risk assessment tool (59–60, 63, 83–84).

Very few studies have expressed absolute fracture risk as a function of BMD such as the Rotterdam study (74). However, since absolute BMD in gm/cm^2 may vary depending on central DXA manufacturer, appropriate conversions are to be implemented prior to the ability to use such data (85). In view of the paucity of absolute fracture risk data published, the practice has been to try to use the more abundant data using RR/SD decrease in BMD, and hence the practice to use T-Scores to assess fracture

risk and to establish T-Score based thresholds for intervention. Two important points are to be made at this juncture: the WHO T-Score cut-points for the diagnosis of osteoporosis are applicable only to central DXA generated data in postmenopausal Caucasian female subjects only (2). Conversely, T-Score derived from other technologies such as pDXA, QUS and QCT are not comparable to DXA derived T-Scores for multiple reasons including differences in what is measured with these technologies, differences in normative databases and the lack of agreed upon diagnostic criteria (86–88). Work in progress between committees from the NOF, the ISCD and ASBMR with the goal of deriving T-Score equivalents that vary depending on the device, to estimate fracture risk may help partially resolve this issue. Alternatively, other algorithms are currently being evaluated to evaluate absolute 5 (or 10) - yr fracture risk using absolute BMD adjusting for variation in densitometer types (DXA, U/S, pDXA, etc.).

The second issue of relevance to non-Western countries in our part of the world is how to use the BMD-fracture data expressed in the European and American Caucasians to our part of the world, the Middle East. That really gets to the question of how do absolute BMD/fracture curves compare across populations within the same racial category, for our purposes, Caucasians. A comparison of absolute BMD vs. fracture risk across populations of the same race would be needed to evaluate that question. Such data is just not available to-date for populations from the Middle East.

Therefore, resorting to T-Score was the next available strategy, to assess fracture risk in individuals in the Middle East. This would be sound if the following two conditions were met:

1. We assume that the absolute BMD/fracture relationship is overall the same in all Caucasians regardless of the population. There is no reason to-date to think otherwise.
2. We use the appropriate device and database in which the BMD-fracture

relationship and therefore T-Score cut-off was derived. These would be a central DXA device and a Caucasian postmenopausal female normative database.

Data available to-date from the Middle East region may help address some of these issues. Peak BMD has been studied mostly in non-population based (89-91) and in population-based samples (92-93). The studies available from our region reveal peak BMD in these subjects may be slightly lower than (in 4 studies) or equal to (in one study) that of European and American Caucasians, possibly due to differences in body size, chronic vitamin D deficiency, less physical activity and genetic factors (90,94-95). The prevalence of vertebral fractures in postmenopausal women and hip fracture rates are comparable to data for Western counterparts (96-99). Finally, mean BMD in hip fracture in Lebanese subjects is comparable to mean BMD in hip fracture subjects from the West (100-101). The latter information suggests that the absolute BMD-fracture relationship may be the same in our region as it is in the West. The situation may very well be different in other races such as Asians or African-Americans etc.

In view of the above observations, the application of Western standards for the diagnosis and assessment of fracture risk in Caucasian subjects from the Middle East is prudent, until additional forthcoming data from the region becomes available. This is consistent with the recommendations from the International Osteoporosis Foundation (36). Therefore, we recommend the use of central DXA devices and Western databases (for e.g. NHANES, etc..) for the derivation of T-Scores to assess fracture risk, or when data comparing BMD to fracture risk such as provided in the Rotterdam study after appropriate transformation of the data to obtain comparable densitometry units (see above). Any other practice will result in a tendency to erroneously diagnose osteoporosis and wrongly estimate fracture risk. WHO T-Score based criteria are not

applicable to non-Caucasian postmenopausal women, to pre-menopausal women, to men, and to children. They are also not applicable to other technologies such as QCT, pQCT, QUS, pDXA and SXA. Algorithms are currently being evaluated to use information gathered from non-central DXA devices to estimate absolute 5-year or 10 year fracture risk, however such data is not readily available yet.

D. Which skeletal sites to measure?

It is generally agreed that the relationship between BMD and fracture risk is an inversely exponential one, as BMD decreases fracture risk increases; expressed differently for each SD decrease in BMD fracture risk increases by 1.6-3.0 folds. This range is due to variations in the skeletal site used to estimate fracture risk (L2-L4, hip, forearm, et.) and the specific fracture for which the risk is predicted (wrist, hip, or vertebral fracture).

Several risk estimates have been derived to evaluate fracture risk. These include global risk, and site specific fracture risk.

Global risk of fracture: Several studies have established that the global relative risk of fracture, relative risk of developing an osteoporotic fracture anywhere in the skeleton is the same 1.4-1.6/SD decrease in BMD as measured at any site in the skeleton (84).

Site-specific fracture risk: although site-specific fracture risk assessment can be estimated by measuring BMD at any skeletal site, the predictive value is higher if a site-specific assessment is conducted: e.g. whereas spine, hip and forearm all predict fracture risk at the hip and spine, hip BMD is the best predictor of hip fracture and spine BMD is the best predictor of vertebral fracture (59-60, 83-84).

A large meta-analysis of 11 cohort studies from 1985 to 1994, which included 90,000 person-years and >2,000 fractures and in which BMD was measured using central DXA, provided the following estimates for site-specific fracture risk (84):

RR/SD decrease in BMD:

Spine BMD for vertebral fractures
2.3 [1.9–2.8]

Femoral neck BMD for hip fractures 2.6
[2.0–3.5]

Distal radius for wrist fractures
1.7 [1.4–2.0]

How many skeletal sites to measure:

The following observations are to be noted in making recommendations with regard to the number of sites to measure:

1. Although there is correlation in BMD between one site and the other ($r=0.4-0.6$), it is not perfect. Therefore, measuring only one site may underestimate a subject's osteoporosis risk (87,102–104).
2. Hip BMD is the best predictor of hip fractures and spine BMD is the best predictor of vertebral fractures, as outlined in the previous section.
3. At menopause, accelerated bone loss takes place more at the spine than at the hip; measuring only a hip BMD, therefore, may miss the lower bone mass at the spine (103).
4. Aging results in degenerative changes at the spine that may falsely increase BMD by 0.5–1SD (105–106). Measuring the hip in the elderly is of particular importance.
5. The spine is the skeletal site most responsive to pharmacologic intervention and may be important in monitoring a patient (69).
6. Forearm: Some clinical conditions, such as primary or secondary hyperparathyroidism, may lower FA BMD the most (107). In such instances, a forearm measurement is indicated. A forearm measurement is also indicated in the very obese patient, in whom a spine or hip measurement cannot be performed because of large size.

FFFO position:

A position paper from the European Foundation for Osteoporosis (now IOF) has suggested measuring only one skeletal site for the young patient (spine, hip or forearm) and the hip only in the elderly, as it best predicts the occurrence of the most important fracture and avoids running into the problems of DJD of the spine (36).

ISCD position:

The ISCD recommends measuring the spine and hip for all patients. Non-dominant forearm is to be added if one of the above two skeletal sites cannot be used, if the patient has suspected hyperparathyroidism, or if the patient is obese. Total body BMC measurement is recommended in children (108).

NOF position:

The NOF recommends measuring the hip. Indeed, NOF cost-effectiveness was all based on BMD measurement at the hip.

Although it is controversial whether measurement of more than one skeletal site improves our discriminative ability in predicting the patient at risk for fractures, a two-site central DXA measurement is preferred for the above-mentioned reasons. *We therefore recommend following the guidelines of the ISCD (108) for skeletal site selection:*

- *Spine and hip for all patients.*
- *Non-dominant forearm is added in the following situations:*
 - When one skeletal site cannot be used (arthritis, prosthesis, etc.).*
 - When hyperparathyroidism is suspected.*
 - When the patient is obese and exceeds the weight limit recommended by the manufacturer.*

For spine, the use of L1-L4 is recommended; and for the hip, ISCD suggests the use of the lowest T-Score of all three hip sites (Total hip, femoral neck, trochanter).

What skeletal sites to use to monitor the patient

The purpose of this discussion is not to advise whether a patient (on therapy or not) should have serial BMD measured. Rather, it is to advise the physician who has made the decision to repeat BMD measurements on the specific skeletal sites used to monitor BMD response, as well as on the time intervals at which follow-up scans are to be performed. A complete and detailed

overview of that topic is provided in the ISCD position statement (108).

A. Skeletal sites to monitor BMD change over time to determine what is a significant change. In order to assess change over time, the following conditions should be met:

1. The same skeletal site should be measured on the same device, not just on the same model. In the event of a change in the machine, careful cross-calibration is mandatory.
2. Absolute BMD, rather than T-Scores, should be used.
3. T-scores derived from devices from different manufacturers should not be compared. This is because of the differences in normative databases (93,109) and differences in identifying ROI between manufacturers (e.g., L1–L4 versus L2–L4 and differences in algorithm used to define ROI for femoral neck).
4. The ROI of BMD sites being compared should be identical, otherwise the comparison of areal BMD is not valid. Ideally, the area should be within 2% between the two duplicates, although this specification was removed from the latest recommendation by the ISCD.
5. Strict adherence to manufacturer guidelines for position and analysis are of utmost importance.
6. The skeletal site to be chosen for monitoring BMD change over time is the one that has the highest precision (<1%), that is the most responsive to change with treatment and that is the least affected by potential artifacts. The spine definitely fulfills the first two criteria (81–82). In the case of DJD of the spine, the total hip (rather than the femoral neck) is the next preferred site, because better precision is achieved, due to the greater area of the site. The forearm, because of its lower bone turnover, is unlikely to show changes over time.
7. Center specific precision data should be available. Ideally, such precision (duplicate BMD scans on the same

patient, performed a few days apart on over 30 individuals) should be calculated in each center on its own machine in the population being evaluated, namely postmenopausal women (79). Indeed, we have demonstrated that same day precision is better than different day precision, and that precision derived from osteoporotic patients is worse than that derived from normal subjects (82). Use of in-vitro precision based on phantom duplicate measurements, provided by the densitometer manufacturers and used by the densitometry software to assess significance of changes in an individual over time, should be discouraged. Indeed, these estimates are not applicable to the real clinical situations, but are unfortunately used by many centers.

8. The mean SD (rather than CV) derived from all duplicate scans should be calculated; and the root mean square average for the entire group should then be calculated by summing the square of the SD, dividing it by the number of patients (e.g., N=30), and then taking the mean square root MSR (79).
9. A change over time is significant if it exceeds the least significant change (LSC)—a number derived from the precision, preferably calculated from the SD derived from duplicates rather than from CV%. LSC is calculated as $2.77 \times \text{MSR}$ of the data, for a 95% confidence interval (79). Even in the centers with the best precision, one should not repeat BMD before 1.5–2.0 years, unless one expects accelerated bone loss (see below).

B. Interval time for repeating BMD to assess response to therapy:

The interval of time is determined by the expected change in BMD over time (the latter depending on the type of therapy used and the specific skeletal site) and the center's precision derived from the LSC. The minimal time interval = $\text{LSC} / \text{expected change per year}$ (79).

This implies that even in expert centers with an MSR of 1, a LSC of 2.77, and an expected mean change in BMD of 0.03 gm/cm², repeating a BMD before 1.5–2 years is not indicated. The interval time is obviously shorter in cases of anticipated fast increments and/or decrements in BMD (as seen in post-oophorectomy, during GnRH therapy with high doses of chronic corticosteroid therapy, or with bone anabolic therapies), in which instances the interval may be as short as six months to a year.

To conclude, if the decision is to monitor the patient, it is strongly recommended to evaluate the patient on the same device, not just the same model, with strict quality assurance (QA) measures for scan acquisition and analysis. This includes choice of scanning mode, choice of skeletal site, region of interest (ROI), and the derivation of center specific patient-based precision data for the skeletal site of interest. This will determine a center specific LSC measure and therefore the significance of a change in an individual patient. The skeletal site we recommend for monitoring is the spine; the hip can be used instead in select situations or in addition. The monitoring interval depends on the center specific LSC data and expected changes in BMD in each patient/year. Usually, follow-up scans should not be done before 1.5–2 years.

“WHEN TO TREAT”

Over the last decade, there has been an effort to expand guidelines from “who to test” to “who and when to treat,” using the body of evidence provided by the large randomized osteoporosis trials with the solid endpoints of osteoporotic fractures. With the increasing evidence for a relatively rapid rate of treatment onset and variable timing for offset of these interventions, there has been a move away from long-term preventive strategies towards the use of shorter-term therapy in high-risk individuals, as outlined below and in published guidelines or reviews on that topic (28, 36, 110–112). The pivotal randomized

controlled trials that are responsible for the switch in the treatment strategies will also be highlighted in this overview. Any physician faced with the decision of treating a patient with or at risk for osteoporosis may include in his evaluation a work-up to rule out secondary causes of osteoporosis. This could include a 24-hour urinary calcium, serum calcium and serum PTH of all postmenopausal women with osteoporosis, and a TSH of those on chronic supplementation (113).

Definition of Prevention and Treatment Strategies and the Evidence for Intervention:

- **Prevention** is defined by primary prevention; i.e., prevention of bone loss in early postmenopausal women without established osteoporosis (with a BMD T-Score between –1 and –2.5).
- **Prevention** studies are conducted with a primary endpoint of BMD not fracture. In these women, the absolute risk of fracture is very low; thus, within the relatively short time frame of the majority of these studies, anti-fracture efficacy cannot be tested. As with any preventive treatment, prevention of osteoporosis should be cost-effective and easy to use in large populations.
- **Treatment** is defined as reduction in fracture risk in postmenopausal women with established osteoporosis (BMD T-Score below –2.5, with or without a previous prevalent fracture). Usually, the much higher risk of fragility fracture in the treatment populations of late (older) postmenopausal women enables assessment of anti-fracture efficacy.

To help in evaluating known evidence related to these interventions, the Royal College of Medicine established the following grading of evidence. The grading of evidence levels, as well as Tables I and II,

are taken from the *Royal College of Medicine Guidelines*, updated in July 2000 (114). The United States Preventive Services Task Force and the Osteoporosis Society of Canada have also recently reviewed osteoporosis treatment efficacy and issued clinical guidelines for osteoporosis screening (34,115).

Grade A:

Meta-analysis of randomized clinical trials (RCT) or at least one RCT. At least one well-designed controlled study without randomization. Valid cohort study for prognosis or risk assessment purposes.

Grade B:

At least one other type of well-designed quasi-experimental studies. Well designed non-experimental descriptive studies (comparative, correlations or case-control studies).

Grade C:

Expert committee reports/opinions and/or clinical experience of authorities.

Among the risk factors for osteoporosis, some may be modified through behavioral or environmental interventions (see Tables I and II), whereas others may be targets for pharmacological intervention.

A. General or universal measures:

There are many non-pharmacological interventions that might decrease the number of osteoporotic fractures, but not all have been subjected to rigorous definite assessment. Strategies based on data generated from observational studies or trials with surrogate endpoints include (28, 34):

1. Provision of a diet which maintains normal body weight throughout life and provides a total elemental calcium intake (from dietary and supplemental sources) of some 1000 mg/day from late childhood to midlife; and 1500 mg after age 65 years.
2. Encouragement of a physically active lifestyle.

3. Avoidance of smoking and of high alcohol intake.
4. Promotion of vitamin D supplementation with 600-800 IU of vitamin D per day and/or regular time spent outdoors in the elderly.
5. Fall prevention programs in the elderly and use of hip protectors in those at very high risk of falls.

B. Pharmacological interventions:

The aim of osteoporosis management is to reduce the incidence of both vertebral and hip fractures. Consistent anti-fracture efficacy is demonstrated in postmenopausal women with established osteoporosis for:

1. Radiographic and clinical vertebral fractures with alendronate, risedronate and raloxifene (116–120).
2. Clinical non-spine fracture with alendronate and risedronate (116–119).
3. Hip fractures in community-dwelling women with alendronate and risedronate (116, 121).
4. Post-hoc analyses demonstrated the efficacy of bisphosphonates in the prevention of morphometric vertebral fractures in postmenopausal women treated with corticosteroid-induced bone loss, see below (122–124).
5. Data on anti-fracture efficacy in men is very scarce (125–126).
6. There are no data on the use of anti-resorptive therapies in normally cycling premenopausal women, since use of such therapy in this group of women is unwarranted.

As to whether efficacy on fracture risk is demonstrated with bisphosphonates in postmenopausal women with unknown or low bone density, this has been answered in two studies. In the osteopenic arm of the FIT study (127) and in the elderly arm of the HIP study (121), there was no evidence of anti-fracture efficacy in non-osteoporotic women (T-Score higher than -2.5). In studies with both alendronate and risedronate, BMD increased to the same extent in osteopenic as in osteoporotic women, but a significant decrease in

fractures could be demonstrated only in osteoporotic women. However, analyses from the MORE trial suggest vertebral fracture reduction with raloxifene in women with osteopenia at the hip (128). There is, albeit less abundant, evidence-based data for anti-fracture efficacy of intranasal calcitonin and etidronate in postmenopausal women (129–132). Hormone replacement therapy was supported with strong evidence from the Women’s Health Initiative as an efficient means to prevent hip as well as non-vertebral fractures. However, the increased risk of breast cancer and cardiovascular mortality may offset the bone benefits observed (133).

Anti-fracture efficacy of Ca/D has been demonstrated for spine, non-vertebral and hip fractures only, in nursing homes and in elderly individuals with low intakes of those nutrients at baseline (134,135). However, in most randomized controlled trials over the last decade, pharmacological agents other than Ca and Vitamin D have provided benefits beyond those of calcium and vitamin D, as Ca/D has been the treatment strategy in the “placebo” arm of most of these trials.

A direct comparison of the relative anti-fracture efficacy of the various osteoporosis therapies is not possible. However, the overwhelming evidence for anti-fracture efficacy is derived from studies using second-third generation bisphosphonates such as alendronate and risedronate, in which over 15,000 patients were enrolled in the respective randomized controlled trials.

Four randomized controlled trials have demonstrated the efficacy of bisphosphonates in the maintenance of bone mass in patients on chronic corticosteroid-therapy, whether used in a primary prevention mode (that is when bisphosphonate therapy is instituted at the start of steroid therapy) for etidronate, and risedronate (122, 124) or in secondary prevention mode (that is when bisphosphonate therapy is instituted after patients have been on chronic steroid

treatment) for alendronate and risedronate (123,136). Post-hoc analyses in these studies also demonstrated the efficacy (or trend of efficacy) of etidronate, risedronate and alendronate in the prevention of morphometric vertebral fracture in the subgroup of postmenopausal women only (122–124). Bisphosphonates are approved by the FDA for patients on chronic glucocorticoid therapy.

C. Treatment strategies guidelines published to date:

Since the early 1990s and with the increasing evidence for a relatively rapid rate of treatment onset and variable timing of offset for these interventions, there has been a move away from long-term preventive strategies towards the use of shorter-term therapy in high risk individuals. In addition, pharmacological interventions are expensive and should, therefore, be targeted for those at highest risk of fracture in order to be most cost-effective. To-date, treatment guidelines are still uniformly anchored around DXA-based BMD T-Scores. This is anticipated to change once algorithms that provide 5 or 10 yr fracture risks based on BMD and clinical risk factors are fully developed and validated.

Universal measures are recommended in all the population, especially in women with osteopenia or osteoporosis, as they are cost-effective and safe. Furthermore, most of the guidelines published to date favor pharmacologic intervention in high-risk individuals, as defined with a T-Score of <-2.5 or a T-Score of <-2 in the presence of additional independent risk factors for fracture (28, 33, 36). These would include, high on the list, prevalent fracture at entry and glucocorticoid use. Indeed, the number needed to treat to prevent a vertebral fracture in older postmenopausal women with a low T-Score at entry and prevalent fractures varied between 9 and 20, depending on the study (116,118–120,133,137). In similar analyses of treatment conducted on older

postmenopausal women with a BMD T-Score at entry of less than 2.5 but without fractures, the number was calculated at 35 for alendronate and 45 for raloxifene (116,120). In contrast, subgroup analyses of the FIT trial revealed that the number needed to treat to prevent a vertebral fracture, even in older postmenopausal women, increased from 35 if the T-Score at study entry was <-2.5 , to 59 if the entry T-Score was between -2 and -2.5 , and went as high as 363 for older postmenopausal women with an entry T-Score between -1.6 and -2 (116). Despite the increasing awareness of people as well as physicians about osteoporosis and its related complications, a high percentage of people with osteoporotic fractures remain untreated (99, 138). This paradox between scientific data and current clinical practice is common worldwide (138)—in particular in Lebanon, where a recent study has shown that no more than 5% of people over 50 with a fracture were receiving anti-resorptive treatments (99).

D. In conclusion:

The only patients in whom fracture prevention with pharmacological intervention has been proven are those at high risk of fracture: elderly postmenopausal women with preexisting fracture or with a BMD T-Score lower than -2.5 , or postmenopausal women on chronic glucocorticoid therapy, albeit with more limited evidence. Treating young postmenopausal women who do not have osteoporosis for several years with anti-resorptive therapy preserves bone density, but it does not seem to be associated with reduction in spine or hip fractures. Therefore, the timing of the institution of pharmacological intervention in that subgroup after menopause remains to be determined.

TREATMENT OF ACUTE VERTEBRAL FRACTURE

Treatment of acute and chronic pain related to vertebral fractures depends on specific

measures and not on anti-osteoporotic drugs. The measures used include pain-killers, NSAIDs, bed rest, back support and soft massages, as well as mild exercises for sub-acute and chronic pain, although there are no trials to assess the efficacy of any of the above. Calcitonin may have additional analgesic effects. Vertebroplasty—that is, injection of intra-vertebral metacrylate—can be helpful in alleviating morbidity from vertebral fractures in the case of prolonged pain or refractory conditions. It should not be routinely used, as its safety and long-term effects are unknown (139,140).

RECOMMENDATIONS FOR WHEN TO TREAT

The universal measures recommended independent of BMD measurement:

- *Maintain a physically active lifestyle with adequate exposure to sunlight.*
- *Avoid smoking and high alcohol intakes.*
- *Maintain a total dietary calcium intake of around 1.5 gm of elemental calcium in postmenopausal estrogen-deficient women or men >65 years, as well as a vitamin D intake of 600 to 800 IU/day, even under the sun-drenched latitudes of Lebanon. Provide calcium and vitamin D supplementation to the elderly.*
- *Avoid a low weight <60 kg in men or < 50 kg in women or a low body mass index (BMI) of <20 kg/m².*
- *The prevention of osteoporosis begins with optimal bone mass acquisition during growth. Factors hindering bone mass acquisition, such as malnutrition, should be considered, identified and addressed during childhood.*
- *Address known factors that stimulate bone resorption or inhibit bone formation, including hypogonadism, primary hyperparathyroidism,*

hyperthyroidism and hypercortisolism.

- *Develop fall prevention awareness and programs in the elderly, including hip protection and/or soft floor covering in elderly environment.*

Pharmacological Intervention:

It is warranted in high-risk individuals. BMD assessment is pivotal in clinical decision-making regarding pharmacological interventions. Specifically, it is definitely indicated in postmenopausal women who:

- 1. Have a BMD T-Score of < -2.5 .*
- 2. Show prevalent fragility fractures of the vertebrae, as further documented with low BMD.*
- 3. Are on chronic corticosteroid therapy, with a BMD T-Score of < -1.5 .*

No clear evidence is available to demonstrate the efficacy of pharmacological intervention in postmenopausal women with $-2.5 < T\text{-score} < -1$ in the absence of fragility fractures. No treatment (in addition to universal measures) is indicated if the BMD T-Score is > -1 .

In pre-menopausal women:

All known treatments were studied in postmenopausal women, hence their efficacy in premenopausal women is unknown. Thus, in the absence of any established treatment for normally cycling premenopausal women with low bone density, such patients should be referred to specialized centers for investigation of possible underlying causes and advice on further management. Treatment should not be started in such patients before appropriate investigations and diagnoses are achieved.

In men:

Given the small number of osteoporosis studies done on men, no definite recommendations other than universal measures can be made for men. These universal measures, as outlined above, include reversal of conditions associated with bone loss. Preliminary data from one trial only suggests treatment efficacy of high-risk individuals with alendronate. Alendronate is approved by the FDA for the treatment of low bone mass in men.

Treatment is probably indicated in men who:

- 1. Who show prevalent fragility fractures, as further documented with low BMD.*
- 2. Are > 70 years and have a BMD T-Score of < -2.5 .*
- 3. Are on chronic (> 3 months) corticosteroid therapy and have a BMD T-Score of < -1.5 .*

Treatment is less definitely indicated in men who:

- 1. Have $-1 < T\text{-score} < -2.5$ in the presence of risk factors.*
- 2. Are < 70 years and have a T-Score of < -2.5*

The above guidelines are meant to provide a structural framework to be used by the physician treating the patient at risk for or with osteoporosis. They are certainly not meant to supercede the ultimate decision of the practicing physician. In the case of rare and/or difficult cases, referral to an osteoporosis specialist is highly recommended. We anticipate periodic revisions of these guidelines, based on forthcoming data on osteoporosis locally and our evolving knowledge about this silent disease.

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Table I: Bone- and non-bone-related risk factors for fractures

A. Bone-Related Risk Factors

- White or Asian women (genetic factors)
- Low BMD
- Maternal history of hip fracture
- Early menopause
- Prolonged amenorrhea
- Preexisting fracture
- Low trauma fracture since age 45
- Thin body build
- Chronic CS use
- Medical conditions predisposing to osteoporosis (see Table II)
- High bone turnover

B. Non-Bone-Related Risk Factors

- Age > 65
- Propensity to falls
- Medications: anxiolytics, sedatives
- Neurologic disorders leading to altered vision/proprioception

Smoking, alcohol use and physical inactivity are less strong risk factors.

Table II: Causes of osteoporosis/osteopenia

1. Genetic
 - White or Caucasian
 - Maternal family history
 - Thin body habitus
 - Genetic polymorphisms: Vitamin D receptor, COLA1, Estrogen receptor
2. Lifestyle/Nutritional
 - Smoking
 - Excessive alcohol
 - Prolonged amenorrhea
 - Inactivity/Prolonged immobilization/Spaceflights
3. Medical Conditions
 - Endocrine
 - Anorexia nervosa
 - Hypogonadism
 - Hypercortisolism
 - Hyperparathyroidism
 - Hypercalciura
 - Prolactinomas
 - Thyrotoxicosis
 - ? Diabetes
 - Connective tissue/Rheumatologic
 - Osteogenesis imperfecta
 - Scurvy
 - Homocystinuria
 - Ehlers-Danlos syndrome
 - Ankylosing spondylitis
 - Rheumatoid arthritis
 - Process affecting the marrow
 - Multiple myeloma
 - Leukemia, lymphoma
 - Anemias-sickle cell disease, thalassemia
 - Gastrointestinal (GI) diseases
 - Cystic fibrosis
 - Post-gastrectomy
 - Primary biliary or alcoholic cirrhosis
 - Malabsorption /Sprue
 - Crohn's disease
 - Others
 - Post-transplantation
 - Renal failure chronic
4. Drugs
 - Anticonvulsants
 - Cyclosporine
 - Chemotherapy
 - Glucocorticoids
 - GnRH agonists
 - Heparin
 - Excess thyroid hormone
 - Methotrexate?
 - Aromatase Inhibitors

(Adapted from El-Hajj Fuleihan, G., 1999.. Leb Med J 47:221–228.)

Table III: Effect of interventions on the prevention/reduction of postmenopausal bone loss (BMD data as an endpoint)

Calcium	A
Vitamin D + Calcium	A
Physical exercise	A
Cessation of smoking	B
Reduced alcohol consumption	C
HRT	A
Alendronate	A
Raloxifene	A
Risedronate	A
Calcitonin	A
Calcitriol	A
Cyclic Etidronate	A
Tibolone	A

Table IV: Anti-fracture efficacy of interventions in the treatment of postmenopausal osteoporotic women (fracture data as an endpoint)

Grade	Spine	Non-vertebral	Hip
Calcium	A	B	B
Vitamin D	nd	B	B
Vitamin D + Calcium	nd	A	A
Physical exercise	nd	B	B
Hip protectors	-	-	A
HRT	A	A	A
Alendronate	A	A	A
Raloxifene	A	nd	nd
Risedronate	A	A	A
Calcitonin	A	B	B

nd = not demonstrated