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Short Report

Interim Report and Recommendations of the World Health Organization Task-Force for Osteoporosis

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Introduction

The World Health Organization has established a task force charged with the mission of developing a world-wide strategy for osteoporosis management and prevention. A direct response to the Fifty-first World Health Assembly Resolution on Noncommunicable Diseases Prevention and Control, this international osteoporosis education project – which is expected to improve the diagnosis and care of osteoporosis patients throughout the world – will include an emphasis on developing countries, and will provide a generic master document from which separate guidelines can be derived for the use of governments, health services, and individual patient groups.

The cornerstone of the project is the development of a master document on osteoporosis management and prevention. This document, developed in collaboration with leaders in osteoporosis research and patient care throughout the world, will be reviewed by the major academic, governmental and non governmental organi-

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zations concerned with osteoporosis before being submitted for approval by the World Health Organization. A series of 'Practical Guides for Osteoporosis Management' will be prepared from the master report. The Guides are intended for the use of primary care physicians throughout the world, and will be translated and adapted for clinical use in different cultures, medical communities and countries. The educational materials being developed for use in conjunction with the Guides, as well as the master document, will carry the scientific message of the WHO Task-Force on Osteoporosis and are expected to have a major impact on osteoporosis management throughout the world. An interim report will be published late this year, and the master document should be available in approximately two years. It will be disseminated to health care providers and purchasers globally, via the regional framework of the WHO.

To initiate this effort, a meeting was convened by Dr Nikolai Khaltaev, a responsible officer for the WHO Department of Noncommunicable Diseases Management, at WHO headquarters in Geneva in July 1998. A list of task force members was drawn up, representing approximately 25 leaders in osteoporosis from around the world, including the developed and developing countries. The major areas of the master document were outlined: Definition of the global problem; Epidemiology of osteoporosis; Diagnosis and Assessment; Pathogenesis; Prevention and Treatment; Socioeconomics; Delivery of Care and Education; and Summary and Recommendations.

The second meeting of the task force was held in September 1998 during the European Congress on Osteoporosis in Berlin. The mission of the working group was further defined and smaller groups were organized to work on specific chapters. In December 1998 the third meeting of the task force was convened in San Francisco, in conjunction with the ASBMR meeting. Outlines of the chapters were reviewed and revised, and plans were made to complete a draft document for review in the spring of 1999. The fourth meeting was held in June 1999 at WHO headquarters in Geneva. The drafts of the chapters were reviewed and it was decided to publish an interim report of the chapter summaries along with preliminary recommendations. The publication of this interim report in *Osteoporosis International* in October 1999 will coincide with 'World Osteoporosis Day' on October 20, 1999, which was proposed by the International Osteoporosis Foundation (IOF), cosponsored by WHO and endorsed by the National Osteoporosis Foundation (of the USA).

Finally, in the winter of 2000, after input and reviews by relevant national and international societies with an interest in osteoporosis, the completed chapters will be combined into the master document. Financial support from these societies as well as other donors will be secured, allowing the entire working group to convene in April 2000 at WHO in Geneva to formally adopt and disseminate the master document of the WHO Task Force on Osteoporosis.

Definition of the Global Problem

The view of osteoporosis as a global problem is based on the recognition that it is a common disease in the developed countries and is likely to become so in the developing countries, where longevity is rapidly increasing. Dr Gro Harlem Bruntland, Director General of WHO, stated in a recent interview: 'In recognising the global problem posed by osteoporosis, WHO sees the need for *a global strategy* for prevention and control of osteoporosis, focusing on three major functions: prevention, management and surveillance.'

Osteoporosis is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue. The consequent increase in bone fragility greatly increases the risk of *fractures* which represent the major relevant clinical aspects of the disease. Osteoporosis affects mainly post-menopausal women but also men, in either primary or secondary forms. There are three major fracture sites in osteoporosis – the hip, the vertebrae, and the distal radius (although other sites are also affected). Hip fractures are known to have a high morbidity and mortality and their absolute number is expected to double in the next 25 years, at least in the developed world and probably elsewhere. The higher occurrence of these fractures in women is related to important postmenopausal changes in bone metabolism and to women's greater longevity than men. However, these fractures should not be regarded as an unavoidable price for a longer life because substantial advances have recently been achieved in the identfication of risk factors, in early diagnosis – before the first fracture – and in the development of new agents that are effective in both prevention and treatment.

An estimated 1.7 million hip fractures occurred throughout the world in 1990. Due to increasing population and increased life expectancy, that number is expected to exceed 6 million by 2050. Currently, the majority of hip fractures occur in North America and Europe but demographic shifts over the next 50 years however, will lead to huge increases in the number of elderly in Asia, South-America and Africa. Consequently, there will be a shift of the burden of the disease from the developed to the developing world. Some 75% of hip fractures are expected to occur in the developing world by the year 2050. Therefore, it will be necessary to develop and disseminate prevention strategies which can be used in these regions.

Early detection can be made at any age by measuring bone mineral density (BMD) to identify those individuals who need intervention for preventing fractures. Various medications are currently available for the management of osteoporosis and some of them have proven, through randomized controlled trials, to be effective against fractures. In addition, several other medications and approaches are in development, and some non-pharmacological interventions, such as ex-

ercise and nutritional programmes, contribute to prevention and to improving the quality of life of patients with postmenopausal or other forms of osteoporosis.

Epidemiology of Osteoporotic Fractures and Low BMD

Hip, wrist and vertebral fractures are most closely associated with osteoporosis although fracture risk in other bones is also increased in the presence of osteoporosis. Hip fractures account for most of the morbidity, mortality and costs of the disease. For example, of those living independently before a hip fracture, only about half are able to live independently after the fracture. Hip fracture rates increase exponentially with age; by age 80, a Caucasian woman has about a 3% annual risk of hip fracture.

Independent of age, postmenopausal women are at about three times the risk of elderly men; the lifetime risk for a Caucasian woman is about 15%. Compared to Caucasians, Blacks have about one third the risk and Asians and Hispanics about half the risk of hip fracture.

There are a number of important clinical risk factors for hip fracture among Caucasian women, including low body weight, history of fracture, family history of fracture, smoking, use of glucocorticoid steroids and physical inactivity. However, the main risk factor is age (the mean age of women with hip fractures is 80 years) but vitamin D deficiency has also been implicated. Genetic factors are important although specific genes remain to be identified. There have been few studies of risk factors for hip fractures in ethnic groups other than Caucasians, or in men.

Vertebral fractures are also strongly related to age (mean age 65 years) but even more strongly to menopause. They are also more common in women than men and more common in Caucasians than in Blacks. Rates in Asians are variable but are generally midway between those in Caucasians and Blacks. The consequences of vertebral fractures include back pain and disability, kyphosis and loss of height. Future risk of osteoporotic fractures is greatly increased among those with vertebral fractures. Unfortunately, little is known about other clinical risk factors for vertebral fractures.

The incidence of wrist, and other non-hip peripheral fractures, follows a different pattern, rising by a factor of about 10 in the fifteen years after the menopause but remaining fairly constant thereafter.

Diagnosis and Assessment

Osteoporosis was not classified as a disease until relatively recently; previously it was considered an inevitable accompaniment of aging. Now, an internationally accepted definition describes osteoporosis as a progressive systemic disease characterized by low bone density and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. This provides the framework for an operational definition on the basis of bone mineral density measurements. According to the recommendations of a WHO task force, osteoporosis is defined in Caucasian women as a bone mineral density (BMD) that lies 2.5 standard deviations or more below the average for the young healthy female population. The same absolute BMD value (after adjustment for larger body size) can, provisionally, be utilized for men.

The preferred site for diagnostic assessment, particularly in the elderly, is the hip, using dual X-ray absorptiometry. However, other sites and techniques are useful to assess fracture risk and response to treatment. The emphasis on hip measurement arises from the relative clinical importance of hip fracture and the strength of the relationship between hip BMD and hip fracture, specifically. Prospective studies have shown, however, that the risk of fracture in general increases progressively the lower the prevailing BMD, regardless of measurement site. For each standard deviation decrease in bone mineral density, fracture risk approximately doubles. The performance characteristics of BMD to predict fractures are at least as good as the measurement of blood pressure to predict stroke. Universal screening of populations by bone densitometry has not been shown to be cost-effective at present but should be applied to individuals identified by the presence of one or more strong risk factors; it could be argued that the menopause is one such risk factor.

There is considerable lack of uniformity in the presentation of BMD values, in part due to technical differences in equipment, differences in normal ranges, and the complexity of the computer output. Uniform criteria should be used for diagnostic purposes utilizing the *T*-score or other standardized approaches and appropriate reference ranges. Further delineation of diagnostic thresholds across anatomic sites and BMD techniques is an important research front.

Other techniques for assessing skeletal status have been less well validated than absorptiometry but quantitative ultrasound and computed tomography are helpful for fracture risk assessment. BMD measurements may also be used to monitor response to treatment.

Biochemical indices of skeletal turnover are useful in fracture risk assessment and in the monitoring of treatment but further research is needed to determine their precise value in clinical practice.

Diagnostic assessment of individuals with suspected osteoporosis should include the measurement of BMD. Other factors to consider in such assessment are the cause of the osteoporosis, and the management of any associated morbidity. Recommendations are included for the routine investigation of these patients.

Bone densitometry is recommended (because the result could influence management) in the presence of:

- Radiographic evidence of osteopenia and/or vertebral deformity
- Loss of height, thoracic kyphosis

- Previous low-trauma fracture (i.e. a fall from standing height)
- Prolonged corticosteroid therapy
- Hypogonadism in either sex (possibly to include most menopausal women)
- Chronic disorders associated with osteoporosis (e.g. hyperthyroidism and hyperparathyroidism)
- A maternal history of hip fracture
- A low body mass index (<19 kg/m^2)
- A low calcium intake

Subjects with BMD values more than 2.5 standard deviations below the young normal mean should be offered appropriate treatment but intervention can also be directed at menopausal women with BMD values between -1 and -2.5 SD because of their increased future fracture risk, as well as to those with other risk factors. The more general use of bone densitometry may be costly but it is less costly than indiscriminate and frequently expensive treatment.

Pathogenesis of Osteoporosis and Related Fractures

Bone is a specialized form of connective tissue composed of a collagen matrix which is mineralized by deposition of 'calcium phosphate'. This tissue composition confers rigidity and strength on the skeleton while still maintaining some elasticity. Morphologically there are two forms of bone: cortical or compact, and cancellous or spongy. Bone serves several important functions in the body: protection against trauma, locomotion and provision of a calcium reservoir.

Bone is a living tissue. It is constantly resorbed and formed in the process known as remodelling. Thus, bone formation takes place not only during growth but throughout life. Osteoblasts are the cells responsible for bone formation and osteoclasts are the cells specialized to resorb bone. During growth, bone formation exceeds bone resorption. From age thirty to age fifty, the amount of bone formed approximately equals the amount resorbed. From the menopause in women and from about the sixth decade in men, bone resorption starts to exceed bone formation. The mass of bony tissue present at any time during adult life is the difference between the amount accumulated at maturity, i.e. the so-called peak bone mass, and that lost with aging.

Pathogenetic factors favoring the osteoporotic process are those impairing the accumulation of bone during growth and those accelerating the loss of bone during later life. There is great inter-individual variation in peak bone mass; it is largely determined by body size but is also subject to heredity factors in its own right. Some degree of physical activity and a minimum threshold of calcium intake are necessary to optimize bone mass acquisition.

During growth, bed rest due to illness, as well as under-nutrition or malnutrition, particularly when associated with low calcium and/or protein intakes can hinder optimal bone mass acquisition. Various paediatric disorders can impair optimal bone mass gain. In some diseases, such as glucocorticoid excess or growth hormone deficiency, the inadequate bone mass accrual can be attributed to a single hormone. In other disorders, such as anorexia nervosa and exercise-associated amenorrhea, the cause is a combination of malnutrition and sex steroid deficiency. Several severe chronic paediatric diseases which require immunosuppressive-, chemo- or radio- therapies can also retard bone formation.

After middle life, hypogonadism is a major cause of bone loss in both sexes. At the menopause, estrogen deficiency leads to an increase in bone turnover with an imbalance between bone formation and resorption. The pathophysiological mechanism involves the release in the bone marrow environment of cytokines, such as tumour necrosis factors and interleukins, which stimulate osteoclastic bone resorption. In aging men, loss of bone seems to be associated with low bone formation rather than high bone resportion, and that may be related to declining androgen levels. Other endocrine diseases such as primary hyperparathyroidism, hyperthyroidism and hypercortisolism can induce bone loss. In the elderly, low calcium intake and/or insufficiency of vitamin D due to inadequate sunlight exposure may accelerate bone loss, probably by enhancing the secretion of parathyroid hormone.

The Prevention and Treatment of Osteoporosis

There are many possible interventions which might decrease the number of osteoporotic fractures, but not all have been subjected to definitive assessment. Strategies for which there is broad support, based on observational data or trials with surrogate end-points, include: provision of a diet which maintains normal body weight throughout life and provides a calcium intake of some 1000 mg/day from late childhood to midlife – at least in the developed countries; encouragement of a physically active lifestyle; maintenance of eugonadism; avoidance of smoking and of high alcohol intake; minimization of glucocorticoid use and consideration of osteoporosis prophylaxis when these drugs are used; promotion of vitamin D supplementation and/or regular time spent outdoors (to permit endogenous vitamin D synthesis) in the elderly; falls prevention programmes in the elderly; and use of hip protectors in those at very high risk of falls.

Interventions for which there is consistent randomized controlled trial evidence of anti-fracture efficacy include calcium and vitamin D supplementation in the elderly, hormone replacement therapy in postmenopausal women, and the bisphosphonates in established osteoporosis. Calcitonin and selective estrogen receptor modulators (SERMs) may also prevent vertebral

fractures. The inconsistent results from trials with fluoride preclude its widespread use in the treatment of osteoporosis at present.

In general, pharmacological interventions are expensive and can produce adverse effects in certain individuals; they should, therefore, be targeted to those at highest risk of fracture in order to be most cost-effective. Current knowledge of fracture prediction allows intervention in many women before any fracture has occurred. However, it is never too late to intervene in patients with osteoporosis.

Socioeconomic Aspects of Osteoporosis: Cost Effectiveness and Quality of Life

Osteoporosis and associated fractures are a major public health concern because they account for significant morbidity, disability, decreased quality of life, and mortality. The adverse effects of vertebral and forearm fractures on most of the activities of daily living are almost as great as those of hip fracture. The cost of care is high and the implications for public health expenditure serious. In developed and developing countries, osteoporosis will become a major burden as the population ages.

Socioeconomic evaluation of osteoporosis can be obtained by calculating a cost-effect ratio. For this analysis in osteoporosis, *cost per fracture avoided* may be used. This method can be applied both for diagnostic procedures and pharmacological agents.

The costs of osteoporosis can be divided into direct (fracture-related) and indirect costs. The indirect costs depend on a number of assumptions, in particular the impact of working definitions of osteoporosis based on bone densitometry thresholds and on vertebral deformity indices.

The cost of treatment for hip fractures is considerable; hospitalization for this fracture represents more than 80% of all costs for osteoporotic fractures. The side effects of drugs, both positive (bone-cardiovascular) and negative (breast/endometrial cancer) need to be included in the cost-effectiveness evaluation.

In the cost-effectiveness analysis, the outcome of an intervention needs to take into account the years of life gained, corrected for quality of life using specific validated instruments such as the IOF questionnaire, the cost of the fractures saved, and number of subjects who need to be treated to prevent one facture. The functional outcome of osteoporotic fracture is not only related to mortality and long-term nursing care but also to the associated impairment of the activities of daily living. It should be noted that the quality of life years after hip replacement following hip fracture are superior to those obtained by a coronary bypass, organ transplantation or hemodialysis.

Prevention is either population based or directed to high risk case finding. A relatively expensive but effective intervention with substantial non-compliance may prevent fewer fractures than an inexpensive, safe and somewhat less effective intervention with a higher compliance.

A cost-effective intervention profile is obtained when bone-active drugs are used at the time of the first fracture or for the treatment of high risk patients, including those with low bone density.

Delivery of Care and Education

Proper provision for osteoporosis requires a clear structure, sufficient facilities with reimbursement, effective guidelines and monitoring of the system.

A shared approach between primary care and specialist facilities will ensure an integrated approach to the care of patients with osteoporosis. A local strategy for osteoporosis care and proper organisation of health professionals within a district should be developed by local osteoporosis planning and coordinating teams, on the basis of international consensus. Concerted action in each country should be coordinated by an appropriately skilled and experienced national osteoporosis planning and coordinating group, which could be responsible for launching a comprehensive osteoporosis programme.

Facilities for diagnosis and treatment of osteoporosis are inadequate in many countries. This is especially true for the availability of bone densitometry systems. The number of hospital beds dedicated to patients with hip and certain other fractures is not sufficient in some regions of the world. Apart from the shortage of densitometry equipment and hospital beds, there are few specialists with adequate expertise in bone diseases.

Reimbursement of bone densitometry measurements is absent, partial or restricted in many countries thus limiting the use of this procedure even where resources are available. Reimbursement of effective bone active agents is different and varies among countries from 0% to 100%.

Comprehensive and useful international guidelines have been developed and published in the field of osteoporosis. However, guideline documents should always be adapted and distributed by local osteoporosis teams taking into account the regional characteristics of the population and osteoporosis care. In addition to setting up a system to deliver care to patients, it is also essential to set up a system for monitoring effectiveness and appropriate use of diagnostic tools and quality control.

Ignorance about osteoporosis is still common among health professionals, patients and the public. Therefore, education should target all of these groups. The aim of an extensive education and communication programme is to increase the knowledge of bone physiology and osteoporosis, to raise the awareness about major risk factors and to educate about possibilities of primary and secondary prevention and management of the disease. Patient compliance can be increased by using proper methods of patient education and individualizing education in a stepwise manner.

Recommendations

Recommendations for the General Population

a) Maintain a physically active lifestyle with adequate exposure to sunlight, particularly among the elderly in northern latitudes.
b) Avoid smoking and high alcohol intakes.
c) Maintain a dietary calcium intake which meets the relevant Recommended Dietary intakes in the country or region concerned.
d) Maintain a Body Mass Index of not less than 19 kg/m^2.

Recommendations for Physicians

a) Remember 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.
b) Address known factors that stimulate bone resorption or inhibit bone formation, including hypogonadism, primary hyperparathyroidism, hyperthyroidism and hypercortisolism.
c) Make use of bone densitometry when available. Remember that postmenopausal women in the lower part of the young normal range are at increased risk of becoming osteoporotic later on. Intervene when the BMD falls into the osteoporotic range, if not before.
d) Provide vitamin D supplementation in the elderly and the housebound when appropriate for the climate.
e) Develop falls prevention programmes in the elderly. Consider hip protectors in those at very high risk of falls.
f) Minimize glucocorticoid use and consider osteoporosis prophylaxis when these drugs are used.

Recommendations for Health Authorities

a) Facilitate access to bone densitometry for individuals at risk for oestoporosis to allow appropriate targetting of therapies. Ensure quality control of the systems.
b) Seek to reduce the risk of fracture by environmental measures such as enriching widely used foods with calcium and/or vitamin D if necessary.
c) Take into account the recently published WHO 'Guidelines for preclinical evaluation and clinical trials in osteoporosis' when considering approval of new drugs for osteoporosis.
d) Support the comprehensive education of health professionals, including general practitioners, in osteoporosis management. Osteoporosis and bone disease should be studied at all levels of medical education and perhaps constitute a sub-specialty.
e) Support patient education and the establishment of self-help groups regionally and locally. Raise awareness of risk factors for osteoporosis and prevention strategies.
f) Support national osteoporosis programmes to be instituted in association with the WHO Task-Force on Osteoporosis and with other international organizations.

Recommendations for Further Research

a) Fundamental aspects of bone biology taking advantage of progress in molecular genetics.
b) Good clinical investigations into the factors influencing bone maintenance and bone loss in different nations across the globe.
c) Evaluation of biochemical markers of bone turnover in clinical practice.
d) The development of cheaper BMD tools for diagnosing osteoporosis and the assessment of these tools for optimal monitoring of treatment response.
e) The definition of diagnostic thresholds across anatomic sites and BMD techniques.
f) The development of agents to stimulate bone formation.
g) More controlled trials of the effects of lifestyle and dietary interventions on fracture risk.
h) Controlled trials of the effectiveness of combination therapies and of comparisons between different therapies.
i) Fracture epidemiology across the globe.
j) Development of inexpensive prevention strategies which can be used in the developing world.