WHO SCIENTIFIC GROUP ON THE ASSESSMENT OF OSTEOPOROSIS AT PRIMARY HEALTH CARE LEVEL

Summary Meeting Report
Brussels, Belgium, 5-7 May 2004

World Health Organization

CONTENTS

OVERVIEW

A WHO Scientific Group on the Assessment of Osteoporosis at the Primary Health Care Level met in Brussels from 5 to 7 May 2004. The meeting was opened by Dr N. Khaltaev, Responsible Officer for Chronic Respiratory Diseases and Arthritis, who welcomed the participants on behalf of the Director-General of the World Health Organization (WHO).

Background

Following the publication of the report of a WHO Study Group meeting on *Assessment of fracture risk and its application to screening for postmenopausal osteoporosis,* osteoporosis has been recognized as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan *(1)*. Osteoporosis causes more than 8.9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe *(Table 1.1)*. The lifetime risk for a wrist, hip or vertebral fracture has been estimated to be in the order of 30% to 40% in developed countries – in other words, very close to that for coronary heart disease. Osteoporosis is not only a major cause of fractures, it also ranks high among diseases that cause people to become bedridden with serious complications. These complications may be life-threatening in elderly people. In the Americas and Europe osteoporotic fractures account for 2.8 million disability-adjusted life years (DALYs) annually, somewhat more than accounted for by hypertension and rheumatoid arthritis *(2)*, but less than diabetes mellitus or chronic obstructive pulmonary diseases *(Fig. 1.1)*. Collectively, osteoporotic fractures account for approximately 1% of the DALYs attributable to noncommunicable diseases.

Figure 1: Burden of diseases estimated as disability-adjusted life years (DALYs) in 2002 in the Americas and Europe combined
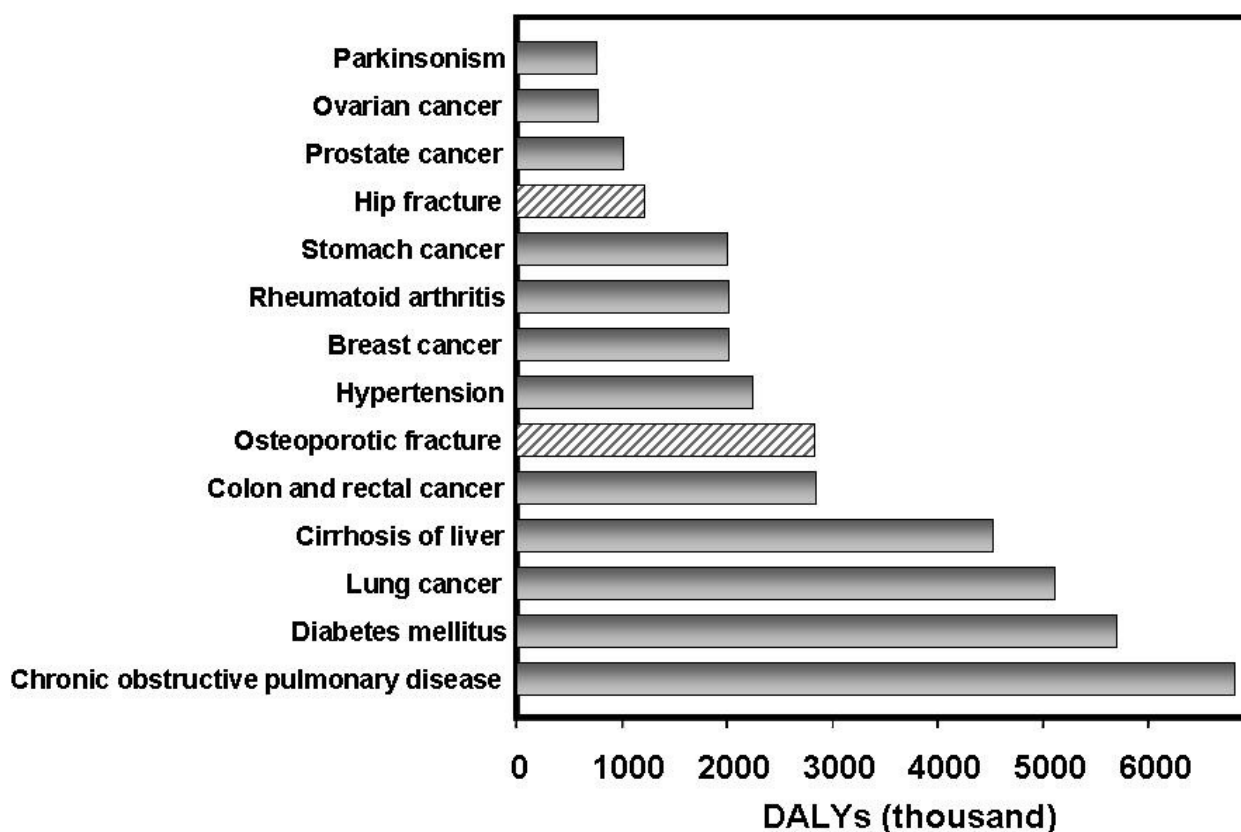
Source: reference *2* (data extracted from Annex Table 3, pp. 126-131) and WHO unpublished data.

Table 1: Estimated number of osteoporotic fractures by site, in men and women aged 50 years or more in 2000, by WHO region

WHO region	Expected number of fractures by site (thousands)				All osteoporotic fractures	
	Hip	Spine	Proximal humerus	Forearm	No.	%
Africa	8	12	6	16	75	0.8
Americas	311	214	111	248	1 406	15.7
South-East Asia	221	253	121	306	1 562	17.4
Europe	620	490	250	574	3 119	34.8
Eastern Mediterranean	35	43	21	52	261	2.9
Western Pacific[a]	432	405	197	464	2 536	28.6
Total	1 672	1 416	706	1 660	8 959	100

Source: O Johnell & J A Kanis, unpublished data, 2006.
[a] Includes Australia, China, Japan, New Zealand and the Republic of Korea.

Because of the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population. In May 1998, the Fifty-first World Health Assembly, having considered *The world health report 1997: conquering suffering, enriching humanity (3)*, which described the high rates of mortality, morbidity and disability from major noncommunicable diseases – including osteoporosis, adopted a resolution requesting the Director-General to formulate a global strategy for the prevention and control of noncommunicable diseases *(4)*. A scientific group meeting subsequently reported on the prevention and management of osteoporosis *(5)*. The report of the present Scientific Group on Assessment of Osteoporosis at the Primary Health Care Level is a further step in the development of cohesive strategies for tackling osteoporosis in response to the World Health Assembly resolution *(4)*. It is expected that the report of this meeting will lead to improvements in the assessment of osteoporosis patients throughout the world, and make a valuable contribution to the development of effective global strategies for the control of this important disease.

Osteoporosis has been operationally defined on the basis of bone mineral density (BMD) assessment. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <-2.5 SD) *(1,6)*. This criterion has been widely accepted and, in many Member States, provides both a diagnostic and intervention threshold. The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DXA), and diagnostic criteria based on the T-score for BMD are a recommended entry criterion for the development of pharmaceutical interventions in osteoporosis *(7–9)*. Since therapeutic trials in osteoporosis usually require a low BMD value as an entry criterion, drugs are licensed for use in patients below a given BMD threshold. The implication is that BMD should be assessed before treatment is considered.

There are, however, several problems with the use of BMD tests alone. In many Member States, BMD tests using DXA are not widely available, or are used predominantly for research, in part because of the high capital costs of DXA. In other Member States, BMD tests are not reimbursed despite the availability and approval of effective drug treatments. For this reason, many other techniques for measuring bone mineral have been developed, which have lower costs and are more portable. The experience with several of these is limited, however, and there is no clear guidance as to how these should be used with or without DXA, either for the diagnosis of osteoporosis or for the assessment of fracture risk. This report updates criteria for the diagnosis of osteoporosis in the light of these developments.

A second major problem with bone mineral measurement is that these tests alone are not optimal for the detection of individuals at high risk of fracture. Over most reasonable assumptions, the tests have high specificity but low sensitivity (1). In other words, the risk of fracture is very high when osteoporosis is present, but by no means negligible when BMD is normal. Indeed, the majority of osteoporotic fractures will occur in individuals with a negative test. Thus, the potential impact of widespread testing of BMD on the burden of fractures is less than optimal, and this is one of the reasons why many agencies do not recommend population screening of BMD (1,10,11). Current recommendations for the assessment of patients also have several difficulties. None is suitable for international use. Those produced by nongovernmental organizations are either conservative, e.g. the European Foundation for Osteoporosis guidelines (12), or border on a population screening strategy, e.g. National Osteoporosis Foundation of the USA (13–15). Both approaches rely critically on testing of BMD, and there is little guidance for Member States without such facilities.

In the past decade, a great deal of research has taken place to identify factors other than BMD that contribute to fracture risk. Examples include age, sex, the degree of bone turnover, a prior fracture, a family history of fracture, and lifestyle risk factors such as physical inactivity and smoking. Some of these risk factors are partially or wholly independent of BMD. Independent risk factors used with BMD could, therefore, enhance the information provided by BMD alone. Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. For this reason, the consideration of well-validated risk factors, with or without BMD, is likely to improve fracture prognostication and the selection of individuals at high risk for treatment.

Against this background, WHO approved a programme of work within the terms of reference of the WHO Collaborating Centre at Sheffield. The project also had the support of the International Osteoporosis Foundation, the National Osteoporosis Foundation (USA), the International Society for Clinical Densitometry and the American Society for Bone and Mineral Research. A position paper on the general approach was endorsed by the International Osteoporosis Foundation and the United States National Osteoporosis Foundation (16). The aims of the programme were to identify and validate clinical risk factors for use in fracture risk assessment on an international basis, either alone, or in combination with bone mineral tests. A further aim was to develop algorithms for risk assessment that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available.

Risk factors

Risk factors for any osteoporotic fracture and for hip fracture were identified from 12 prospectively studied population-based cohorts in many geographic territories using the primary databases. The cohorts included the European Vertebral Osteoporosis Study (Pan-European), the Dubbo Osteoporosis study (Australia), the Canadian Multicentre Osteoporosis study (Canada), Rochester (USA), Sheffield (UK), Rotterdam (Netherlands), Kuopio (Finland), Hiroshima (Japan), the OFELY (*L'os des femmes de Lyon*) cohort from Lyon and the multicentre EPIDOS (*Epidémiologie de l'osteoporose*) cohort from France, and two cohorts from Gothenburg (Sweden). The cohort participants had a baseline assessment documenting clinical risk factors for fracture. Approximately 75% also had BMD measured at the hip. The follow-up was approximately 250 000 patient–years in 60 000 men and women during which more than 5000 fractures were recorded.

Model synthesis

Work over the past few years has clarified many of the features necessary for improved patient assessment. A central component is that the diagnostic criterion for osteoporosis using the WHO definition is not always an appropriate threshold to identify patients at high fracture risk for intervention. The use of the T-score alone is inappropriate since age is as great a risk factor as BMD. Rather, thresholds should be based on a more global evaluation of risk, and in particular on that risk which is amenable to an intervention (i.e. modifiable risk). There are problems with the use of relative risks, and these have contributed to the view, now increasingly accepted, that the risk of patients for fracture should be determined according to absolute probability of fracture. A 10-year probability of fracture is preferred to lifetime risks because:

■ Assumptions on future mortality introduce increasing uncertainties for risk assessment beyond 10 years.

■ Treatments are not generally given feasibly over a lifetime.

■ The long-term prognostic value of some risk factors may decrease with time.

■ The 10-year interval accommodates clinical trial experience of interventions (generally 3–5 years) and the reversal phase (offset time) when treatment is stopped.

Models have been created that are based on the hazard functions for fractures and for death in Sweden, which are used to compute the long-term probability of different fracture types. The models accommodate risk factors such as age, sex, BMD at the hip (femoral neck) and clinical risk factors that have proven international validity.

The first operational model was based on Sweden because of the robustness and extent of the epidemiological data available in that country. Fracture rates, however, differ markedly in different regions of the world. Even within Europe, the risk of hip fracture varies more than 10-fold between countries *(17,18)*, and there is comparable variation in the rate of hospitalization for vertebral fracture *(19)*. The lowest absolute risk of hip fracture is found in the developing world, in part because of the lower fracture risk, but also because of lower life expectancy.

Notwithstanding, the general pattern of osteoporotic fracture is broadly similar across nations. Since extensive epidemiological data exist worldwide for hip fracture, the methodology has been extended to quantify osteoporotic fracture probabilities where hip fracture rates alone are available. This permits probabilities of fracture to be quantified in many regions of the world. Separate models have been constructed for countries with very high risk (e.g. Scandinavia), high risk (e.g. western Europe), moderate risk (e.g. southern Europe) and low risk (e.g. the developing countries). The models have been validated in independent cohorts that did not participate in the model construct.

The choice of risk factors examined was governed by availability of data, and the ease with which the risk factors might be used in primary care. Potential risk factors were examined by a series of meta-analyses using

Poisson models for each risk factor in each of the study cohorts and for each sex. Covariates examined included age, sex, BMD, time since assessment and the covariate itself, e.g. to determine whether BMD or body mass index (BMI) are equally predictive for fracture at different levels of BMD or BMI. Results from the different studies were merged using the weighted β-coefficients.

Candidate risk factors included age, sex, glucocorticoid use, secondary osteoporosis, family history, prior fragility fracture, low BMI, smoking, excess alcohol consumption and femoral neck BMD. Risk factors for falling were not considered, since there is some doubt whether the risk identified would be modified by a pharmaceutical intervention. Risk factors recommended for use were selected on the basis of their international validity and evidence that the identified risk was likely to be modified by subsequent intervention (modifiable risk). Modifiable risk was validated from clinical trials (BMD, prior fracture, glucocorticoid use, secondary osteoporosis), or partially validated by excluding interactions of risk factors on therapeutic efficacy in large randomized intervention studies (e.g. smoking, family history, BMI).

A further step was then to merge these meta-analyses of each risk factor so that account could be taken of the interdependence of the risk factors chosen, and therefore the risk provided by any combination of risk factors, with and without the additional use of BMD.

The prediction of hip fracture and other osteoporotic fractures was based on the assessment algorithms (FRAX™) which includes clinical risk factors alone, or the combination of clinical risk factors plus BMD (available at www.shef.ac.uk/FRAX). The FRAX algorithms are suitable for men and women. Guidance is given on the economic use of BMD where resources for BMD exist but must be used sparingly.

Given that the probability of fracture can be quantified, information is required on the level of risk that is sufficiently high to merit intervention. This is a complex issue that depends on the wealth of Member States, the place of osteoporosis in the health-care agenda and the proportion of gross domestic product spent on health care, as well as on fracture risk. Against this background, intervention thresholds will vary markedly around the world. Examples of intervention thresholds are provided, based on cost-effectiveness analyses which can be tailored to national requirements. There will be some Member States where supportive programmes only are appropriate, such as attention to adequate physical activity, nutrition and the avoidance of smoking. In other Member States, case-finding can be based on the use of clinical risk factors alone. In many developed countries, the clinical risk factors can be used with the selective use of BMD. There will be segments of society or countries where BMD will always be used. The guidance in this report accommodates these very different approaches to case-finding.

Possibilities for the future

Until recently, osteoporosis was an under-recognized disease and considered to be an inevitable consequence of ageing. Perceptions have changed since epidemiological studies have highlighted the high burden of the disease and its costs to society and health care agencies, as well as the adverse effects on millions of patients worldwide. The past 15 years have seen major improvements in diagnostic technology and assessment facilities; it is now possible to detect the disease before fractures occur. This has been associated with the development of treatments of proven efficacy *(4)*.

The scope of the report is to direct attention away from the sole use of BMD to determine who will receive treatment and to shift towards the assessment of absolute fracture risk, whether this be determined by BMD testing or other validated instruments. The use of clinical risk factors together with BMD provides a mechanism for the effective and efficient delivery of health care to individuals at high risk and the avoidance of unnecessary treatment to others. The application of this approach may be expected to reduce, though not eliminate, the burden of osteoporotic fractures.

Against this background, WHO has considered osteoporosis to be of increasing importance. The former Director-General of WHO, Dr Brundtland, has stated that "WHO sees the need for a global strategy for prevention and control of osteoporosis focusing on three major functions; prevention, management and surveillance" *(20)*. In order to amplify the existing and past activities of WHO in osteoporosis, the object of this Scientific Group meeting was to review the scientific basis for the identification of patients at high or low risk of osteoporotic fracture with or without the use of BMD. The aim was to optimize the detection of high risk patients so that therapy can be better directed. The meeting did not consider specific pharmacological interventions. Rather, the approach to be developed was a case-finding strategy where risk factors are identified to quantify absolute risks.

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

The following conclusions and recommendations for research represent the unanimous views of the Scientific Group.

With the development of treatments that favourably alter the natural history of osteoporosis, there is an increasing need to develop strategies for fracture risk assessment so that treatments can be targeted more effectively to those in need and, conversely, that unnecessary treatment can be avoided in those at low risk of fracture.

Consequences of osteoporosis

Age-related bone loss is asymptomatic, and the morbidity of osteoporosis is secondary to the fractures that occur. Common sites of fracture include the spine, hip, forearm and proximal humerus.

Fractures at the hip incur the greatest morbidity and mortality, and give rise to the highest direct costs for health services. Their incidence increases exponentially with age.

Osteoporotic fractures at other sites are generally of less economic significance, but they also give rise to significant morbidity and, in some instances, to increased mortality. They occur more commonly than hip fractures at younger ages, and their neglect in evaluating assessment strategies disadvantages the younger segment of the osteoporotic population.

The remaining lifetime probability of osteoporotic fractures in women at the age of 50 years exceeds 40% in developed countries. For hip fracture alone, the remaining lifetime probability at the age of 50 years exceeds 20% in women in these countries. In many regions of the world, the risks in men are about half those of women.

The number of osteoporotic fractures is certain to increase in both men and women (by more than 3-fold over the next 50 years) as a result of the ageing population. The major increases will occur outside of Europe and the United States, particularly in Asia and Latin America.

Over and above changes in population demography, the age- and sex-specific incidence of osteoporotic fractures appears to be increasing in developing countries. This may more than double the expected burden of osteoporotic fractures over the next 50 years.

The age- and sex-specific incidence of hip fracture varies markedly around the world, as does the incidence of other osteoporotic fractures. For hip fracture, age- and sex-specific incidence varies by more than 10-fold. More modest variations are observed for vertebral fracture risk.

Reasons for the secular changes and geographic variations in fracture risk are unknown, but cannot be explained completely on the basis of differences in bone mineral density.

In high-income countries, osteoporotic fractures account for more hospital bed days than those for myocardial infarction, breast cancer or prostate

cancer. The burden of hip fracture alone accounts for 1.4% of disability-adjusted life years in the established market economies.

Bone mineral measurements and diagnosis of osteoporosis

Many techniques are available to assess bone mineral at multiple sites including those where osteoporotic fractures predominate. The most widely validated technique is dual energy X-ray absorptiometry (DXA) applied to sites of biological relevance, including the hip, spine and forearm.

The pivotal requirement for the use of bone mineral testing in diagnosis and assessment of osteoporosis is its performance characteristics for fracture prediction.

There are significant differences in the performance of different techniques to predict fractures at different skeletal sites. For the prediction of any fracture, DXA at sites of biological relevance gives measurements of bone mineral density (BMD) that predict fracture with an increase in fracture risk of approximately 1.5/SD decrease in bone mineral density (termed the gradient of risk). The highest gradient of risk is provided by DXA at the femoral neck for hip fracture prediction, where the gradient of risk is approximately 2.6/SD.

The validation of BMD measurements and the increase in epidemiological information permit diagnostic criteria for osteoporosis to be more precisely defined than previously. The international reference standard for the description of osteoporosis in postmenopausal women and in men aged 50 years or more is a femoral neck BMD of 2.5 SD or more below the young female adult mean, using normative data from the NHANES reference database on Caucasian women aged 20–29 years.

Although the reference standard for the description of osteoporosis is BMD at the femoral neck, other central sites (e.g. lumbar spine, total hip) can be used for diagnosis in clinical practice.

T-scores should be reserved for diagnostic use in postmenopausal women and men aged 50 years or more. With other technologies, and other populations, measurement values should be expressed as Z-scores, units of measurement or preferably in units of fracture risk.

Provision is still made for the description of osteopenia as a T-score at the femoral neck of between –1.0 SD and –2.5 SD below the young female adult mean.

Clinical risk factors for fracture

A plethora of clinical risk factors have been identified that are associated with an increase in fracture risk. In many instances their suitability for inclusion in assessment algorithms for the prediction of fracture has not been well validated. In this report, evidence-based criteria are developed for the assessment of risk factors including for BMD. These include hierarchical levels of evidence for the ability of risk factors to identify a fracture risk that is modifiable by pharmacological interventions.

Risk factors validated by their use as inclusion criteria in randomized controlled trials include low BMD (DXA at spine or hip), prior vertebral fracture, long-term glucocorticoid treatment, and age. Risk factors that do not adversely affect the efficacy of intervention in randomized controlled trials include family history of fracture, prior non-vertebral fracture, biochemical markers of bone turnover, peripheral measurements of bone mineral including quantitative ultrasound at the heel, smoking, body weight or body mass index, and alcohol intake.

In this report, the international validity of candidate risk factors was examined by meta-analyses of population-based cohorts from Asia, Australia, Europe and North America. Risk factors were assessed by age, sex, duration of follow-up, and their dependence on BMD. Those validated comprised BMD at the femoral neck, low body mass index, a prior fragility fracture, glucocorticoid exposure, a parental history of (hip) fracture, smoking, excessive intake of alcohol, and rheumatoid arthritis.

The interdependent relationship among these risk factors was used to construct models of fracture probability.

Other risk factors of potential utility, but less extensively validated, included BMD measured at the spine or total hip, quantitative ultrasound applied to the heel, peripheral estimates of BMD, and biochemical indices of bone turnover.

Assessment tools for case-finding

Screening with BMD is recommended in some Member States, most notably in North America, but is not widely practised elsewhere. Reasons include the lack of availability of machines, variable access, expense, and poor sensitivity (detection rate for future fractures) when specificity is high.

Current evidence-based guidelines focus on the use of BMD as a criterion for intervention.

Several algorithms are available for the prediction of osteoporosis with the use of clinical risk factors alone. The most widely tested predictor of osteoporosis is the osteoporosis self-assessment tool. These tools have comparable performance characteristics with high sensitivity (detection rate) but poor specificity. The high sensitivity provides opportunities for cost savings by excluding patients who do not need a BMD assessment. Such tools require calibration in each Member State because of heterogeneity in sensitivity and specificity. They have not been well validated in men.

Sensitivity is improved by the use of multiple independent risk factors and can be used to optimize the prediction of fracture. Four FRAX™ assessment models have been constructed from the meta-analyses of risk factors for the calculation of fracture probabilities. These comprise the 10-year probability of hip fracture, with and without BMD at the femoral neck, and the 10-year probability of other osteoporotic fractures, with and without BMD at the femoral neck. Other osteoporotic fractures comprise forearm, clinical spine and proximal humerus fractures. The probability of any osteoporotic fracture is, therefore, underestimated. The FRAX algorithms are suitable for use in men (from the age of 41 years) and women from the age of menopause.

For hip fracture prediction, the use of BMD at each age out-performed the use of clinical risk factors alone in predictive value, but clinical risk factors in combination with BMD improved the gradient of risk still further, so that the test had improved sensitivity without loss of specificity. For the prediction of other osteoporotic fractures, gradients of risk with clinical risk factors were marginally improved with the addition of BMD, but the performance characteristics were as good as, or better than, the assessment of risk with BMD using peripheral measurements. The performance characteristics have been validated in several independent cohorts from different regions of the world.

The FRAX models were calibrated to different Member States to reflect the high heterogeneity in fracture risk worldwide. These included countries at very high risk (Sweden, United States), at high risk (United Kingdom), at moderate risk (China, Japan and Spain), and at low risk (Turkey). The models are available at www.shef.ac.uk/FRAX.

The FRAX models can be simplified with the omission of some of the clinical risk factors, making them amenable to paper versions.

Fracture probabilities assume clinical utility once an intervention threshold is established, namely the risk above which intervention is worthwhile. Intervention thresholds should be fixed by Member States and will depend upon the priorities that osteoporosis has in a region or country, the absolute risk of fracture, and the ability to pay. An example, based on cost–utility analysis, is provided for the United Kingdom.

Assessment and the formulation of therapeutic strategy

Population-based (i.e. public health) prevention programmes are appropriate for all Member States. Global programmes should include attention to nutritional factors, particularly related to adequate intakes of calcium and vitamin D. Cigarette smoking should be avoided, not solely because of its possible effects on skeletal metabolism, but for the many other adverse effects associated with smoking. Preventing excessive alcohol consumption and the avoidance of immobility are also recommended as public health measures.

In Member States without access to densitometry, case-finding strategies can be pursued with use of clinical risk factors alone. The performance characteristics of the FRAX model are at least as good as those provided by peripheral assessment of BMD.

In Member States where BMD is universally recommended (e.g. at the age of 65 years or more in North America), the stratification of risk can be improved by consideration of clinical risk factors in conjunction with BMD. This is particularly valuable in the context of younger individuals for hip fracture prediction.

In Member States with limited access to DXA, clinical risk factors can be used to stratify target populations to those at very high risk in whom a BMD test would not alter their risk category, those with very low risk in whom a BMD would not alter the risk category, and those at intermediate risk where a BMD test would be helpful for the characterization of fracture probability.

The recommendations in this report are flexible and will require that Member States make suitable accommodation to cater for regional variations in medical care. Even so, the implementation of these recommendations poses many challenges for the future. There will need to be agreement on the principles of fracture risk reporting among stakeholders, including regulatory agencies, ministries of health, payers as well as the manufacturers of bone mineral measurement technologies. Ultimately, it will also become necessary to validate the responsiveness of patients so identified to the large number of interventions now available.

Recommendations for research

Health service data are required in many Member States on length of hospital stay, morbidity, mortality and institutionalization associated with osteoporotic fractures, together with the associated costs, so that osteoporosis can be placed in an adequate health-care perspective.

Hip fracture risks have been estimated for less than 40 Member States, and risks for other osteoporotic fractures in far fewer. More information is needed on the epidemiology of fracture so that FRAX algorithms can be calibrated for more communities.

The present approaches to the identification of patients at risk for fracture focus on a few clinical risk factors and on femoral neck BMD. More information is required on other risk factors and their validity to permit further refinements to the models available. Topics for study thus include:

- clinical risk factors for falls

- the use of DXA at other skeletal sites, such as the total hip and lumbar spine

- indices of bone turnover

- the use of other technologies, such as quantitative ultrasound

- secondary causes of osteoporosis other than rheumatoid arthritis.

Assessment algorithms need further validation in men and non-Caucasian populations.

Case-finding strategies require validation in clinical trials to test whether pharmacological agents reduce fracture risk in individuals identified by the use of clinical risk factors with and without the selective use of BMD.

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