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A review on Osteoporosis and its Diagnosis.

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ABSTRACT

Osteoporosis is a systemic skeletal disease that is related to decreased bone mass and microscopic changes in bone tissue that comes with with high fragility and fracture risk. There are no methods for the diagnosis of osteoporosis, thus it is diagnosed based on the bone mineral density, BMD. According to a definition by WHO, osteoporosis is diagnosed by comparing the mean BMD of the population of the same gender to one's BMD. Routine laboratory evaluation such as cell blood count, calcium levels in serum and 24-hour urine and kidney and liver functional tests should be performed. Marking the skeleton with tetracycline makes us able to determine the regeneration level and also evaluate other bone metabolic diseases. Bone biopsy is mostly replaced with current usage of BMD tests, with evaluating hormone and other biochemical parameters of bone regeneration. Factors except BMD involved in fracture risk evaluation are aging, prior fracture, falling down, glucocorticoid administration, hip fracture family history and current smoking. Having a T-score equal or below -2/5 means osteoporosis detection. A T-score between -1 to -2/5 categorizes as low bone mass (osteopenia) while -1 or higher is normal. Fracture prevalence in people with BMD T-score in osteopenia range is more than people with a T-score in osteoporotic range. In 2008, World Health Organization developed a tool called FRAX to estimate the fracture risk which expresses the probability of hip or vertebra fracture in the next 10 years. This tool was approved in 11 cohorts and was tested on more than a million patients. According to the economic conditions of different countries, FRAX could be used to determine whether BMD is necessary to use and also to start the treatment. In countries with limited access to DXA, FRAX could be used. In FRAX algorithm, the probability of fracture occurrence (including hip fracture and major fracture risk) in the next ten years is estimated based on age, sex, weight, height, history of previous fracture, smoking, corticosteroid administration, rheumatism history, secondary osteoporosis, the level of alcohol consumption and patient's T-score. If Major Fracture Risk is higher than 20% and/or Hip Fracture is higher than 4%, the person categorizes in high risk group. This study was conducted to review osteoporosis, its routine evaluation and diagnosing and to review literature related to it.

Keywords: Osteoporosis, Review Article, FRAX

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INTRODUCTION

General checking include cell blood count, calcium levels in serum and 24-hour urine and kidney and liver functional tests. This is useful to determine the secondary selective causes of low bone mass, especially in women with fracture or too low Z-score [1].

In case of hypercalcemia, PTH serum level is variable between the hyperparathyroidism (high PTH) and malignancy (low PTH) range and high PTHrP level may confirm malignant humoral hypercalcemia [1, 2].

Low urine calcium level (<50mg/24h) poses osteomalacia, malnutrition or malabsorption [1].

High urine calcium level (>300mg/24h) poses hypercalciuria [1].

Hypercalciuria mostly occurs in three conditions as followed [2,3]:

1- Calcium renal leak, which more common in men with osteoporosis.
2- Absorptive hypercalciuria, which could occur idiopathic or with 1,25(OH)2D increment in granulomatous disease.
3- Hematologic malignancies or conditions with too much bone recoveries like Paget's disease, hyperparathyroidism and hyperthyroidism.

25(OH)2D serum levels of people with osteoporosis-related fractures or with bone density in osteoporotic range should be measured since vitamin D absorption level is so variable and must pass the target level of 23 ng/ml. vitamin D levels in all patients undergone osteoporosis treatment must pass the target level. It is necessary to evaluate hyperthyroidism by measuring thyroid stimulating hormone (TSH) [2].

When there is no clinical signs to Cushing's syndrome, urine free cortisol or serum cortisol levels should be measured while fasting after taking dexamethasone overnight [1].

In suspected cases to intestinal disease, malabsorption or malnutrition, measuring serum albumin and cholesterol levels and also cell blood count are necessary [1].

The prevalence of Celiac disease without any clinical signs but with selective malabsorption is increasing and detection requires performing anti gliadin, anti endomysial or transglutaminase antibodies tests. However, endoscopic biopsy might also become necessary. Free-gluten diet test could be confirmative [1, 2].

When osteoporosis occurs with rash, several allergies and flash, mastocytosis should be checked and rejected with 24-hour urine histamine collection test or serum tryptase level measurement [4].

Bone biopsy

Marking the skeleton with tetracycline makes us able to determine the regeneration level and also evaluate other bone metabolic diseases. Bone biopsy is mostly replaced with current usage of BMD tests, with evaluating hormone and other biochemical parameters of bone regeneration. Though, bone biopsy is still of importance in clinical studies [1,3].

Biochemical parameters

They are mostly defined as the parameters related to bone generation or reabsorption. The tests measure the total bone regeneration condition in a specific time. Clinical usage of these tests is limited due to biologic changes (somehow related to body circadian rhythm) and also changes in their analysis. The latter is editing, though [1].

Regeneration parameters could not predict the level of bone mass decrement, which causes not using this data in clinical cases. However, bone regeneration parameters might be helpful in predicting the probability of having a fracture and the bone density level independently (especially in the old). In women older than 65, treatment should be considered immediately whenever the bone density test results are more than the common treatment thresholds in case of high level of bone reabsorption. The primary usage of biochemical parameters is to monitor the response to the treatment. Upon start taking anti-reabsorption therapeutic medications, the bone regeneration decreases rapidly (bone reabsorption decrement occurs earlier than decreasing its generation level). The inhibition of bone reabsorption maximizes in 3-6 months. Therefore, measuring bone reabsorption level prior to treatment and 4-6 months after provide us faster estimation to response to the treatment than bone densitometry [2,5].

Fracture evaluation

Factors except BMD involved in fracture risk evaluation are aging, prior fracture, falling down, glucocorticoid administration, hip fracture family history and current smoking [3].

BMD-independent risk factor's collection increases the necessity of evaluating bone fracture risk followed by improving the therapeutic interventions [1].

Age, prior fracture history and BMD are important predictors of fracture risk [4].

Evaluating fracture risk: in 1994, World Health Organization categorized bone mineral density (BMD) based on SD difference between BMD patients and a young adult of the healthy. Nowadays, this is commonly expressed by T-score. Having a T-score equal or below -2/5 means osteoporosis detection. A T-score between -1 to -2/5 categorizes as low bone mass (osteopenia) while -1 or higher is normal [6].

Many studies determined that low BMD correlates with fracture risk increment. People with T-score lower than -2/5 exposed to the highest fracture risk. However, the number of people with osteopenia is much more than people with osteoporosis [3].

Fracture prevalence in people with BMD T-score in osteopenia range is more than people with a T-score in osteoporotic range [4].

Since more fractures occur in patients with T-score lower than -2/5, therapeutic interventions rely only on BMD test. This will cause omitting many patients with fracture risk [1].

Evaluating the BMD-independent clinical risk factors is important to predict the fracture. In addition to BMD, aging, fracture history, corticosteroid long administration, low BMI, hip fracture history of the parents, smoking and alcoholism are risk factors which predict the fracture [2, 3].

Combined BMD-risk factors methods would be a better choice to determine the probability of fracture than solely relying on BMD. Therefore, evaluating the fracture risk should include both BMD and clinical risk factors [3].

Fracture risk expression

Actual risk (AR) is the fracture probability which is usually expressed as the percentage of a specific period [2].

Relative risk (RR) is the ratio of the actual risk in two ways. It results in overestimating the fracture risk in some while underestimating in others [1].

FRAX

In 2008, World Health Organization developed a tool called FRAX to estimate the fracture risk which expresses the probability of hip or vertebra fracture in the next 10 years. This tool was approved in 11 cohorts and was tested on more than a million patients [3].

According to the economic conditions of different countries, FRAX could be used to determine whether BMD is necessary to use and also to start the treatment. In countries with limited access to DXA, FRAX could be used [4].

In FRAX algorithm, the probability of fracture occurrence (including hip fracture and major fracture risk) in the next ten years is estimated based on age, sex, weight, height, history of previous fracture, smoking, corticosteroid administration, rheumatism history, secondary osteoporosis, the level of alcohol consumption and patient's T-score. If Major Fracture Risk is higher than 20% and/or Hip Fracture is higher than 4%, the person categorizes in high risk group [6].

Prevention

Why prevention? Preventing osteoporosis is preferred to the treatment since bone microstructure changes related to too much bone decrement are irreversible. Treatment may fix and/or increase BMD while decreasing the fracture risk but hardly ever reverses the bone quality and strength to the primary condition completely [3,5].

BMD is determined by peak bone mass (PBM) and the level of bone decrement in adults. Preventing osteoporosis or BMD decrement depends on PBM increment and decreasing the bone loss decrement to keep the bone strength and to prevent the fracture ultimately [1, 4].

Increasing the peak bone mass

PBM is the peak bone mass that could be achieved during the life. Time of PBM is not accurately detected but probably in 30s of people's lives. The difference in time of PBM is due to genetic and hormonal differences, skeletal region (bone type) and the method to measure BMD [7].

Studies on identical twins revealed that 60-70 % of difference in PBM size is determined by genetics and appears phenotypically as race, sex and body size. The remaining 30-40 % is related to environmental factors like diet, exercise, habits, diseases and medications [3, 6].

A study on 668 healthy perimenopause women indicated that low body weight, menarche in 15 years old or later and physical activity of the teenagers are predictors for low bone mass by DXA and quantitative ultrasound [2].

Other studies on menopause women suggested smoking, low body mass index and Caucasian and Asian races as the risk factors for low BMD. Smoking is also related to BMD decrement and decrease in cortex thickness of 18-20 year young men. Patients with congenital disorders like osteogenesis imperfect and cystic fibrosis could be successfully managed in their childhood. This results in more livability and low PBM in adulthood [7, 8].

Preventing fractures: all patients should receive non-medication therapy to keep BMD, bone infrastructures and bone strength [5].

Since it was shown that approved medications for preventing osteoporosis decrease the fracture probability in the women at the beginning of free osteoporosis menopause, it should be noted that most fractures occur in women that do not have osteoporosis based on T-score criteria [7].

Patients with osteoporosis are clinically at risk for fracture but many fractures in patients with low bone mass or osteopenia exist (with -1 to -2/5 T-score) since many patients are categorized in this group [2, 6].

Because medicinal therapy is expensive and high risk, only a few patients candidate for medicinal prevention. Patients with fracture high risk are those benefit from medicinal therapy. Hence, selecting patients should be based on fracture risk determined by the combining BMP and clinical risk factors [7].

Based on USA adopted WHO algorithm (FRAX), Osteoporosis National Institute recommended the treatment for patients with low bone mass (T-score between -1 to -2/5 in femur neck or vertebral column) if hip fracture probability is >4% or big osteoporotic fracture probability is > 20 % [8].

Treatment

Non pharmacologic treatment: interventions to improve PBM and skeletal health should focus on healthy life style in years of generation. This could be categorized in nutrition, physical activity and other life style factors [4, 7].

Nutrition

Good nourishment from infancy to adolescence with emphasizing in receiving enough daily amounts of calcium and vitamin D is a key part to maximize PBM. This was highlighted in some studies [8].

A 3-year study on 6 to 14 years old identical twins indicated that BMD in those received calcium supplement (1000 mg/day) was increased significantly compared with those not received the supplements [9].

A study on 106 girls before their healthy menarche indicated that those received vitamin D supplement in their childhood had higher bone mass only in femur neck, not in vertebral column, compared with those not received [7].

Some studies indicated that drinking carbohydrate drinks might disturb the bone absorption and increase the fracture risk in girls. However, other studies indicated that the effect is due to drinking more nutrient drinks and the effect could reverse by taking calcium daily [7,9].

Anorexia nervosa is an increasing common disorder of eating in female teenagers which is related to BMD decrement and fracture risk increment [3].

Other nutritional disorders detected in bone growth disorders of teenagers include IBD, celiac disease and cystic fibrosis [1].

Physical activity: perspective and retrospective random and observational studies determined the beneficial effects of exercising on bone aggregation during the growth period with high benefit of high effects of exercise [4].

On the other hand, if too much exercising is with poor nutrition and body fat decrement, it could be harmful for the skeleton as seen in teenagers and young adults with triad sports women (eating disorder, amenorrhea, and osteoporosis) [5].

Other life style risk factors: smoking and alcoholism should be given up. Also, medications that could be harmful to skeletal health, such as glucocorticoids and anticonvulsants, should be avoided or prescribed for a short time or at a low dose [8].

Pharmacologic treatment: pharmacologic treatment plays a role in PBM increment just in special cases. For example, replacing hormones for their insufficiency in the childhood like growth hormone and pharmacologic

dose of vitamin D might be necessary in some children receiving anticonvulsant treatment and suffering from celiac disease to improve their skeletal health [3, 9].

Bone loss: Bone loss might begin right after PBM occurrence. Factors effective in the level and intensity of bone loss include hormone concentration, body weight, BMI, calcium and vitamin D administration, physical activity, drinking alcohol, osteoporosis family history and smoking [1].

Menopause

Common bone loss amount in women with estrogen deficiency is about 0.5-1/5 % annually at the beginning of post menopause. A few of women are involved in rapid bone loss and lose 3-5 % of bone mass annually [1, 10].

The level of bone loss is highly dependent on hormone, environmental and genetic factors. For example in a regional study on 272 healthy women before and about the menopause, no bone loss was seen in women before the menopause. While intensified bone loss 2-3 years before the menopause observed with a significant correlation between the level of bone loss, FSH level increment and bone activity markers [1, 4].

Age-related bone loss

The level of age-related bone loss in older women and men was approximately 0.5-1 %. The level of bone loss is reported based on the study type (periodic- descriptive versus regional (longitudinal)), skeletal location, skeletal compartment (trabecular versus cortical), type of measurement, race, sex and other debilitating factors [8].

In a regional study on 620 men and 20 to 88-year women, little bone loss (<0.4 % yearly) in hip and vertebral column of women before the menopause indicated while the level was three times higher in the beginning years post-menopause. In men younger than 50 years old, less amount of bone loss in hip and not in the vertebral column is noticed while persistent for the whole life [8, 10].

Decreasing bone loss

Keeping BMD or decreasing the level of bone loss is the primary aim to prevent osteoporosis. In lighted PBM, a general surgeon report about the bone health and osteoporosis suggested a daily pyramid to prevent and treat the osteoporosis that in base, life style changes including nutrition, physical activity and fall prevention could be noticed while in the second row, medications and bone loss related diseases and in the third row, drug therapy are located [5,7].

Calcium and vitamin D: Calcium and vitamin D are necessary for normal skeletal hemostasis. Vitamin D increases the intestinal absorption of calcium and is as necessary as appropriate muscle function and coordination for bone mineralization. Low levels of vitamin D are related to calcium level disturbance, calcium negative balance, and compensative increment of parathyroid hormone and therefore to high bone absorption [1, 11].

Since it is often difficult to differentiate calcium than vitamin D effects in clinical studies, some meta-analysis studies indicated BMD increment and fracture risk decrement in old patients taking calcium and vitamin D supplements [5].

The recommended dose of calcium for post-menopause women is 1200 mg which is much more than average daily consumption rate in general. Though the recommended sufficient use of vitamin D by United States Department of Health and Human Services is 400-600 unit, many experts agree that in case of not exposing enough to the sunlight, adults may need a higher daily dose [12].

We recommend daily taking of 800 IU vitamin D and 1200 mg elemental calcium (complete diet with supplementation) for the old [4].

In patients with too high osteoporosis risk that it is clinically suspected the daily common doses are not sufficient for them, measuring 25 OHD concentration to assure the sufficiency of the supplements is necessary. However, it should be noticed that the partial changeability might be significant [12].

Physical activity: Body weight- tolerating sports are related to little but significant improvement in BMD of the women before and after the menopause and also the men. These could improve the muscle tone and decrease the risk of falling down. The head of Military Health Center recommended a physical activity included at least 30 minutes jogging in most days but not every day [12].

Other life style factors: Meta-analysis indicated that smoking is related to BMP decrement and increases the fracture risk. Therefore, preventing to start smoking of stop it should be attempted. For several reasons, drinking too much alcohol is harmful for skeletal health. Though in some studies drinking some alcohol showed bone mass increment, it should not be recommended to patients to start drinking alcohol for skeletal health improvement [1, 9].

Medication therapy for bone mass decrement:

In the US, FDA approved some medication to prevent and to treat osteoporosis. The difference was significant and some guidelines were published to design clinical studies to support registering newer medications for osteoporosis [13].

To prevent, the study population should involve 45-year or older women able to move around 1-2 years post-menopause and not suffered from osteoporosis (It is defined based on -2 or less T-score point of vertebral column and/or one or having more fragile fractures in the vertebral column by FDA). In case of removing the ovaries, FSH level increment and low serum estradiol level could be observed [14].

The studies should take at least 2 years and be random and double blind while they are controlled with placebo and several doses with sufficient samples size are considered for their effectiveness and health.
Medications currently approved for osteoporosis prevention include Alendronate, Risedronate, Ibandrunate and Raloxifen [12].

For most women after the menopause, it is noticed that medication therapy should not be used to prevent osteoporosis. Although for women candidate post-menopause or those tend to medication therapy, Raloxifen and an oral bisphosphonate could be reasonable choices [13].

Selective estrogen-receptor modulator (SERM): Raloxifen (60 mg daily) is the only SERM that is currently used in the US to prevent osteoporosis post-menopausely. It is indicated that it could increase BMD and decrease the fracture risk but has no effect on non-vertebra fractures [11].

Important non-skeletal risks of Raloxifen include decreasing the breast cancer's risk, increasing the tromboemboli risk and hot flashes. A significant effect of the medication on heart diseases and endometrium has not been reported [7].

Other developing SERMs for osteoporosis treatment are Lasofoxifene and Bazedoxifene [6].

Quotation of article abstracts

"Osteopenia is a term to define bone density that is not normal but also not as low as osteoporosis. By definition from the World Health Organization osteopenia is defined by bone densitometry as a T score -1 to -2.5. There are many causes for osteopenia including calcium and vitamin D deficiency and inactivity. Genetics plays an important role in a person's bone mineral density and often Caucasian women with a thin body habitus who are

premenopausal are found to have osteopenia. Correction of calcium and vitamin D deficiency and walking 3 to 5 miles a week can often improve bone density in the hip and spine. There are a variety of pharmaceutical agents that have been recommended for the treatment of osteopenia and osteoporosis including hormone replacement therapy, selective estrogen receptor modulator therapy, anti-resorptive therapy. In addition patients with osteoporosis who have failed anti-resorptive therapy can have a significant improvement in their bone density with anabolic therapy." [1]

"The decrease in bone density may occur as a result of inflammatory bowel disease (IBD). Studies conducted on this issue generally focused on treated IBD patients. It is thus difficult to discriminate the role of disease from the effect of therapy on bone density reduction. We evaluated the prevalence of osteopenia/osteoporosis and abnormalities in indices of bone metabolism in patients with newly diagnosed IBD. METHODS: Evaluation of dual-energy X-ray absorptiometry (DXA) at the lumbar spine and intact parathormone (PTH), 25-hydroxy vitamin D and urinary cross-links, on 37 (26 females, median age 35.6+/-14.5 years) consecutive patients. RESULTS: Sixteen of 37 patients (43%) had normal DXA, 17 (46%) were osteopenic and 4 (11%) osteoporotics. Most male patients >30 years (63%) old as well as young women (62%) had osteopenia/osteoporosis. Mean value of intact-PTH was significantly higher in women >50 years (55.0+/-18.1 pg/mL) compared with those aged 16-20 years (30.0+/-14.6 pg/mL) (P=0.042). Furthermore, there was a significant difference between mean value of 25-hydroxy vitamin D in women >50 years old (16.2+/-4.7 ng/mL) compared to those aged 21-30 years (26.6+/-7.9 ng/mL) (P=0.041). Intact-PTH was significantly higher in osteoporotic patients (55.7+/-12.7 pg/mL) compared to normal subjects (28.3+/-13.0 pg/mL) (P=0.0014). CONCLUSION: High prevalence of osteopenia/osteoporosis was observed in this population. On the basis of these data, we propose to perform DXA in male patients aged >30 years and in all women with new diagnosis of IBD." [2]

"The current (metabolic) conception of bone-weakening diseases regards bone strength as determined by a systemically-controlled "mineralized mass" which grows until it reaches a peak and then is lost at individually-specific rates. This concept disregards bone biomechanics. Skeletons are structures, it reaches of which depends on the stiffness and the spatial distribution rather than the volume of the calcified material. Rather than allowing a systemic regulation of their "mass" as a way to optimize their strength, bones autocontrol their stiffness by orienting bone formation and destruction as locally determined by the directional sensing, by osteocytes, of the strains caused by mechanical usage (gravity, muscle contractions). Bone mass and strength are just side products of that control. Endocrine-metabolic systems modulate non-directionally the work of bone cells as required for achieving a mineral equilibrium, despite the biomechanical controls, and can determine osteopenias and osteoporoses. Osteoporoses are not "intense osteopenias" (as per the current WHO's conception) but "osteopenic bone fragilities" (as recently stated by the NIH). The diagnosis of osteopenia is an anthropometric problem that can be solved densitometrically; but that of bone fragility is a biomechanical matter that requires evaluation of bone material's stiffness and distribution by other means ("resistometry"). For therapeutic purposes, osteopenias and osteoporoses should be also evaluated according to the relationship between bone mass or strength and muscle mass or strength in order to distinguish between "mechanical" (disuse) and "metabolic" etiologies (intrinsic bone lesion, or systemic disequilibrium), in which the bone/muscle proportionality tends to remain normal or to deteriorate, respectively." [3]

"Because bone mineral density (BMD) measurements at various sites differ in the relative amounts of cortical and trabecular bone that they assess, they also differ in their sensitivity for detecting osteopenia. Lateral spine dual energy x-ray absorptiometry (DXA) allows measurement of BMD of the vertebral bodies, which contain mainly trabecular bone, without contribution from the posterior vertebral elements, which are rich in cortical bone. Thus, we hypothesized that lateral spine DXA would detect osteopenia more frequently than anterior-posterior (AP) spine DXA. To assess the ability of DXA to estimate trabecular bone mass, we compared AP and lateral DXA spine measurements with trabecular bone measurements by quantitative computed tomography (QCT) in 58 patients. We then compared AP vs. lateral spine DXA measurements in 1) 300 women referred for routine bone densitometry, 2) 30 glucocorticoid-treated women, and 3) 44 women with vertebral compression fractures. To compare short term reproducibility, we performed repeat AP and lateral DXA scans in 50 women. The association between QCT and DXA measurements was stronger when DXA measurements were made in the lateral (r = 0.784) or midlateral (r = 0.823) projection than in the AP (r = 0.571) projection. The association of BMD with age was stronger when DXA measurements were made in the lateral (r = 0.536) or midlateral (r = 0.536) projection than in the AP (r = 0.382) projection. The declines in BMD with age for AP, lateral, and midlateral DXA

measurements were 0.48%, 0.60%, and 0.88%/yr, respectively. In the women referred for routine densitometry, lateral DXA measurements were significantly ($P < 0.05$) more abnormal than AP measurements compared with those in young women. This was also true in the women treated with glucocorticoids and women with vertebral compression fractures. Lateral DXA often detected osteopenia in patients whose AP DXA was normal. The 95% confidence limits for changes in BMD attributable to measurement error for AP, lateral, and midlateral DXA were 0.027, 0.038, and 0.057 g/cm2, respectively. These results indicate that lateral DXA measurements identify patients with osteopenia more often than AP DXA measurements, probably because lateral DXA more accurately estimates trabecular bone mass. Short term reproducibility of lateral DXA is nearly as good as that for AP DXA." [4]

"Bone mineral density (BMD) assessed by double-energy X-ray absorptiometry (DEXA) accurately estimates the bone mass in living individuals, and is thus the method usually employed in the diagnosis and follow-up of osteopenia. It is preferred, in clinical settings, to the more invasive and destructive histomorphometrical assessment of trabecular bone mass in undecalcified bone samples. This study was performed in order to examine the value of DEXA-assessed BMD at the proximal end of the right tibia, either alone or in combination with the cortico-medullary index at the midshaft point of the right tibia (CMI), in the diagnosis of osteopenia in a prehistoric sample composed of 95 pre-Hispanic individuals from Gran Canaria. Age at death could be estimated in 34 cases. Diagnosis of osteopenia was performed by histomorphometrical assessment of trabecular bone mass (TBM) in an undecalcified bone section of a small portion of the proximal epiphysis of the right tibia. A high prevalence of osteopenia was found among the population of Gran Canaria. Both TBM and BMD were significantly lower in the older individuals than in younger ones, and BMD was also significantly lower in female individuals. BMD was moderately correlated with TBM ($r = +0.51$); the correlation was higher if CMI was included (multiple $r = +0.615$). BMD values lower than 0.7 g/cm2 showed a high specificity (>93%) at excluding normal TBM values. These methods were prospectively applied in a further sample of 21 right tibiae from Gran Canaria, Tenerife, and El Hierro. The results were similar to those obtained in the larger sample. Thus, DEXA-assessed BMD combined with CMI (noninvasive procedures) may be useful in detecting osteopenia in ancient populations." [5]

"Skin and bone share a similar organic constituent (type I collagen) which decreases with time after menopause due to hypoestrogenism. The interdependence of skin and bone atrophy has been reported. This study was conducted to assess the predictive value of an ultrasonographic measurement of skin thickness in the diagnosis of osteopenia (BMD below -1.5 SD.) in perimenopausal and early postmenopausal women. All patients had skin thickness measured by the same radiologist and had a dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine and the femoral neck. Of the 77 women studied, the mean age was 50.9 +/- 3.0 years. Thirty patients were in perimenopause and 47 in early postmenopause. Mean skin thickness was 2.1 +/- 0.4 mm. Women with a skin thickness of < or = 1.7 mm carried a higher risk for developing osteopenia at the lumbar spine (odds ratio 8.41, 95% confidence interval 2.19-32.35) and the femoral neck (odds ratio 3.88, 95% CI 1.14-13.17). Patients with a skin thickness of > or = 2.4 mm had a lower probability of osteopenia at the lumbar spines (odds ratio 0.17, 95% CI 0.035-0.845) and the femoral neck (odds ratio 0.22, 95% CI 0.055-0.899). In conclusion, a low skin thickness measurement by ultrasonography may be used as an indicator for osteopenia in perimenopausal and early postmenopausal women." [6]

"Three cases of chronic hip pain with radiographic periarticular osteopenia and normal joint spaces are reported. The articular nature of symptomatology, periarticular demineralization, and radionuclide localization suggested intraarticular disease. Computed tomography did not disclose the cause of hip pain when utilized in two instances. Positive contrast hip arthrography was the only diagnostic modality which demonstrated the chondromatosis or adhesive capsulitis responsible for pain. Differential diagnosis and pathophysiologic mechanisms are briefly reviewed." [7]

"An increased awareness of the higher incidence of osteopenia and osteoporosis associated with a number of gastrointestinal disease states has occurred over the last few years. High rates of bone loss have been reported in luminal diseases such as inflammatory bowel disease and celiac disease as well as in cholestatic liver diseases and in the post-liver transplant setting. The post-gastrectomy state and chronic pancreatitis are also associated with decreased bone density. Publications over the last year have provided a better understanding of the true incidence of osteoporosis and fracture risk in these gastrointestinal disease states. Dual-energy x-ray

absorptiometry remains the diagnostic procedure of choice. Biochemical markers of bone resorption have a role in identifying those patients with ongoing bone loss and monitoring their response to therapy. Identification of patients at risk and initiation of measures to prevent bone loss form the optimal therapeutic strategy. This article reviews advancements in the understanding of the development and activation of osteoblasts and osteoclasts. It also reviews the recent data concerning the diagnosis and treatment of bone loss associated with various gastrointestinal disease states." [8]

"Mandibular autopsy specimens of 100 Danish subjects without known systemic diseases were obtained. Microradiograms of 100-micrometer-thick undemineralized vertical buccolingual grounds cross-sections and these sections, stained with basic fuchsin, were used. Microradiographic and histologic readings of bone turnover foci on Haversian canal and endosteal-trabecular surfaces were compared and combined. The analyses show the following. 1) number/area Haversian canals with bone formation and resorption foci and total of Haversian canals are reproducible and representative measures for bone turnover, while estimation of % bone turnover surfaces on periosteal and endosteal-trabecular surfaces in biopsies of mandibles has no diagnostic value. 2) Percentage of bone mass and mean cortical width in standard locality indicate the level in group of mandibles. 3) the cortical variables of bone turnover are sex independent; number/area Haversian canals with resorption foci is age independent; number/area Haversian canals with bone formation foci, total of Haversian canals and percentage of subendosteal (Haversian canals + marrow spaces) are increased with age." [9]

"Osteopenia is far more widespread than osteoporosis, its incidence in the older age-groups being roughly three times that of osteoporosis. Furthermore, almost one-sixth of the young-adult population are--by definition--osteopenic (< 1% have osteoporosis). The National Osteoporosis Foundation guidelines suggest intervention at T-scores of -2.0 or lower; however, risk factors are built into various sets of guidelines, such that intervention may be desirable at T-scores of -1.0. The risk of fracture is, in fact, greater at lower bone mineral densities (BMD) throughout the entire range of BMD values. Thus, osteopenia is a management issue. This article considers the risks of fracture in terms of BMD and other factors, and recommends action that answers the prevention needs of the individual patient." [10]

"The global trend toward increased longevity has resulted in aging populations and a rise in diseases or conditions that primarily affect older persons. One such condition is osteoporosis (fragile or porous bones), which causes an increased fracture risk. Vertebral and hip fractures lead to increased morbidity and mortality and result in enormous healthcare costs. Here we review the evolution of the diagnosis of osteoporosis. In an attempt to separate patients with normal bones from those with osteoporosis and to define the osteoporosis diagnosis, multiple factors and characteristics have been considered. These include pathology and histology of the disease, the endocrine regulation of bone metabolism, bone mineral density (BMD), fracture type or trauma severity, risk models for fracture prediction, and thresholds for pharmacological intervention. The femoral neck BMD -2.5 SDs cut-off for the diagnosis of osteoporosis is arbitrarily chosen, and there is no evidence to support the notion that fracture location (except vertebral fractures) or severity is useful to discriminate osteoporotic from normal bones. Fracture risk models (including factors unrelated to bone) dissociate bone strength from the diagnosis, and treatment thresholds are often based on health-economic considerations rather than bone properties. Vertebral fractures are a primary feature of osteoporosis, characterized by decreased bone mass, strength, and quality and a high risk of another such fracture that can be considerably reduced by treatment. We believe that the 2001 definition of osteoporosis by the National Institutes of Health Consensus Development Panel on Osteoporosis is still valid and useful: 'Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture'" [11]

"The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy. The statement provides state-of-the-art information and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. The target audience of clinicians for this statement includes, but is not limited to, family practitioners, internists, gerontologists, orthopaedic surgeons, rheumatologists, obstetricians and gynecologists, and preventive medicine specialisits. PARTICIPANTS: A nonfederal, nonadvocate, 13-member panel

representing the fields of internal medicine, family and community medicine, endocrinology, epidemiology, orthopaedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. In addition, 32 experts from these same fields presented data to the panel and a conference audience of approximately 700. EVIDENCE: The literature was searched using MEDLINE and an extensive bibliography of references was provided to the panel. Experts prepared abstracts for their conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience. CONSENSUS PROCESS: The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement, which was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel's final revisions [13-15]

CONCLUSIONS

Osteoporosis occurs in all populations and at all ages. Though more prevalent in white postmenopausal females, it often goes unrecognized in other populations. Osteoporosis is a devastating disorder with significant physical, psychosocial, and financial consequences. The risks for osteoporosis, as reflected by low bone density, and the risks for fracture overlap but are not identical. More attention should be paid to skeletal health in persons with conditions known to be associated with secondary osteoporosis. Clinical risk factors have an important, but as yet poorly validated, role in determining who should have BMD measurement, in assessing risk of fracture, and in determining who should be treated. Adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation of these two components in bioavailable forms may be necessary in individuals who do not achieve recommended intake from dietary sources. Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children. Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce the risk of falls in older individuals. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis. Fracture prevention is the primary goal in the treatment of patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures. These include therapies that enhance bone mass and reduce risk or consequences of falls. Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for the presence of osteoporosis and given appropriate therapy." [12].

"At first glance the human bone appears to be solid, rigid and unchangeable. But in point of fact this is not so, for a process of change is continuously going on, during which bone mass is resorbed and formed. Up until the age of 30 bone mass continues to be formed, although at an increasingly slower pace. A few years of equilibrium between bone formation and bone resorption follow. Thereafter, from about the age of 40, a continuous slow loss of bone mass sets in. This is considered to be a normal process of aging. But if the speed of resorption exceeds a certain degree and bone resorption increases, osteoporosis can develop after several years. Osteoporosis is therefore an illness in which bone mass has been massively resorbed over the past years and/or is being acutely resorbed. Given the altered demographic structure--an ever larger number of people living to an advanced age--the number of people affected by osteoporosis is increasing. Once the bone loss reaches a certain degree, there is a greater susceptibility to bone fractures. Particularly affected are the vertebrae, the neck of the femur, and the forearm." [13].

"To identify regions of interest (ROIs) relevant to periarticular osteoporosis in RA with low precision error and sufficient inter-rater reliability and to test diagnostic validity for RA. METHODS: Periarticular BMD was measured using dual-energy X-ray absorptiometry (DXA). Five ROIs were defined around MCP and/or PIP joints II-V, II-IV and mid-metacarpal to mid-phalangeal. They were evaluated for precision using the root mean square coefficient of variation (RMS-CV) and the intra-class correlation coefficient (ICC) for inter-reader reliability. To test validity, established RA patients (n = 25) and early arthritis patients (n = 25) were compared with healthy controls (n = 37) matched on sex, age and menopausal status using paired t-tests, ROC curves and scatterplots. RESULTS:

The RMS-CV was 0.45-1.07%. The ICC was 0.99. Mean BMDs of the five ROIs ranged from 0.321 to 0.372 g/cm(2) in established RA, from 0.321 to 0.382 g/cm(2) in early arthritis and from 0.342 to 0.401 g/cm(2) in healthy controls. Mean differences ranged from 0.012 to 0.032 g/cm(2) for established RA and from 0.023 to 0.033 g/cm(2) for early arthritis patients compared with matched controls, with $P < 0.05$ for ROIs 1-5 in early arthritis and the whole hand in established RA. ROC curves indicated low discriminative power, with an area under the curve (AUC) of 0.61-0.64, and scatterplots showed great overlap between BMD values of patients and controls. CONCLUSIONS: Periarticular BMD measured with DXA seems not to be a useful diagnostic feature due to strong overlap of BMD values between healthy controls, established RA patients and early arthritis patients." [14]

"T-score-based diagnosis of osteoporosis might lead to diagnostic misclassification when using multiple-site bone mineral density (BMD) measurements. To compare the diagnostic concordance of T-score-based diagnosis of osteoporosis among different skeletal sites and its correlation to osteoporotic fracture, we studied 1200 postmenopausal women with (441) and without (759) fragility fracture after measuring BMD at the femoral neck, Ward's triangle, trochanter, and spine. Agreement rates of T-score-based diagnosis of osteoporosis were statistically different between pairs of measurements taken at different skeletal sites (McNemar test, $p < 0.001$). Fragility fractures poorly matched T-score-based diagnosis of osteoporosis (Cohen and Younden indexes <0.4). Technique inaccuracies support these discrepancies as also shown by the large range of T-score values (from -2 to -3) with similar abilities to predict fractures by ROC curve area comparison. Concordance rates between T-score and fragility fracture diagnosis of osteoporosis (marginal homogeneity test, $p < 0.001$) were also different across the various measurement sites. Our data show that the T-score leads to diagnostic inconsistencies among different skeletal sites and low concordance with fragility fracture based diagnosis of osteoporosis. Integration of the T-score with multiple risk assessment from clinical sources should be tested to better diagnose osteoporosis and related fracture risk." [15]

Osteoporosis and osteopenia are two terms that are related to low bone density. Bone densitometry is the main tool for diagnosing this disease. However, other lab data are required for the diagnosis. This disease can actively reduce the quality of life and affect the activity of an individual. It can change many routine activities of the afflicted patient and pose many complications such as fracture. It can also cause economical difficulties and issues. Thus, recognizing its diagnosis and treating it are the most important part once we encounter this disease and its patients [12,15].

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