

Evolutionary Pathways of Diagnosis in Osteoporosis

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1. Introduction

Osteoporosis was formally identified as a disease by a group of World Health Organization (WHO) experts in 1994 resulting in publication of "Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis" (WHO Technical Report Series, 1994).

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation and mineralization (NIH Consensus, 2001).

Osteoporosis occurs in all populations and at all ages and is a devastating disorder with significant physical, psychosocial and financial consequences. The WHO operationally defines osteoporosis as a bone density at least 2.5 standard deviations below the mean peak bone mass for healthy young adult white women, also referred to as a *T-score* of -2.5 . Because of the difficulty in accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion. So different instruments have not the same performance in regard to a accurate bone density measurement.

The aims of this chapter are stated in table 1.

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| <ol style="list-style-type: none"> 1. Identify the technique, safety and limitations of dual energy X-ray absorptiometry (DEXA or DXA) scanning. 2. Explain the value of utilizing bone densitometry to assess and monitor fracture risk. 3. Incorporate clinical risk factors that predict future fracture. 4. Explain the value of identifying the different components that make up the bone metabolism. 5. Open new tracks for diagnosis of osteoporosis |
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Table 1. Statement of objectives

In the evolutionary pathways of diagnostics in bone loss the osteoporosis diagnosis is often performed by measuring bone mineral density (BMD) that measures the amount of calcium in different regions of the skeleton as femur neck or/and 1-4 lumbar vertebrae .

In establishing diagnosis of osteoporosis three parameters should be considered as stated in table 2.

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| <ol style="list-style-type: none"> 1. The diagnosis of osteoporosis. 2. The diagnosis of bone metabolism components. |
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Table 2. Statement of objectives

2. Osteoporosis and fracture risk: Monitoring and assessment

Several methods are available to measure BMD. In general, the lower bone density the greater osteoporotic fracture risk. Unfortunately osteoporosis frequently remains undiagnosed until a fracture occurs. BMD methods involve DEXA or quantitative computer tomography scans (Osteo CT or QCT) of bones in the spine or femur. The most widely used technique is DXA.

2.1 Technique, safety and limitations of DXA scanning

Bone densitometry is the *gold standard method* for measuring BMD. Bone densitometry is the method used to determine the drug efficacy in recent large clinical trials and to characterize fracture risk in large epidemiological studies. DXA, previously DEXA, is a method of measuring BMD. A DXA scan uses low energy X-rays. A machine sends X-rays from two different sources through the bone being tested. Bone blocks a certain amount of the X-rays. The more dense the bone is, the fewer X-rays get through to the detector. By using two different X-ray sources rather than one it greatly improves the accuracy in measuring the bone density. The amount of X-rays that comes through the bone from each of the two X-ray sources is measured by a detector. This information is sent to a computer which calculates a score of the average density of the bone. A low score indicates that the bone is less dense than it should be, some material of the bone has been lost, and is more prone to fracture. Older methods such as single photon absorptiometry (SPA) do not predict hip fractures as well as DXA.

But currently there is no accurate measure of overall bone strength. Osteoporosis is related to decreased bone strength, which encompasses both BMD and bone quality. Notwithstanding BMD assessed by DXA remains the *gold standard* for the diagnosis of osteoporosis.

DEXA is the most widely available method of bone densitometry. The measurement of BMD by DEXA has served as a fit surrogate for the measurement of bone strength and accounts for approximately 70 percent of bone strength, it was said. DEXA measures the BMD in the spine, hip or total body.

Based on the 1994 WHO report, osteoporosis is defined as a BMD value from at least -2.5 SD below the mean value of a young healthy population (T-scores \leq -2.5). Any bone can be affected, but of special concern are the fractures of the hip and spine.

Diagnosis of osteoporosis is generally on the basis of BMD assessment at the spine and proximal femur by DXA. Two X-ray beams with differing energy levels are targeted at the patient's bones. But, there are other variables in addition to age which are suggested to confound the interpretation of BMD as measured by DXA. One important confounding variable is bone size. DXA has been shown to overestimate the bone mineral density of taller

subjects and underestimate the bone mineral density of smaller subjects. This error is due to the way in which DXA calculates BMD. In DXA, bone mineral content, measured as the attenuation of the X-ray by the bones being scanned, is divided by the area, also measured by the machine, in the site being scanned.

Because DXA calculates BMD using area (aBMD: areal Bone Mineral Density), it is not an accurate measurement of true bone mineral density, which is mass divided by a volume. In order to distinguish DXA BMD from volumetric bone-mineral density, researchers sometimes refer to DXA BMD as aBMD.

The National Osteoporosis Foundation's guidelines state that women over 65, younger post menopausal women who have any of the osteoporosis risk factors, as well as those with specific fractures should have this test. However, men are also at risk for osteoporosis as they age especially if they have some of the causes of osteopenia or osteoporosis

2.2 Other methods of osteoporosis diagnosis

The bone density test is performed using various methods. Some of these BMD tests are explained here briefly.

2.2.1 Quantitative ultrasound parameters

Quantitative Ultrasound (QUS) is the most basic bone density test performed. It can be the first step in order to diagnose any primary bone related problem. If the ultrasound test finds any defect in the bone density, then the DEXA test is recommended. QUS can be used to predict fracture risk, but it cannot be used for the diagnosis of osteoporosis or for monitoring the effects of treatment. Ultrasounds measure the BMD in the heel and uses sound waves of different frequencies through water or air, to perform the task. Bone density test is painless, fast and without harmful radiations. Ultrasounds are unable to detect complicated bone problems and hence there are other methods that are capable of detecting the more complicated ones.

Ultrasound axial transmission, a technique using propagation of ultrasound waves along the cortex of cortical bones, has been proposed as a diagnostic technique for the evaluation of fracture healing. Quantitative ultrasound parameters have been reported to be sensitive to callus changes during the regeneration process. The results suggest that the time of flight measured in axial transmission is affected by local changes of speed of sound induced by changes in local mineralization.

2.2.2 Quantitative computer tomography scan

Quantitative Computer Tomography Scan (QCT) is done to find true volumetric bone mineral content by measuring separately trabecular and three-dimensional cortical bone.

Image quality degradation due to subject motion is a common artefact affecting *in vivo* high-resolution peripheral quantitative computed tomography (HR-pQCT) of bones. These artefacts confound the accuracy and reproducibility of bone density, geometry, and cortical and trabecular structure measurements. Observer-based systems for grading image quality and criteria for deciding when to repeat an acquisition and post hoc data quality control remain highly subjective and non-standardized (Sodeab et al, 2011).

The QCT scan is a not so famous form of bone density test because it is expensive, utilizes a high amount of radiation and its accuracy is minimum.

The QCT measures BMD at spine or hip. Bone architecture, measured by CT, is a BMD-independent determinant of bone strength (Bauer & Link, 2009).

Because bone density can vary from one location in the body to another, a measurement taken at the heel usually is not as accurate a predictor of fracture risk as is a measurement taken at the spine or hip. That is why, if the test on a peripheral device is positive, DXA scan should be performed at the spine or hip to confirm the diagnosis. But what happens at the spine or hip is not what happens at the heel or wrist. So, the problem endures.

2.2.3 Bone fracture risk calculators

The fracture risk assessment tool (FRAX®) case finding algorithm has been developed to predict the 10-year risk of major and hip fractures based on clinical risk factors, with and without BMD. The Garvan fracture risk calculator is another tool that is available online to calculate the risk of fracture. The FORE Fracture Risk Calculator™ uses risk factors established by the WHO, such as alcohol use, family history of hip fractures, and certain chronic diseases.

FRAX and Garvan fracture risk calculators estimate the absolute risk of osteoporotic fractures. Garvan estimated higher absolute fracture risk than FRAX. None of the calculators provide better discrimination than models based on age and BMD, and their discriminative ability is only moderate, which may limit their clinical utility (Bolland et al., 2011).

The Framingham Osteoporosis Study, an ancillary study of the Framingham Heart Study, has contributed substantially to the understanding of risk factors for age-related bone loss and fractures in men and women. For the past fifteen years, this research program has been investigating a variety of risk factors for bone loss and fractures by assessing BMD using SPA, dual photon absorptiometry (DPA), DXA, QUS, and by ascertaining fracture incidence in the Framingham Study

The FRAX® tool has been developed by WHO to evaluate fracture risk of patients that integrate the risks associated with clinical risk factors as well as with or without BMD at the femoral neck. The FRAX® algorithms give the 10-year probability of fracture (Kanis et al., 2000).

The prediction of hip fracture and other osteoporotic fractures based on the assessment algorithms (FRAX™) which includes clinical risk factors alone, or the combination of clinical risk factors plus BMD is prediction, but Medicine is Medicine and future prediction is not Medicine and the important is not the statistics but if the human ill being who must be treated or not. In the evaluation of the FRAX and Garvan fracture risk calculators in older women it was found that Garvan calculator was well calibrated for osteoporotic fractures but overestimated hip fractures. FRAX with BMD underestimated osteoporotic and hip fractures. FRAX without BMD underestimated osteoporotic and overestimated hip fractures. In summary, none of the calculators provided better discrimination than models based on age and BMD, and their discriminative ability was only moderate, which may limit their clinical utility. The calibration varied, suggesting that the calculators should be validated in local cohorts before clinical use.

The probability is not certainty of fracture. It is statistics. That is science that deals with the collection, classification, analysis, and interpretation of numerical facts or data, and that, by use of mathematical theories of probability, imposes order and regularity on aggregates of more or less disparate elements. Is that the matter?. May be, but it is not medicine. And osteoporosis is a medical condition. And risk factors do not mean disease. The patient is the

patient and not one year probability. On the other hand “the FRAX® assessment does not tell you who to treat which remains a matter of clinical judgement. In many countries, guidelines are provided that are based on expert opinion and/or on health economic grounds”, what the question remain to be wonder what to do with?. That supposes one first principles answer. Level D evidence-based medicine according to the standards of the UK National Health Service or lower level if any existed in the evidence-based medicine.

2.2.3.1 The Bayes' theorem

Bayes' theorem deals with the role of new information in revising probability estimates. The theorem assumes that the probability of a hypothesis (the posterior probability) is a function of new evidence (the likelihood) and previous knowledge (prior probability).

Specific chart reminders to physicians combined with mailed patient education substantially increased the levels of bone density testing and could potentially be used to improve osteoporosis screening in primary care. Bayesian hierarchical analysis makes it possible to assess practice-level interventions when few practices are randomized (Levy BT et al. 2009).

In probability theory and applications, Bayes' theorem shows how to determine inverse probabilities: knowing the conditional probability of B given A, what is the conditional probability of A given B? This can be done, but also involves the so-called prior or unconditional probabilities of A and B.

This theorem is named for Thomas Bayes and often called Bayes' law or Bayes' rule. Bayes' theorem expresses the conditional probability, or "posterior probability", of a hypothesis H (its probability after evidence E is observed) in terms of the "prior probability" of H, the prior probability of E, and the conditional probability of E given H. It implies that evidence has a confirming effect if it is more likely given H than given not-H. Bayes' theorem is valid in all common interpretations of probability, and it is commonly applied in science and engineering. However, there is disagreement among statisticians regarding the question whether it can be used to reduce all statistical questions to problems of inverse probability. Can competing scientific hypotheses be assigned prior probabilities?

The key idea is that the probability of an event A given an event B depends not only on the relationship between events A and B but also on the marginal probability of occurrence of each event.

As a formal theorem, Bayes' theorem is valid in all common interpretations of probability. However, frequentist and Bayesian interpretations disagree on how (and to what) probabilities are assigned. In the Bayesian interpretation, probabilities are rationally coherent degrees of belief, or a degree of belief in a proposition given a body of well-specified information. Bayes' theorem can then be understood as specifying how an ideally rational person responds to evidence. In the frequentist interpretation, probabilities are the frequencies of occurrence of random events as proportions of a whole. Though his name has become associated with subjective probability, Bayes himself interpreted the theorem in an objective sense.

Bayes' theorem is often more easy to apply, and to generalize, when expressed in terms of odds. It is then usually referred to as Bayes' rule, which is expressed in words as posterior odds equals prior odds times likelihood ratio. The term Bayes factor is often used instead of likelihood ratio.

In statistics, the use of Bayes factors is a Bayesian alternative to classical hypothesis testing. Bayesian model comparison is a method of model selection based on Bayes factors.

The adoption of Bayes' theorem has led to the development of Bayesian methods for data analysis. Bayesian methods have been defined as "the explicit use of external evidence in the

design, monitoring, analysis, interpretation and reporting" of studies (Spiegelhalter, 1999). The Bayesian approach to data analysis allows consideration of all possible sources of evidence in the determination of the posterior probability of an event. It is argued that this approach has more relevance to decision making than classical statistical inference, as it focuses on the transformation from initial knowledge to final opinion rather than on providing the "correct" inference.

In addition to its practical use in probability analysis, Bayes' theorem can be used as a normative model to assess how well people use empirical information to update the probability that a hypothesis is true.

The odds in favor of an event or a proposition are expressed as the ratio of a pair of integers, which is the ratio of the probability that an event will happen to the probability that it will not happen.

Frequency probability is the interpretation of probability that defines an event's probability as the limit of its relative frequency in a large number of trials. The development of the frequentist account was motivated by the problems and paradoxes of the previously dominant viewpoint, the classical interpretation. The shift from the classical view to the frequentist view represents a paradigm shift in the progression of statistical thought.

Frequentists talk about probabilities only when dealing with well-defined random experiments. The set of all possible outcomes of a random experiment is called the sample space of the experiment.

A paradigm is what members of a scientific community, and they alone, share. A paradigm shift (or revolutionary science) is, according to Thomas Kuhn in his influential book *The Structure of Scientific Revolutions* (1962), a change in the basic assumptions, or paradigms, within the ruling theory of science. It is in contrast to his idea of normal science. A proposition is true if it works. Thus, older occupants in motor-vehicle crashes are more likely to experience injury than younger occupants. Crash-injury data were used with Bayes' Theorem to estimate the conditional probability of AIS 3+ skeletal injury given that an occupant is osteoporotic for the injury to the head, spine, thorax, lower extremities, and upper extremities. It suggests that the increase in AIS 3+ injury risk with age for non-spine injuries is likely influenced by factors other than osteoporosis (Rupp et al., 2010).

2.2.4 The radiological assessment of vertebral osteoporosis

Vertebral fracture assessment (VFA) is recognized as the standard in fracture risk assessment. High definition instant vertebral assessment allows identifying spine fractures with one rapid, low dose, single energy image at double the resolution of previously available techniques. VFA differs from radiological detection of fractures, because VFA uses a lower radiation exposure and can detect only fractures, while traditional x-ray images can detect other bone and soft tissue abnormalities in addition to spinal fractures.

2.2.5 Some other methods

1. Morphometry. VFA may be referred to as DEXA or DXA or morphometric x-ray absorptiometry. Magnetic resonance imaging (MRI) is a new method of measuring bone density. MRI has made significant contributions to the diagnosis of acute hip joint disease in adults by enabling early differentiation between such conditions as idiopathic avascular femoral head necrosis, septic coxitis, degenerative disease, and tumors. MRI may provide information pertaining to bone density and structure as well as to occult fracture detection.

Quantitative methods such as morphometry or MRI have been developed over the past years and can be used to assess more precisely the features of vertebral fractures.

2. Single-energy X-ray absorptiometry (SXA) is a method of assessing bone mineral density using a single energy X-ray beam. This may be used to measure the wrist or heel bone density, but SXA is not used as often as DEXA. It is now widely considered inferior to dual-energy X-ray absorptiometry which uses a second energy beam to correct for absorption of X-ray energy by non-calcium containing tissues. Many previous studies of peripheral bone mineral density measurement for instance at the wrist, used SXA to assess bone mineral density.
3. Peripheral dual energy X-ray absorptiometry (PDEXA) is a type of DEXA test that measures the density of bones in the arms or legs, such as the wrist or a finger. It cannot measure the density of the bones most likely to break, such as the hip and spine. PDEXA is not as useful as DEXA for finding out how well medicine used to treat osteoporosis is working.
4. SPA is a method that uses a single-energy photon beam that is passed through bone and soft tissue to a detector. The amount of mineral in the path is then quantified.
5. Dual-photon absorptiometry (DPA) uses a photon beam that has two distinct energy peaks. One energy peak is absorbed more by the soft tissue. The other energy peak is absorbed more by bone. The soft-tissue component is subtracted to determine the BMD.
6. Radiographic absorptiometry (RA) uses an X-ray of the hand and a small metal wedge to calculate bone density. This is an approach that include different methods to significantly increase the proportion of eligible patients tested for low BMD, using a low-cost peripheral BMD system in the primary care physician's office or satellite facility to identify those patients who could receive further BMD assessment by central DXA.

2.3 The diagnosis of bone metabolism control

Bone metabolism control is performed inside and outside the bone. Through lab tests which may be carried out in blood and urine samples, bone metabolism becomes known. The results of these tests can help identify conditions that may be contributing to bone loss. The most common blood tests evaluate: blood calcium levels, blood vitamin D levels, liver function, kidney function tests: both creatinine and BUN are included on the common chemical profiles, thyroid function: TSH, T4, T3 tests, parathyroid hormone levels, estradiol levels in women, follicle stimulating hormone test to establish menopause status, testosterone levels in men, osteocalcin levels to measure bone formation.

A 24-hour urine collection can show if there is a problem with intestinal absorption of calcium (Ca) or leakage of calcium through the kidneys. Blood tests are done to check things such as blood chemistries, blood count, proteins, vitamin D level, thyroid function, and antibodies for celiac disease, a condition that may cause poor intestinal absorption of important nutrients. A simple urine specimen shows the bone metabolism or an important factor in determining bone density and bone strength. With this test, natural bone protein products such as N-telopeptide (NTX) are tested.

Dairy products constitute one of the most important types of functional food. And dairy products-calcium intake and its good intestinal absorption is basic. Renal Ca clearance is other parameter to be measured.

Essential hypertensive (EH) patients have a higher rate of urinary calcium excretion and, according to some reports, somewhat lower levels of serum ionized calcium. The mean renal calcium clearance is somewhat higher, but the difference from controls did not reach statistical

significance. These data indicate an abnormal handling of a calcium load by patients with EH and raise the possibility that such abnormality may not be due simply to a renal defect but perhaps to an altered calcium distribution among different compartments in the body.

Altered regulation of serum calcium level was proposed to be associated with arterial hypertension and to be dependent on a renal Ca leak or altered Ca binding to plasma proteins and cell membrane described in human and experimental hypertension. Hypertensive patients have an altered regulation of serum Ca concentrations, probably due to a different body distribution of Ca, rather than to altered Ca binding to plasma proteins.

It has been reported that changes in salt loading influence parameters of calcium metabolism in hypertensive subjects. It was also reported that response of blood pressure to salt intake is related to salt-induced increase in intracellular calcium and decrease in intracellular magnesium concentrations. Several authors showed that salt-sensitive hypertensive subjects significantly decreased blood pressure after calcium intake which was emphasized by high salt intake.

It has been showed that during high salt intake regimen increase in blood pressure was followed with decrease in serum calcium level, this was explained by the fact that high salt intake stimulates the Ca uptake by cells. They also reported the following characteristics of hypertensive patients with additionally lower blood pressure as a response to Ca intake: salt-sensitive, low serum ionized Ca and plasma renin activity (PRA) values and high parathyroid hormone (PTH) values and 1,25-(OH)₂-D₃ values.

A number of abnormalities in the extracellular and intracellular handling of Ca in arterial hypertension, namely an increased urinary Ca excretion, a reduced serum ionized Ca level and an enhanced intracellular free calcium concentration, have previously been reported. The total body Ca clearance, calculated from the area under the curve of the serum Ca concentrations, was enhanced in hypertensive patients (P less than 0.03). Although the renal Ca excretion is higher in hypertension, the renal calcium clearance account for only a minor fraction of the total body clearance, suggesting that the reduced serum Ca levels achieved by the hypertensive patients are not explained by the renal Ca leak. The enhanced total body Ca clearance found in hypertensive subjects is therefore due to an increased tissue Ca uptake. This finding provides indirect evidence of altered cell Ca handling in hypertension.

Ca metabolism has been investigated in patients with essential hypertension and normal renal function to evaluate the renal calcium handling and the reported increase in renal Ca loss. The results support the hypothesis of primary renal Ca leak in essential hypertension. Enhanced urinary calcium excretion rate may cause compensatory PTH overactivity.

Increased gut Ca absorption or reduced renal tubular Ca reabsorption have been alternatively reported in idiopathic hypercalciuria with kidney calculi. Although renal Ca excretion is higher in hypercalciurics, renal Ca clearance account for only a minor fraction of the total body clearance, suggesting that the reduced serum Ca levels found in the hypercalciurics could not be explained by the renal Ca leak. The enhanced total body Ca clearance found in hypercalciuric subjects is therefore due to an increased tissue Ca uptake. This finding provides indirect evidence of altered cell Ca handling in idiopathic hypercalciuria with no difference between the so-called absorptives and renals in terms of the pathophysiologic mechanism.

2.3.1 Testing collagen in urine or blood

Laboratory tests that measure the amount of collagen in urine or blood samples can indicate bone loss. Lab tests may also be used in conjunction with DEXA or other methods of bone

densitometry to diagnose and monitor osteoporosis, such as beta-crosslap, a biochemical bone marker of bone resorption. Biochemical bone markers, such as the bone isoenzyme form of alkaline phosphatase, have been used to assess the bone formation phase of bone turnover in health and disease. Markers of biochemical bone remodeling can be used in assessing and managing osteoporosis in conjunction with DEXA.

2.3.2 The active vitamin D

Chronic uremia is characterized by decreased levels of plasma 1,25-dihydroxyvitamin D₃(1,25-(OH)₂D₃), a hormone with immunomodulatory properties, due to decreased renal 1-hydroxylase activity and by decreased renal phosphate excretion. The consequence is an increased synthesis and secretion of parathyroid hormone--secondary hyperparathyroidism--due to the low levels of plasma calcium, low levels of plasma 1,25(OH)₂D₃ and high levels of phosphate. The association between renal bone disease and chronic renal failure is well described. An association also exists between secondary hyperparathyroidism and increased mortality and cardiovascular calcifications in chronic uremic patients.

Calcium carbonate and calcium acetate were used as phosphate binders. Until recently, the most commonly used active vitamin D drug was either the natural 1,25(OH)₂D₃, or the 1 alpha-hydroxylated analog, 1alpha(OH)D₃ which after 25-hydroxylation in the liver is converted to 1,25(OH)₂D₃. This increases the intestinal absorption of calcium and improves skeletal abnormalities. The combined treatment with calcium containing phosphate binders and active vitamin D induces an increase in plasma Ca and hypercalcemia became a clinical problem. It was demonstrated a direct suppressive effect of intravenous 1,25(OH)₂D₃ on plasma PTH.

The use of 1 alpha-hydroxyvitamin D₃ (1 alpha(OH)D₃) derivatives in a uremic patient is justified only in the treatment of hyperparathyroidism. The following prerequisites have however to be satisfied: a good vitamin D₃ repletion should be secured by plasma 25-OH-D₃ levels of 20-30 ng/ml, and phosphate retention and the consequent possible hyperphosphatemia should be prevented or corrected by the oral administration of alkaline salts of calcium given before the meals as phosphate binders without inducing hypercalcemia.

In X-linked hypophosphatemia, phosphate wasting results from increased circulating levels of fibroblast growth factor 23 (FGF-23). Administration of calcitonin causes a drop in serum levels of FGF-23. Calcitonin might have the same effect in patients with X-linked hypophosphatemia. Serum levels of 1,25-dihydroxyvitamin D rose similarly in untreated patients with X-linked hypophosphatemia and in controls after a single subcutaneous injection of 200 IU of salmon calcitonin in both groups for 21 hours but diverged thereafter (P=0.008). The rise in serum levels of 1,25-dihydroxyvitamin D is probably due to the direct stimulatory effect of calcitonin on renal 1 α -hydroxylase. Both groups had slight and similar changes in serum levels of calcium and PTH. Serum phosphate levels rose after treatment.

Recently, it was reported that osteocytes express the calcitonin receptor and respond to calcitonin with an increase in sclerostin production. Sclerostin has an inhibitory effect on the lifetime of the osteoblast. Sclerostin production by osteocytes is inhibited by PTH.

2.3.3 The PTH, serum Ca, insulin and vitamin D

PTH is the most important endocrine regulator of Ca and phosphorus concentration in extracellular fluid. It enhances the release of Ca from the large reservoir contained in the bones. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly

stimulated by PTH. Stimulation is indirect since osteoclasts do not have a receptor for PTH; rather, PTH binds to osteoblasts, the cells responsible for creating bone. In the kidney it enhances active reabsorption of Ca and magnesium from distal tubules and the thick ascending limb. It enhances the absorption of calcium in the intestine by increasing the production of activated vitamin D.

Patients with primary hyperparathyroidism have impaired glucose tolerance more often than do controls, and parathyroid resection sometimes improves this derangement. However, it is unclear whether serum Ca or PTH is more strongly related to impaired glucose metabolism in subjects without primary hyperparathyroidism. Multiple regression analyses showed that the significant and positive correlations between serum Ca vs fasting plasma glucose and homeostasis model assessment insulin resistance in men still remained after adjustment for intact PTH as well as age, body weight, height, creatinine, albumin, phosphate, bone metabolic markers, and estradiol ($P < .05$). Serum Ca level is positively associated with impaired glucose metabolism, independent of PTH or bone metabolism, in men with type 2 DM.

In the relationship between biochemical parameters, parathyroid adenoma volume, and bone mineral density with respect to intact parathyroid hormone (iPTH) levels in patients with primary hyperparathyroidism, it was found there was no correlation between iPTH, serum calcium levels and total T scores at the femur and lumbar spine. After excluding patients with 25-(OH)D3 insufficiency, there was still no correlation between serum iPTH and calcium levels. Parathyroid adenoma volume, serum iPTH and calcium levels were also not different between patients with and without 25-(OH)D3 insufficiency.

Primary hyperparathyroidism (PHPT) and vitamin D insufficiency are two very frequent conditions. Vitamin D treatment is recommended and may decrease PTH levels in PHPT. However, there is no randomized controlled trial to prove any beneficial effect. For safety reasons, it is recommended to monitor plasma and urinary Ca during treatment. Furthermore, the effect of vitamin D repletion on other outcomes like quality of life, muscle function and central nervous system symptoms should be assessed.

2.3.4 Ghrelin and bone mass density

Serum ghrelin is positively correlated with trabecular BMD in a cohort of elderly healthy Italian women. The fact that trabecular is more metabolically active than cortical bone and the larger number of females might explain this selective association.

Previously undetected contributors to secondary osteoporosis and metabolic bone diseases (SECOB) are frequently found in patients with osteoporosis, but the prevalence in patients at the time they present with a clinical fracture is unknown (Napoli et al. 2011). At presentation with a fracture, 26.5% of patients have previously unknown contributors to SECOB, as monoclonal proteinemia, renal insufficiency grade III or greater, primary and secondary hyperparathyroidism, hyperthyroidism, and hypogonadism in men. Newly diagnosed SECOBs, serum 25-hydroxyvitamin D less than 50 nmol/liter (in 63.9%), and dietary calcium intake less than 1200 mg/d were found at any age, in both sexes, after any fracture (except SECOB in men with finger and toe fractures) and at any level of bone mineral density, which are treatable or need follow-up, and more than 90% of patients have an inadequate vitamin D status and/or calcium intake. Systematic screening of patients with a recent fracture identifies those in whom potentially reversible contributors to SECOB and calcium and vitamin D deficiency are present (Bours et al., 2011).

2.3.5 Calcitonin and PTH

Calcitonin is a 32-amino acid linear polypeptide hormone that is produced in humans primarily by the parafollicular cells (also known as C-cells) of the thyroid, and in many other animals in the ultimobranchial body. It acts to reduce blood Ca, opposing the effects of PTH. The hormone participates in calcium Ca and phosphorus metabolism. In many ways, calcitonin counteracts PTH.

2.3.6 Environmental contaminants

Polybrominated diphenyl ethers (PBDEs) are flame retardants that have been widely used in manufacturing. They are major household and environmental contaminants that bioaccumulate. Humans are exposed primarily through dust inhalation and dietary ingestion of animal products. PBDEs increase rodent circulating T3 and T4 concentrations and gonadal osteopontin mRNA, and activate the osteopontin gene promoter. These changes may have clinical implications as others have shown associations between human exposure to PBDEs and subclinical hyperthyroidism (Blake et al., 2011).

2.3.7 Vitamin K₂ (menaquinone)

Vitamin K₂ (menaquinone), is itself a category of vitamin K that includes many types of vitamin K₂. The two subtypes of vitamin K₂ that have been most studied are menaquinone-4 (MK4) and menaquinone-7 (MK7). MK4 is produced via conversion of vitamin K₁ in the body, in the testes, pancreas and arterial walls. Studies demonstrate that the conversion of vitamin K₁ to MK4, is not dependent on gut bacteria .

In contrast to MK4, MK7 is not produced by humans but is converted from phylloquinone in the intestines by gut bacteria. However, bacteria-derived menaquinones appear to contribute minimally to overall vitamin K status. MK4 has been approved for the prevention and treatment of osteoporosis, and it has been shown to decrease fractures up to 87%. MK4 has also been shown to prevent bone loss and/or fractures caused by corticosteroids, anorexia nervosa, cirrhosis of the liver and postmenopausal osteoporosis. MK7 has never been shown in any clinical trials to reduce fractures and is not approved by any government for the prevention or treatment of any disease. MK7 has been approved in the purpose of increasing bone mineral density.

3. Overture

BMD is only bone mineral density, risk factors for osteoporosis are only risk factors and the mixing of both parameters does not make quite more sense. It is not better than each one separately. BMD is a subrogate parameter for diagnosing bone strength that is good but it is not enough, because with a suitable BMD caused by sodium fluoride bone fragility is increased and some individuals with decreased BMD undergo quantitatively and objectively bone fractures and another different person does not suffer this bone condition. Bone risk factors are good for diagnosis but they do not mean necessarily one disease and nor are they sufficient to osteoporosis. With and without them there are persons with and without suitable bone strength and with and without fractures. It is important to understand that bone is not a hard and lifeless structure; it is, in fact, a complex, living tissue.

The confounding effect of differences in bone size is due to the missing depth value in the calculation of BMD. It should be noted that despite DXA technology' s problems in estimating volume, it is still a fairly accurate measure of BMD.

Methods to correct for this shortcoming include the calculation of a volume which is approximated from the projected area measure by DXA. DXA BMD results adjusted in this manner are referred to as the bone mineral apparent density (BMAD) and are a ratio of the bone mineral content versus a cuboidal estimation of the volume of bone. As aBMD, BMAD results do not accurately represent true bone mineral density, since they use approximations of the bone's volume.

It is important to get repeated BMD measurements done on the same machine each time, or at least a machine from the same manufacturer. Error between machines, or trying to convert measurements from one manufacturer's standard to another can introduce errors large enough to wipe out the sensitivity of the measurements.

It is possible to use a scaling system for pixels which has a one to one correspondence to the concentration of what you are studying. Sample concentrations can be determined using optical, electronic, and most importantly for our purposes, a computer based imaging technique. Densitometric science was described originally by Bouguer and Lambert who described loss of radiation (or light) in passing through a medium. Later, Beer found that the radiation loss in a media was a function of the substance's molarity or concentration.

According to Beer's law, concentration is proportional to optical density (OD). The logarithmic optical density scale, and net integral of density values for an object in an image is the proper measure for use in quantitation. By Beer's law, the density of a point is the log ratio of incident light upon it and transmitted light through it.

$$OD = \text{Log}_{10}(I_0 / I)$$

When dealing with noisy data if there is a region of interest (ROI) or image area that is calibrated, such as is done during concentration calibrations, which method for calculation of a the calibrated mean is preferable?

1. Adding up a calibrated value for each pixel in terms of the calibrated unit, then finding the average calibrated unit value and calling this the calibrated mean.
Calibrated mean = $(\text{sum}(\text{cvalue}(P[i,j])) / N$ where $\text{cvalue}(P[i,j])$ is the calibrated value for each pixel in your ROI, and N is the total number of pixels in the ROI
2. Adding up all the pixel values in pixel intensity units, finding the mean pixel intensity value, finally finding the one calibrated value for the mean pixel intensity and calling this the calibrated mean.

Calibrated mean = $\text{cvalue}(\text{sum}(P[i,j]) / N)$ where $P[i,j]$ is each pixel intensity in the ROI, and N is the total number of pixels in the ROI. In an ideal world, it would not make any difference. Both methods would yield the same value. However in the real world, measurement and other types of error enter in, and we should think of the problem in a statistical context. If the errors (i.e. the standard deviation) are small, the method used does not matter much. But how small is small? What really matters is the relationship of the standard deviation to the curvature of the calibration curve.

If the calibration curve were truly linear, the order of operations would not matter (a property of linear functions). However, in the current context, the calibration curve is always nonlinear, at least in some regions.

The key question then becomes which of the two methods is appropriate on the data? The answer is: it depends. Some cases are clear cut others are in-between. It is safe to assume that, if there is a fairly uniform grey level region of interest, where the only variation is caused by the noise of the imaging process (all noises), method two produces a better estimation of the mean. In cases where the region contains two highly differing density

regions included in one ROI (the variation is not caused by noise or the imaging process), then the method one produces a better estimation of mean.

The error of method one is directly proportional to the noise of the system used and becomes highest when data is measured nearest the asymptote of the curve fit used to calibrate the data. Most data unfortunately have some natural density variation and some variation caused by the imaging process (noise).

We are facing a big concern: Osteoporosis is a major public health threat. How can we treat it if we have not the adequate diagnosis tool?.

An expert technical assessment of the many factors that influence the risk of osteoporotic fracture in postmenopausal women need to be considered when planning the most effective public health interventions. In view of growing awareness of the need to prevent and treat postmenopausal osteoporosis, it is good to resolve several controversies concerning the usefulness of screening programmes, the appropriate target populations, the most effective methods for predicting fracture risk, techniques for assessment, and the comparative effectiveness of currently available preventive and therapeutic interventions. There are advantages and limitations of the methods for predicting future fracture risk: assessment of bone mass, assessment of bone loss, and clinical assessment of risk factors. It is needed information on non-invasive physical techniques for bone mass assessment. The aims and design of screening programmes are not clear.

By reason of the two-dimensional nature of DXA, assumptions must be made regarding the tridimensional nature of the bones involving a great deal to cope with. Therefore it is deduced, that this method seems to be very sensitive to error, and it is necessary to know how to deal with these errors, especially with the systematic errors introduced by using a parameterized model. Even though a high concordance between the densitometers was observed on a single measurement occasion, a significant discordance in longitudinal changes in BMD was observed.

Bone strength is comprised of many components, which include architecture, geometry, cortical porosity, and tissue mineralization density. These components are contained within the measurement of BMD but cannot be individually distinguished.

Bone strength is comprised of many components including, but not limited to bone architecture, geometry, cortical porosity and tissue mineralization density.

The exceptional mechanical properties of bones are not only the result of the amount and type of the micro-constituents, but also of their morphological organization at the different lower scales.

Mechanical properties of bone are determined not only by BMD, but also by tissue trabecular structure and organic composition. Direct measurement of these components of bone strength may result in improved fracture risk prediction or therapeutic monitoring than is currently possible using the surrogate measure of BMD.

In addition to loading in axial compression, long bones are also and, in fact, primarily loaded in bending. In linear coupled bending and extension of an unbalanced bonded repair the tensile forces are exerted on the bending-created convex surface, whereas compressive forces are exerted on the concave surface. This bending increases the stress intensity in the underlying crack and causes adhesive peel stresses and bending of the repair which can, relative to a repair that is restrained against bending, lead to early failure and certain assumptions must be made about the symmetry of the bone in cross-section at the different ROIs, which are not entirely accurate. Additionally, cortical thickness must be assumed to

be uniform about the circumference of the cross-section. Many of these assumptions are necessitated by the 2-dimensional nature of DXA and may be addressed with 3-dimensional imaging.

The geometric parameters are predictive of fracture risk although they do not seem to be better predictors of risk than a conventional measurement of BMD. DXA measured *in vivo* "BMD" methodology shows to be an intrinsically flawed and misleading indicator of bone mineral status and an erroneous gauge of relative fracture risk.

DXA methodology to provide accurate, quantitative, and meaningful *in vivo* (not in cadaver) area bone mineral density ("aBMD") determinations have been proven to be unwarranted and misplaced. The underlying systematic of sizable, inherently unavoidable and uncorrectable inaccuracies in the DXA output values of *in vivo* "BMD" have been shown to be quantitatively consistent with being the root cause of unreliable, misdirected, and misinterpreted aspects of consensual knowledge of bone fragility, osteoporotic diagnostics/prognostics, and remodelling therapies.

So, as said above, BMD is only BMD, risk factors to osteoporosis are only risk factors and mixing of both parameters does not make quite more sense. It is not best than each of them alone. Although spatial information is currently recorded in the form of a DXA image, this information is not utilised clinically. It should be noted that BMD assessment provides an areal density measure, where the cross-sectional scan area is known but not the tissue thickness, providing units of g/cm².

Precise *in vivo* measurement of the trabecular bone mechanical properties is very important, being essential a method for quantitatively and objectively assessing bone mass and anisotropy and not only in a qualitative manner and with risks which sometimes are not. The cortical bone properties constitute another system with microsystems, isotropy and anisotropy and variety of cross-section of the long bone. But the mechanical properties of bones are not only the result of the amount and type of the micro-constituents, but also of their morphological organization at the different lower scales. Measurement of BMD has served as a fit surrogate for the measurement of bone strength. DXA is one osteoporosis imaging diagnosis testing. By reason of the two-dimensional nature of DXA, assumptions must be made regarding the tridimensional nature of the bones, dealing with an inference problem from a set of measurements. It is needed to make inference about certain parameters which help to make predictions of a certain fracture risk. The main limitation for a proper inference is that only 2d information is got from detectors, and therefore all 3d information is lost, as it is integrated out due to the nature of detector. It is necessary to be very careful when using models for data inference, because we obviously will never know the underlying truth contained in the data. Therefore, it is tried to regain some information about the third dimension by building a model of the bone, which assumes axial symmetry.

By using a model, to be arranged the parameter of this model in such a way that they best fit the data, so it is only gained information about how good the model can explain the data, but it is not gotten any information of how good this model actually is, and maybe there is a much better model, which we do not know it yet. It is very difficult to make good inference of the bone strength due to the noisy character of the data, and dealing with the errors of the apparatus is crucial for making inference.

Therefore it is deduced, that this method seems to be very sensitive to error, and it is necessary to know how to deal with these errors, especially with the systematic errors introduced by using a parameterized model.

There is concern that the additional 3d information which is gained in this inference process comes entirely from the model, which then would increase the systematic uncertainties about the quantities that are inferred from the data.

And there is an anisotropic problem, and therefore different inferences must be done making measurements from different directions. But we wonder should the anisotropies are really that bad problem.

It should be very easy to test the reliability of this method, by making inferences from datasets taken from different sides, and see to what degree they agree, this would give a simple estimate about some of the systematic errors introduced in the inference method, and how reliable the entire method is. If the reliability is sufficiently high for purposes to study then it would be say there is no use in making a more complicated model. A much deeper investigation of these effects can be carried out in the framework of Bayesian statistics, which is very well suited for problems like this.

But if the reliability is not within the desired range, then of course the only way to tackle this problem is to introduce more complexity to the model to also pick up effects coming from the anisotropies. Which would also means more data might be needed. Treating anisotropies in data inference is in general a very hard business, and a lot of work is going on at the moment to tackle this problems.

In this case we have good chances of attacking this problem, because the anisotropies which might occur are not so nasty, so it might be feasible to build a slightly more general model by allowing elliptic shapes, which introduces two parameters $a(x)$ and $b(x)$ for semi and major axis at each point x along the bone axis, or use other Kernel functions which can describe the shape more precisely.

3.1 The finite element method

The finite element method (FEM), its practical application often known as finite element analysis (FEA), is a numerical technique for finding approximate solutions of partial differential equations (PDE) as well as of integral equations. FEA was first developed in 1943 by R. Courant, who utilized the Ritz method of numerical analysis and minimization of variational calculus to obtain approximate solutions to vibration systems. FEA has been developed to an incredible precision. It consists of a computer model of a material or design that is stressed and analyzed for specific results. It is used in new product design, and existing product refinement. Modifying an existing product or structure is utilized to qualify the product or structure for a new service condition. In case of structural failure, FEA may be used to help determine the design modifications to meet the new condition.

FEA is a widely-used technique for the computer modelling of structures under mechanical loading. A finite element is an individual regular shape that has a known stiffness so that any applied load will give a predictable corresponding displacement. Elements are joined together at nodes and along edges. Complex designs are created as an assembly of elements to which restraints and loads may be applied. During the computer analysis of the model, a series of simultaneous equations are established that represent the overall stiffness of the structure. The equations are then solved giving the nodal displacements resulting from the applied loads. For the analysis of bone structures, finite element analysis would therefore be dependent upon the density of each element, the arrangement of elements (eg trabecular structure), the composition (eg cortical shell or cancellous) and the external shape (eg length, angle and width of femoral neck).

FEA has previously been applied to computer modelling of several bioengineering situations incorporating bone including cellular remodelling, prosthetic loosening, fracture progression and fracture healing. Studies related to osteoporosis have tended to utilise the full 3D potential of FEA via incorporation of computed tomography data.

FEA predicts the mechanical behaviour (displacement or stress) of a structure under loading rather than the exact yield point (fracture); but since osteoporosis fracture risk assessment requires only a proportional, rather than exact, measure of fracture load, FEA derived stiffness (load / displacement) should have significant clinical potential. FEXI (finite element analysis of x-ray images) provides a thin plate computer simulation of a bone being mechanically tested.

Finite element analysis inherently offers dependence upon the external shape and internal structure of a bone and should, therefore, have the potential to provide a superior prediction of mechanical integrity than simple areal density (BMD). The novel feature of the FEXI approach is that a conventional mechanical compression test is simulated. An important aspect of the technique is that, being based upon conventional 2D DXA images or radiographs, it could be readily utilised into routine clinical practice.

Thus, bone microarchitecture and biomechanical properties in men have been investigated (Vilayphiou et al. 2011). Patient-specific finite element (PSFE) models based on QCT are generally used to predict the biomechanical response of human bones with the future goal to be applied in clinical decision-making (Trabelsi & Yosibash, 2011). The biomechanical mechanisms underlying sex-specific differences in age-related vertebral fracture rates are ill defined. To gain insight into this issue, we used finite element analysis of clinical CT scans of the vertebral bodies (Christiansen et al., 2011).

4. Conclusion

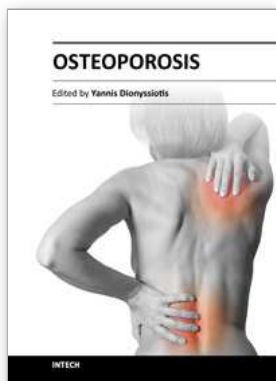
Therefore it is necessary to carry out more research and to open new tracks to have any further reliable tool in the diagnosis of osteoporosis. Precise *in vivo* measurement of the bone mechanical properties is very important, being essential a method for assessing quantitatively and objectively bone mass and anisotropy and not only in a qualitative way and with risks which sometimes are not. Thus, a mathematical, physical and physiological 5-dimensional model must be developed in order to gauge bone properties including geometry(2-dimensional DXA), space, time, motion and stress with some portable-computer-devices that uses the body space of the user as an interface with equipment and programs designed to communicate information from one system of computing devices and programs to another. Because the person is not one body died, and is more than one statistic sampling; he is not a 10-year probability of hip fracture; he is alive and not one lifeless inert element; and bones are not quite as strong as one compact material object without life; it is somewhat more flexible and this is useful in bones that are jointed performing its necessary task. Probability is good after the event but not before. It is unknown what is going to happen to one person as the justification is wholly independent of sense experience in *a priori* knowledge. The person to study can be the case who is not concluded from the probability. The probability is not the reality and the patient, to a greater or lesser extent, is not a probability that is to say it is one sophism: a plausible but fallacious argument or deceptive argumentation. This is one poor approach to diagnosis in

osteoporosis. There is not any disease but one ill person and so must be considered irrespective of other philosophies including economic resources. These facts are essential in drawing up any test for diagnosis in osteoporosis.

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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