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Review

Clinical aspects of involutional osteoporosis

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DEFINITIONS AND BONE MICROARCHITECTURE

As a consensus statement from World Congresses in 1993 and 1996, osteoporosis has been defined as 'systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures' [1, 2].

Cancellous bone affected by osteoporosis shows a decrease both in absolute bone mass and bone density. Morphologically, the generalized thinning, micro-fractures, fragmentation or perforations of some trabeculae have occurred in the microarchitecture of cancellous bone. In osteoporosis, such deterioration and reduced bone weaken the mechanical strength, leading to brittleness.

DIAGNOSTIC CRITERIA FOR PRIMARY OSTEOPOROSIS PROPOSED BY THE JAPANESE SOCIETY OF BONE AND MINERAL RESEARCH

About 37% of osteoporosis was diagnosed by outside orthopedic surgeons, about 33% by internists and about 27% by surgeons. Before this survey was conducted, diagnoses by orthopedic surgeons probably made up two-thirds of the total; however, reflecting the aging of society, the number of osteoporosis patients is growing and becoming more diversified, and such cases are being treated by gynecologists and doctors from other departments. This has made it necessary to set up standardized criteria enabling physicians from all departments to diagnose osteoporosis accurately.

In 1988, the Silver Science Research Group of the Japanese Ministry of Health and Welfare proposed criteria for osteoporosis based on a scoring system incorporating evidence of bone mass reduction and clinical symptoms [3]. Since then, bone mass measurement equipment has become more widespread. In 1993, the Research Project on Aging and Health proposed criteria including bone mass measurement data. The pendulum has recently swung too far, however, with importance being placed solely on bone mass evaluation and basing osteoporosis diagnosis solely on such measurements.

Table 1.
Criteria for primary osteoporosis (Japanese Society of Bone and Mineral Research, 1996)

I.	Vertebral fracture evident on X-ray		
	If non-traumatic vertebrae fracture is observed accompanying osteopenia (grade I or higher) or if bone mineral content is less than −20% of the mean value of young adult population.		
II.	Vertebral fracture not evident on X-ray		
		Grade of osteopenia on spinal X-ray image	Bone mineral content
	Normal	No osteopenic appearance	
	Ostopenia	Grade I	−20% or less
	Osteoporosis	Grade II or more	−30% or less

The Japanese Society of Bone and Mineral Research has thus proposed new osteoporosis criteria focusing on diagnosis by exclusion and emphasizing the importance of differential osteopenic disease diagnosis. Despite the widespread use of bone mass measurement equipment, bone mass reduction should be assessed initially by simple X-ray photography [4].

The Japanese Ministry of Health and Welfare Research Group has graded the appearance of osteopenia on X-ray photography and deems a patient's condition 'normal' unless osteopenia is evident on a simple spinal X-ray [5]. Grade I cases having vertebral fracture are diagnosed as osteoporosis; in the absence of fracture, they are diagnosed as osteopenia, which is non-morbid. Grade II or more is diagnosed as osteoporosis, regardless of fracture occurrence (Table 1).

These proposed criteria also use internationally recognized dual X-ray absorptiometry (DXA), which enables bone mass to be measured objectively and highly accurately. They also allow diagnosis from the value of bone mineral density using DXA if simple X-ray evaluation is difficult.

BONE MASS EVALUATION CRITERIA

In 1994, WHO proposed osteoporosis criteria based on bone mass measurements. Patients are diagnosed as osteoporosis if their bone mass measurement values fall below the −2.5 standard deviation (SD) of the mean value of healthy young adult population, those with a bone mass between −1.0 and −2.5 SD are diagnosed as osteopenia, and those with bone mass values below −2.5 SD and vertebral fracture are diagnosed as established osteoporosis [6].

Because bone mass varies by race, the Japanese Society of Bone and Mineral Research committee collected and reviewed related data. Results found the grade I of about −20% of the young adult mean, −1.5 SD; and grade II of about −30% of the young adult mean, −2.5 SD; this corresponds roughly with WHO's definition. Thus, when bone mass values are used, if bone mass has fallen to about −30% or more of the young adult mean, a patient is diagnosed as osteoporosis.

BONE MASS EVALUATION

Many types of bone mass evaluation have been developed and implemented. Initially, such evaluation used simple X-ray photography, dual-photon absorptiometry (DPA) and single-photon absorptiometry (SPA) using gamma-rays. More recently, DXA, which uses X-rays as its radiation source, and single X-ray absorptiometry (SXA) have been developed for peripheral bone evaluation. Quantitative computed tomography (QCT) measures vertebral bone density using computed tomography (CT), but entails high radiation exposure, limiting its use. Further developments include peripheral QCT (pQCT), which measures areas such as the forearm and involves significantly lower radiation exposure. Methods using ultrasound were expected to be able to evaluate both bone mass and structure, but the significance of measurements remains unclear. Ultrasound measurement correlates very highly with bone mass and this may replace bone mass measurement in some cases.

Bone mass evaluations are divided into those that evaluate peripheral bone and those that evaluate the axial bone. The skeleton consists of cortical and cancellous bone whose ratio varies with the bone in question. Consequently, each type of evaluation has inherent attributes based on differences in measurement principles and specific properties of the measured area. Each method also has its relative advantages in measurement accuracy. Improvements in measurement hardware and software have improved accuracy to where each measurement method is roughly able to identify postmenopausal and age-related bone changes.

Summarizing trends in bone mass with aging using these methods, bone mass in females increases rapidly until adolescence, when bone growth is completed, and is maintained until the late 30s. After exponential reductions in bone mass in the decade following menopause, this reduction rate slows. Understanding these aging trends in bone mass provides important data for diagnosing osteoporosis and setting standard examination values.

The practical bone mass measurement for different areas of the body has also made the bone mass area used in diagnosing osteoporosis an extremely important issue. When the bone mass in osteoporosis cases with vertebral fractures and those with hip fractures are compared with those of non-fracture cases using several bone mass evaluations, both cases with fracture show significantly lower values than those of non-fracture cases. Most reports state, however, that the bone mass measurement of lumbar spine should be used to diagnose vertebral osteoporosis and that of proximal femur used to establish the hip fracture risk [7].

Comparing changes with age in bone mass in those aged 60 or older, because the lumbar vertebrae is accompanied by involutional changes, so the bone reductions are not so great in lumbar spine. In contrast, the bone mass of the radius, calcaneus and proximal femur decreases greatly in patients older than 65. This places limitations on diagnosing osteoporosis in the elderly based on the bone mass of the lumbar spine alone. When monitoring the effect of treatment, it is also necessary to interpret bone mass measurements taking into consideration measurement accuracy, specific measurement characteristics, discrepancies in aging-related changes and specific characteristics of measured areas.

BONE STRUCTURE EVALUATION

From here on, bone mass, changes in bone structure, bone elasticity and bone strength must be able to be evaluated non-invasively. Although biopsy and histomorphologic evaluation were once the only way to evaluate bone structure, advances in this field have led to reports on how to understand the bone microarchitecture by evaluating geometrical bone strength by radial QCT and texture analysis using CT.

Although expensive, pQCT extracts detailed images of the tibial microarchitecture. Such devices are expected to eventually make it possible to monitor bone tissue microarchitecture, enabling the continuity and connectivity of bone structures to be evaluated three-dimensionally.

BIOCHEMICAL MARKERS FOR BONE METABOLISM

Even after the completion of bone growth, bone remodeling continues throughout the human life cycle, i.e. bone tissue is repeatedly formed and resorbed. Such bone kinetics have been conventionally observed through histomorphological measurement using bone biopsy. Such invasive measures are increasingly being replaced, however, by quantitative, non-invasive evaluations of bone metabolic markers using urinalysis, blood testing and the like [8–10].

Increasing bone turnover occurred by the uncoupling of bone remodeling with a relative or absolute increase in resorption over bone formation leads to increased bone loss. Such an imbalance of bone remodeling is classified broadly into two types: (i) high bone turnover with excessively raised bone metabolism, especially bone resorption not supplemented by bone formation and (ii) low bone turnover, in which bone resorption and formation slow, markedly impacting on bone formation [11].

In postmenopausal osteoporosis — also called 'high-turnover' osteoporosis — bone resorption is excessive. In 'senile', age- or steroid-related osteoporosis — called 'low-turnover' osteoporosis — involves slow-phase bone loss. Bone metabolic markers enable bone kinetics to be quantitatively evaluated non-invasively.

A variety of bone metabolic markers have been developed. Those reflecting bone formation involve the assay of serum material — conventionally, serum alkaline phosphatase and bone-specific alkaline phosphatase, which has a high bone specificity. The assay of osteocalcin against hyperparathyroidism is authorized under Japan's health insurance. Type I procollagen carboxy-terminal propeptide (PICP), type I procollagen amino-terminal propeptide (PINP) and bone sialoprotein are being studied as formation markers.

Resorption marker assays include tartrate-resistant acid phosphatase and type I collagen carboxy-terminal telopeptides (ITCP) in serum materials, and hydroxyproline and pyridinium cross-links in urine. Measurement is now possible using kits with single antibodies, such as type I collagen cross-linked N-telopeptides (NTX) and NTX should be applied widely in clinical trials.

OSTEOPOROTIC THERAPEUTIC AGENTS

In 1992, about ¥130 billion in therapeutic agents were used for osteoporosis. The largest share was occupied by vitamin D, followed by calcitonin and ipriflavone, in this order. Viewing these statistics worldwide, calcitonin occupies about half, followed by estrogen, calcium and vitamin D, in this order. Viewed by country, estrogen and calcium occupy the majority in the US, with calcitonin accounting for only a tiny percentage and vitamin D hardly used at all. In France, calcitonin and calcium account for the majority, and estrogen is not used. In Italy, calcitonin is by far the most widely used agent.

Thus, the kinds of therapeutic agents differ greatly by country. No clear criteria exist on how to select therapeutic agents during actual treatment. This forces physicians to allocate different therapeutic agents based on the patient's age and clinical symptoms and the therapeutic agent's side effects.

In addition, to selecting the therapeutic agent to treat osteoporosis, the physician must also respond to a number of issues: when should administration of the therapeutic agent start? What combinations, or single-use therapy, would be most effective? Would the simultaneous use of bone resorption suppressants or bone formation promoters be more effective? Should continuous or intermittent administration be used? How long should this treatment be continued? No standardized criteria currently exist on these and other issues — a problem that must be resolved in the future.

OSTEOPOROTIC THERAPEUTIC AGENTS AND BIOCHEMICAL BONE MARKERS

In determining a rational, scientific treatment for osteoporosis, it is important to first accurately understand the bone pathology involved. Bone biopsy, once the only way of identifying bone kinetics, has been largely replaced by assays using different metabolic markers to identify bone kinetics non-invasively and highly accurately.

Identifying individual bone kinetics makes it possible to select therapeutic agents based on individual agent characteristics, e.g. bone resorption suppressant or bone formation promoters. Also, because the measurement of bone metabolic markers enables the prediction of rapid bone mass reduction to some extent, it becomes possible to select patients for appropriate treatment regimens and time periods. Combining this with bone mass evaluation also enables the treatment's effects to be judged more accurately. Thus, the introduction of bone metabolic markers enables osteoporosis to be treated more scientifically.

PROJECTED DIRECTIONS IN OSTEOPOROSIS TREATMENT

Current judgment of the effectiveness of osteoporosis therapeutic agents uses bone mass as the end point and deems therapeutic agents effective when bone mass is increased or maintained.

Worldwide trends, however, are toward judging a therapeutic agent's effectiveness based on bone fracture suppression. Regardless of the actual increase in bone mass,

continued fractures mean continued pain and the patient's quality of life (QOL) remains unimproved. To establish effective future treatment, research must also focus on predicting fractures.

In 1994, Morrison reported the close relationship between vitamin D receptor genotypes and bone mass — a report attracting the attention of researchers worldwide. More recent reports indicate discrepancies in the effect of vitamin D treatment caused by these genotypes. The relationship between estrogen receptor genotypes and bone mass is also attracting attention. Thus, future osteoporosis diagnosis and treatment must be based, in addition to bone mass evaluation and simple X-ray photography, on diagnosis and treatment incorporating genetic factors and bone metabolic markers.

PREVENTION FOR OSTEOPOROSIS AND FRACTURE

The basis of recent osteoporosis prevention has focused on reducing the number of elderly individuals having markedly reduced bone mass. Treatment alone cannot do this, however, and fracture prevention cannot be implemented by discussing only bone mass. It is thus important to identify factors other than low bone mass that contribute to fracture occurrence [12].

Past reports suggested that hip fracture risk factors involve low bone mass and bone brittleness; the increasing possibility of falls in the elderly due to hypokinesis, and reduced mental function; decreased defense abilities in falls; the presence of already existing fractures; and geometrical bone structure characteristics. Each of these factors is reportedly independent of the others [12].

A tendency toward falls among the elderly is regarded as an important risk factor together with low bone mass and, while falls do have an accidental aspect, the living environments of the elderly and their lifestyles encompass several fall risk factors.

We identified the following fall risk factors as being closely related to falls: (i) old age; (ii) complications due to lower limb diseases; (iii) habitual use of sedatives and other medication; (iv) complications of dizziness or paropsia; (v) the need for canes or other aids in ambulation; and (vi) a past history of falls.

Thus, in considering how to prevent hip fractures, in addition to suppressing decreased bone mass, it is important to prevent risk from falls. It is also necessary to consider cases having a high risk factor in hip fractures.

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