測定骨密度術: 與健康護理有關的

Bone densitometry: relevance to health care

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Since low bone density is a risk for fracture, the relevance of bone densitometry as a basis for health care assessment needs to be elucidated. Most patients with fractures are in the lower two quartiles of bone density. Bone densitometry can be used to provide a quantitative estimate of fracture risk and a measurable response to aging, disease or medical treatment in the individual. Some difficulties concerning the efficacy of screening the whole population are discussed, for instance in terms of the success of treatment. Screening to prevent fractures should be advocated in women considering HRT. Research into defining bone quality is needed, as are further studies on the pathogensis of low bone density and on the contributions of low peak bone density and rates of loss to bone density in adults.

The health care problem associated with osteoporosis is fractures. The health care problem in cardiovascular disease is stroke. An important risk factor for fractures is bone fragility due to low bone density. An risk factor for stroke is high blood pressure. The relevance of bone densitometry to health care in osteoporosis is similar to the relevance of sphygmomanometry to health care in cardiovascular disease. These techniques provide accurate and precise quantitative measurements which assist in the definition, detection, pathogenesis, prevention and treatment of disease.

Definition of osteoporosis

The definition, meaning and sense of the word osteoporosis is bone fragility. Historically, this bone fragility is due to a reduction in bone mass without a change in bone volume -a reduction in bone density[1]. In vitro, the breaking strength of bone is linearly related to its mass[2]. Several prospective studies confirm that bone mass measurements in vivo predict fracture risk[3-5]. The method of measurement of bone mass (single or dual-photon absorptiometry, dual-energy X-ray absorptiometry (DEXA), ultrasonography, quantitative computed tomography) and the method of expressing bone mass, as bone mineral content (BMC, grams, g/cm), areal bone mineral density (BMD, g/cm^2), volumetric density (g/cm^3), or bone mineral apparent density (BMAD, g/cm^3) have relevance only insofar as they are a sensitive and specific surrogate of the breaking strength of bone, ie, a surrogate of bone fragility.

Most patients with fractures have reduced bone density with values below the 5th percentile for young normal subjects. Operationally this value, the fracture threshold, defines the lower limit of normal[6]. Fifty per cent of women over 65 years of age with no fractures have bone density below the fracture threshold and are at increased risk for fracture. These women's bone density overlaps with bone density of patients with fractures, ie patients with so-called 'established' osteoporosis. Should these healthy women be called patients with osteopenia? Should they be called patients with osteoporosis[7]?

The clinical definition of postmenopausal osteoporosis is the presence of one or more nontraumatic (or spontaneous) vertebral crush fractures. The clinical definition of senile osteoporosis is the occurrence of hip fracture associated with a fall from no greater than the standing position. These definitions, like hypertension defined by the presence of stroke, defeat the purpose of the health initiative of which they are intended. They have been expedient and used because there have been no methods available for accurately measuring bone density. It is the bone density (or blood pressure) not the presence or absence of a fracture (or stroke) which should be used to define normality. These healthy women have low bone density (osteoporosis) but have not yet had fractures. They are at increased risk for fracture. The overlap in bone density between patients with fractures and women without fractures has caused concern regarding the value of bone densitometry. However, bone density is a continuous variable, the lower the bone density, the greater the risk for fracture, just as the higher the blood pressure or serum cholesterol, the greater the risk of stroke or myocardial infarction, respectively. Standard radiographs are the best means of distinguishing persons with and without fractures. There is no 'fracture threshold' below which there is risk and above which there is no risk. The overlap is found when comparing systolic or diastolic blood pressure in persons with and without stroke or serum cholesterol in persons with and without heart disease.

Detection, prevention and screening

Each of these measurements; bone density, blood pressure, serum cholesterol provide a measure of risk and so provide a means of identifying persons at greatest risk for sustaining fracture if bone loss occurs. The screening method should detect the majority of patients who will come to sustain fractures. The available prospective data does suggest that most

patients with fractures come from the lower two quartiles of bone density[8]. So why not screen everybody and treat the women with body density in the lower two quartiles? Although screening seems to be an obvious and straight forward means of preventing fractures in the community, the decision to initiate screening is difficult for several reasons[9] that can only be dealt with briefly here.

The reason persons have low bone density must be understood. If these persons have low bone density because they attained a low peak bone density, this would support screening, at least in principle. If excessive or rapid bone loss is important, persons with high peak bone density may be excluded by screening as their bone density would be above the decision threshold to initiate treatment[10]. Further studies are needed to determine the pathogenesis of low bone density and to evaluate the relative contributions of low peak bone density and rates of loss to the level of bone density in adults.

Screening cannot be justified unless there is an effective treatment. Hormone replacement therapy (HRT) reduces the risk for fracture but does not eliminate it. Compliance with HRT is about 50 per cent at 12 months[11,12]. Treatment is likely to be needed for longer than this and perhaps permanently, to reduce hip fracture rates. There are concerns about the long term safety of HRT. This is particularly important because illnesses with a baseline risk of about 1 to 2 per 1000 persons per year, the number of persons that need to be treated to prevent one event ranges from one thousand to several thousand, depending on the reduction in risk conferred by the treatment[13]. Thus, most persons treated will derive no benefit from HRT. Consequently, the treatment must be safe, as any small increase in side effects may negate the benefit.

Other aspects that need to be considered before initiating a screening program include the method of screening[9]. A measurement of bone density at the proximal femur is a better predictor of hip fracture than is a bone density measurement of the forearm, calcaneus or spine[5]. At present, a measurement at the spine has not been show to be a better predictor of spine fractures than a forearm measurement. Ease of access (use of mobile screening), the occurrence of radiation exposure, safety, speed of measurement and cost to the individual influence attendance at screening. Ultrasound measures predict the breaking strength of bone and have been used in screening. Ultrasound is free of radiation exposure and is portable[14]. At present DEXA appears to be the method of choice in that it is accurate and precise, almost any region of the skeleton can be measured, the technique is widely available and can measure the axial or appendicular skeleton. QCT is associated with a high radiation exposure.

Screening should result in a reduction in the number of fractures in the community. In a population of 100 000 women over 50 years of age, 500 hip fractures would be expected. If screening was performed and the lower tertial was offered HRT what effect would this have on the fracture incidence? The relative risk for fracture in persons in the lower tertile is ~2. Assuming HRT reduces this risk by 50% and the application of the program reaches 50% of those contacted and 40% take HRT then 33 of the 500 hip fractures would be prevented[15]. Problems associated with attendance at screening, the uptake of treatment, compliance with treatment and efficacy of treatment suggest that screening although sound in principle, may not substantially reduce fracture rates.

Lifestyle, risk and protective factors such as a family history of osteoporosis, alcohol intake, tobacco use, calcium intake, body weight and height do not distinguish persons who come to sustain fractures from those who do not. Nor do they distinguish persons with high or low bone density[16]. Knowledge of risk factors cannot be used to predict bone density or the risk for fracture. The only available predictor of fracture is a single measurement of bone density. For example, using a variety of models incorporating lifestyle risk factors, Slemenda at al[16] showed that these models fail to identify around 30–40% of persons with low bone density when measured and fail to identify a similar number of persons with true high bone density. Prolonged exposure to risk factors results in bone loss. These factors should be identified and modified. They cannot be used as predictors of fracture risk or low bone density.

Pathogenesis

The pathogenesis of the bone fragility can be studied using bone densitometry. The relationship between lifestyle risk factors, hormonal and biochemical factors and fractures can be studied through their effect on bone density. It is not possible to study the relationship between these factors and fractures. The incidence of fractures is about 1 to 2 per 1000 persons under 65 years of age and reaches a maximum of 1 to 3 per 100 persons per year in 80-year-old subjects. With this incidence of fractures the ability to detect an association between a lifestyle risk factor and fractures is very low. However, the association between factors such as dietary calcium deficiency, tobacco use, excessive alcohol use, exercise, and bone density can be more easily studied because of the sensitivity and precision of the techniques. Nevertheless, the difficulties should not be underestimated as the changes in bone density (increase or decrease) may be only 1-3% per year and large sample sizes are required to detect an association between a risk factor and bone loss of this magnitude. These difficulties are compounded by the fact that 80% of the variability in bone density is genetically determined. In addition, the problems associated with quantifying lifestyle factors such as exercise or nutrition should be acknowledged.

Treatment

The usefulness of bone densitometry in treatment is clear when considering the purpose of treatment is to prevent fractures. A reduction in fracture rates must be the required endpoint to demonstrate efficacy of a treatment. This is the case in clinical trials. These trials must be very large because of the low incidence of fractures[17,18]. For example, if the incidence of new vertebral fractures in a high risk population is approximately 1 per year and a drug treatment reduces the fracture rate by 50% then about 100 persons (placebo and control groups) followed during 3 years are needed to demonstrate this effect using a one tailed test with 80% power conducted over 3 years. As the incidence decreases, or the efficacy falls, or compliance decreases then samples sizes needed to detect an effect increase markedly. For hip fractures the difficulty is greater. If a treatment reduces hip fractures by 40% and the incidence in the untreated population is ~1 per 100 persons per year as it is in persons around the age of 70 years[19], then the total sample size required to demonstrate this efficacy is approximately 3000 persons using a one tailed test with 80% power conducted over a period of 4 years.

Thus it is difficult to use antifracture efficacy as an endpoint of successful treatment. In an individual, fracture rates are too uncommon to serve as an endpoint. These decisions must be based on the results of clinical trials. The likelihood

of a clinician observing a fracture in an individual is too small to have clinical utility. Neither the occurrence, nor the absence, of fractures in an individual receiving treatment provide reliable clinical information about antifracture efficacy. This can only be determined by large clinical trials. By contrast, bone densitometry does have clinical utility by virtue of providing a quantitative estimate of fracture risk and a measurable response to aging, disease or medical treatment. The effect of a treatment on bone density can be used in the individual and an inference must then be made about the efficacy of the treatment using this surrogate endpoint.

Summary

Many factors other than bone mass or bone density contribute to bone fragility. Research into defining bone 'quality' is needed[20,21]. What are the relative contributions of bone size, bone structure, bone turnover, microdamage repair, collagen tissue strength, the intervertebral disc, the ligaments in determining the strength of a region of the skeleton? These factors are likely to be important but few have been measured.

Bone densitometry is relevant to health care in that it assists in providing a quantitative definition of bone fragility. It has a role in assisting in the detection of osteoporosis and in identifying persons at risk for fractures, particularly if further bone loss occurs. Bone densitometry can assist in the understanding of the pathogenesis, prevention and treatment of reduced bone density in the elderly by permitting precise and accurate measurement of the magnitude, time course and regional specificity of the earlier gain and later loss of bone, the effect of menopause, illness and drug therapy. Bone densitometry should be used if the result of the measurement will alter management. If the decision to use HRT is to be made based on cardiovascular risk criteria or symptoms of menopause then bone densitometry is not needed. If the patient is asymptomatic and will consider using HRT if bone density is reduced then this is appropriate use of densitometry.

The vast majority of women sustaining fracture come from the lower two quartiles of the normal range for bone density. This suggests that screening should be advocated in women considering HRT to prevent fractures. Broad based screening of a large population of persons is different from the use of densitometric methods in clinical practise. The two are often confused because a decision involving an individual follows both. Concerns regarding safety, and poor compliance with HRT and screening program attendance suggest that mass screening should not be implemented at this time.

Practical information has been obtained about the dose, duration and efficacy of oestrogen replacement therapy in preventing perimenopausal bone loss and the benefits and limitations of exercise, dietary calcium. Information regarding the prevention and treatment of bone loss in exogenous hypercortisolism and the magnitude and reversibility of bone loss associated with many diseases with affect bone has been obtained. Like the sphygmomanometer's contribution to the investigation, prevention and treatment of hypertensive vascular disease, these techniques may prove to contribute measurably in reducing the burden of bone disease on the growing number of elderly persons in our community.

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