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What's BMD and What We Do in a BMD Centre?

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1. Introduction

The main parts of osteoporosis clinics are BMD (Bone Mineral Densitometry) centers. For increasing our knowledge about osteoporosis we have to increase our knowledge about BMD (Bone Mineral Density), and increasing the knowledge about BMD has a close relationship with realizing the principles and appliances of BMD machines and DXA method. For specific development in a BMD department, we need to know some historical, technical and practical points about these method and machines. In this review, the last developments in this field are suggested, also.

2. General information about BMD and BMD centres

2.1 What we do in a BMD centre?

1. Determine patient's BMD
2. Estimate the risk of fracture (pathologic fracture) in a patient

2.2 Some historical points about dual X-ray absorptiometry

It is very useful to know the history of BMD and DXA devices. The first marketing of this machine was in 1987 and in1994 this method described as gold standard for osteoporosis diagnosis by World Health Organisation (WHO). It means osteoporosis disease, as we know now, was described in 1994 for the first time.(Lukaski, 1993; Kanis, 1994).

2.3 Distribution of BMD devices around the world

As Kanis and Johnel reported in 2005, 9 countries from 20 countries (in Europe), had more than 10 DXA units per million of the population (the European standard). However it is unclear which percent of machines were dedicated in part or in full to clinical research. They conclude that the majority of countries are under-resourced. Inequity of geographical location, is an important problem, which is a known problem in Italy, Spain, Switzerland and the UK. (Kanis & Johnell,2005). However the distribution and utilization of these machines are increasing worldwide. This statistics seems interesting when you know there was almost 183 machines in Canada in 1998, and there was no such device in Prince Edward Island (of Canada) around 1998. In Canada there are almost 600 devices, nowadays. The European standard is 0.11 DXA machine per 10 000 population (Mithal et al., 2009).

Asian audit in 2009, show us a very different picture in Asia. DXA technology is relatively expensive and is not widely available in most developing Asian countries, especially in rural areas. There was only 450 DXA machines in China for a population of 1.3 billion. In Srilanka only 4 machines exist. (Mithal et al., 2009). In 2008, Indonesia had a total of only 34 DXA machines, half of them in Jakarta, for a population of 237 million (0.001 per 10,000 population)(IOF, 2011). One of the most extreme examples is found in India, reportedly, there was only approximately 100 DXA units, located in six cities. This inequity results in long waiting times or long distances to travel or in many cases, no access (Kanis & Johnell,2005) (Fig. 1. And Fig. 2.). With above examples about distribution of these machines around the world, we explain here the formula used for calculating standard requirement of these machines (this formula is calculated according to number of population and prevalence of risk factors in target population).

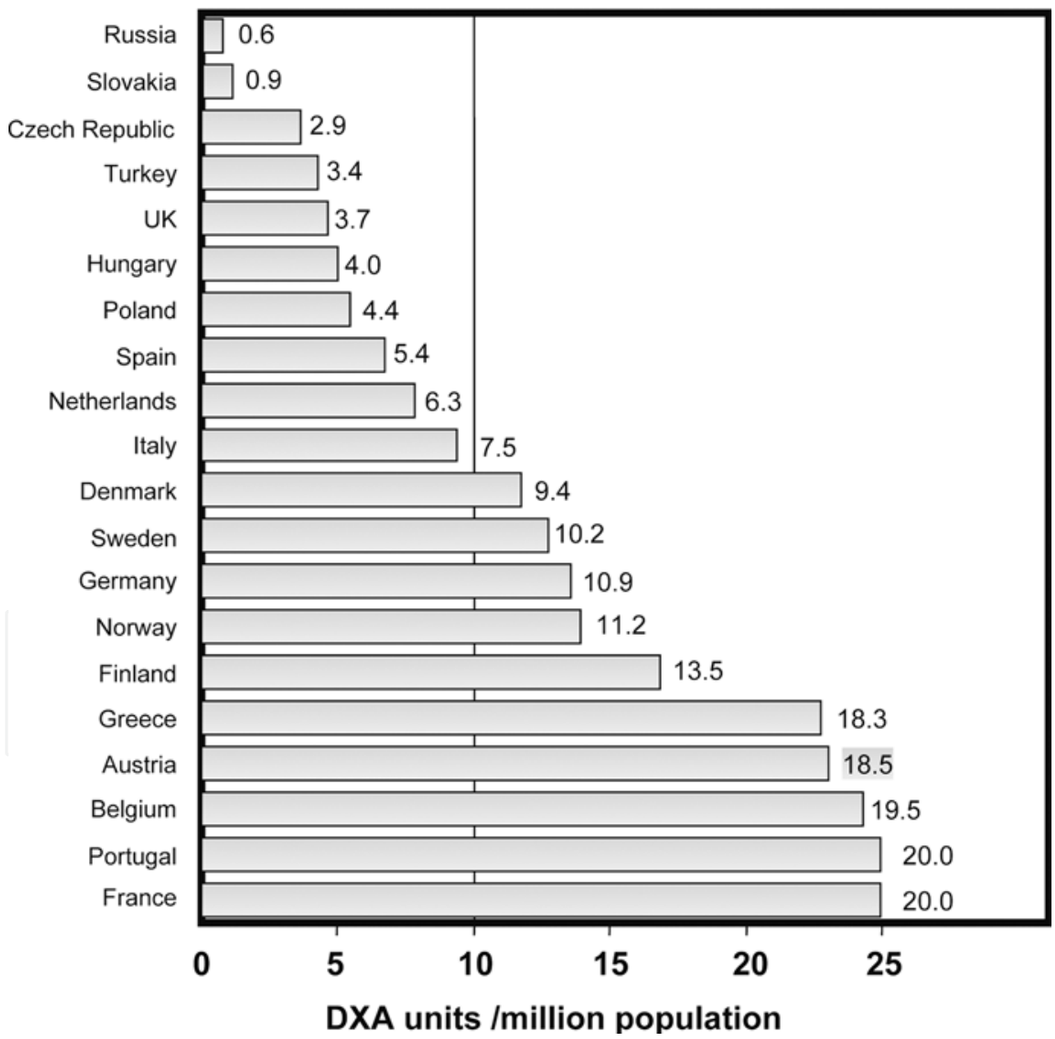

Fig. 1. Density (number /million of the population) of central DXA (spine/hip) units in different European countries in 2003 (from Kanis and Johnell, 2005).

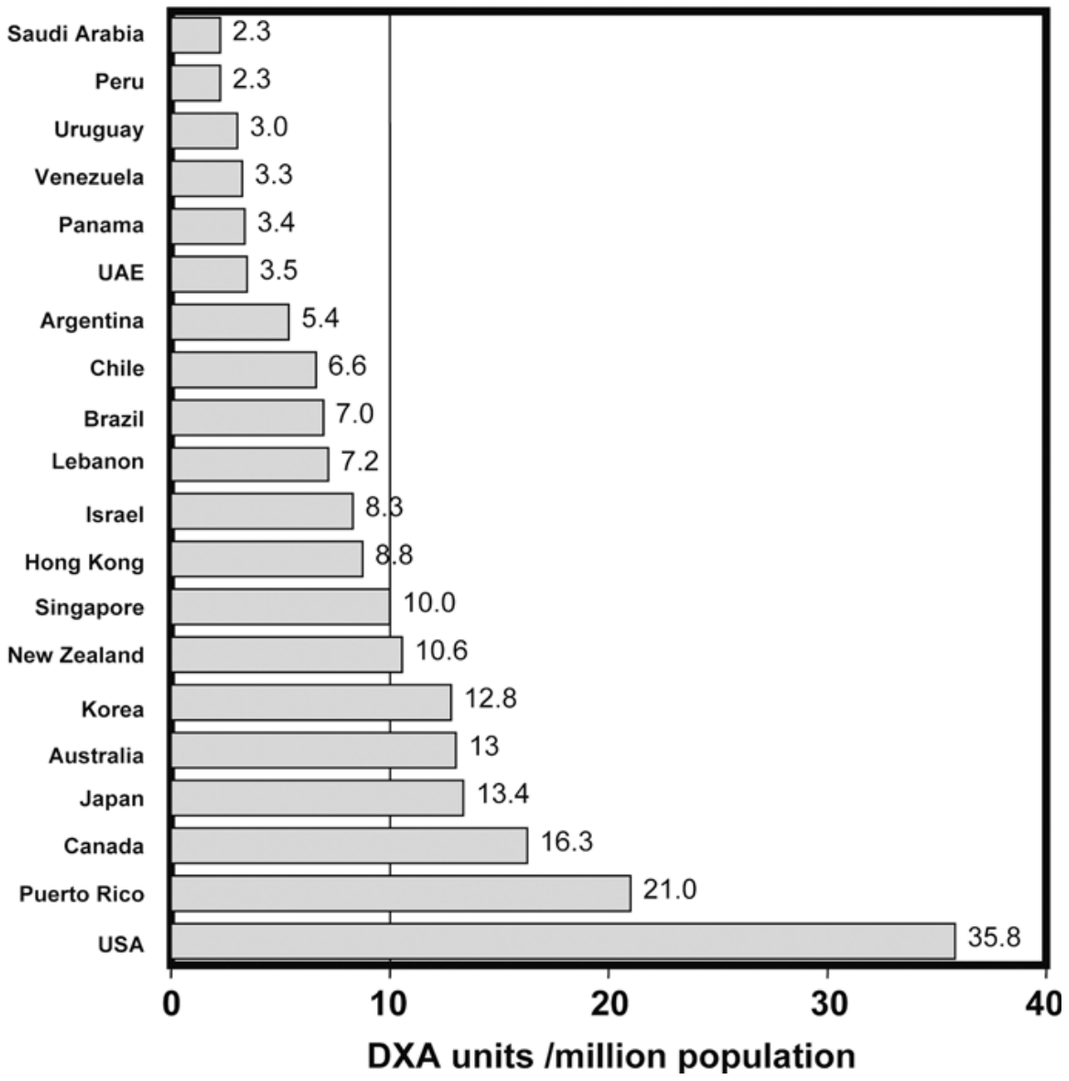

Fig. 2. Density (number /million of the population) of central DXA (spine/hip) units in non-European countries in 2003 (from Kanis and Johnell, 2005).

2.4 Requirement for DXA

Kanis and Johnel, extensively explained the method used for estimation of required number of DXA machines in Europe. As the method is interesting and contained demographic and osteoporotic statistics in Europe, we repeat their explanation as extensive as is used in their article in 2005. Repeat the explanation may be helpful, clearing a guideline for clinicians and researchers, to calculate the requirement of DXA machines in their area or countries. They suggested the requirement for three scenario and in two category, requirements of DXA for risk assessment and requirements of DXA to monitor treatment.

2.4.1 Requirements of DXA for risk assessment

From total population of Europe, it is estimated that, 4 million of them were 65 years old women. The authors assumed that individuals over the 65 years would be tested over the

ensuing 10 years and repeated BMD tests would perform in patient that need treatment or those patients at high risk on the basis of the screening BMD test.

The first scenario (scenario A or screening women with BMD), proposed monitor all women with at the age of 65 years. If the main goal was to measure BMD in all 65 years old women (4.045.000, 65 years old women), this required 3231 DXA units or 4.42 DXA/ million of the total population. In this first scenario, if we assumed that people with the age 66 years and older didn't screen and if they want to screen over a 10- year period, the needs for DXA units would be 6.79/million of total population, giving a total need 11.2 units/million.

The aim of second scenario (scenario B, or clinical case finding with selective use of BMD) was to screen 65 years old women with clinical risk factor referred for DXA at 10 yearly intervals. It means that we sent 65 y/o women for BMD, only when they were high risk for fracture. Finding patients at high risk was based on clinical risk factors. Patients were high risk, when 10-year probability of hip fracture in them (calculated upon risk factors), was 4% and more (This is also called intervention threshold, and the authors considered it a cut-off that treatment is needed for patients). Screening all these patients, need 767 DXA units or 1,05 scan/million of the population. No surprising, the population that need intervention and treatment advances with age. The probability of risk fracture is about 1% at the age of 50 and 52% at the age of 80 years old. Author emphasize that the absolute population size decreases the higher the starting age for testing. They calculated that assessment of women at the older age, (during 10 years period) would require an extra need of 2301 DXA units or 3.16/million of the population (total need for women 65 y/o and older equals to 4.21/million). At younger age, small population is selected for BMD test. So the requirements are not markedly differ by screening policy that starts at age of 50 years. At this age, only nearly 1% of women are selected for treatment. It would be required that more 50,000 DXA tests do for 50 years old women (that add 40 scanning units or 0.05 units/million machines to requirement). After added screened population aged more than 50 years over a 10 year term interval, the total requirement will be 4.5 unit/million. Compare it with 4.21 unit/million required only for screening of 65 y/o women and older.

The third scenario (scenario C, or classic case finding strategy) enlisted only women with strong risk factors for fracture, to do BMD. The authors suggested a different prevalence of risk factors in different age population (29% to 46% depending on age). For testing women of 65 years, 1481 units or 2.03 units/million of the population was required. If BMD considered in women aged more than 65 years and a risk factors prevalence as 46%, 3 million/year over a 10 year interval (30 million, for 10 years) would require testing . This is equal to 3.33 units/million of the population. On the other hand, if BMD tests considered for women aged 50 years or more with one or more these risk factors, BMD testing was needed in 36.9% of the female population aged 50 years or more. Authors calculated this would need 3842 scanning units or 5.3/million of the total population (It seems it is a yearly need, when the whole 10 year need is divided by 10). When only women with incident osteoporotic fracture and aged 65 years or older sent to BMD centers, requirement was 918 scanning visits or 1.3/million of the general population.

2.4.2 Requirements of DXA to monitor treatment

When women referred for treatment, 2 BMD tests may be required. One is at the time of diagnosis, and a second at an interval of 2 years. For scenario B, BMD tests would have been done in 24% of the population at the age of 65 years, some of them do not need treatment

and so don't need a further BMD test in the beginning of treatment (they did't cut the threshold for need to intervention). Additional BMD testing would be required in approximately 10% of women for the purposes of baseline investigation for treatment. If all 65-year-olds were screened, additional pre-treatment BMD tests would equal to 0.4/million scans (322 units) and approximately increase 2-fold after 2 years later. Thus, the steady state requirements would be 966 scanners or 1.33 units/million of the population. Women older than 65 years have a smaller population , but not surprisingly ,a larger proportion would cut an intervention threshold. For example, at the age of 80 years there are approximately 2.15 million women, but with the same test, 73% would be need treatment. But in 50 years old women, approximately 1% of their 5 million population would need treatment. The author emphasized that in women aged 65 years or more, approximately 35% will need treatment and require a BMD tests before and after treatment (2 years later). This gives an annual requirement for 4.6 million scans or 3686 scanning units and a requirement of 5.06/million of the general population. It means for the monitoring of treatment (in 65 y/o women and older), 6.39 uint/million is needed under scenario B. All of these, means the total number 10.6 scanning units/million of the population is needed for assessment plus monitoring of treatment in scenario B (Kanis & Johnell,2005).

2.5 Secular trend of use of DXA

The total number of all older patients performed DXA in the USA has grown up from 501,105 in 1996 to 2,195,548 in 2002. This 4 fold growth during 6 years related to increase the average of lifespan, increase public awareness of osteoporosis and development in therapeutic cares. The maximum application of DXA has been observed in central densitometry. The usage of this method maybe continued for the next few years. However, in some countries, DXA just applied for patients with certain (or specific) risk factors. There are national organization in other countries that prescribe DXA only for patients at multiple risks of osteoporosis. It cause different statistics of use of DXA in different countries (Damilakis et al., 2010).

Results show a great increase in use of bone mass densitometry in Canada. DXA-BMD tests increase 10-fold between years 1993 to 2005, and approximately 500,000 scans perform per year. In Ontario, showed an excessive use of anti-osteoporotic drugs along with the reduction rate of hip and wrist fractures with the increase in BMD test.The growth rate of BMD test appeared to be decreased to 6 to 7% per year. The increase usage rate of BMD-test occurred mainly in 65 years old people or older (Legislative Assembly of Ontario, 2006).

3. Bone densitometry instruments

3.1 Instruments

Lukaski, had a good review of instruments in dual x-ray absorptiometry. Because of its clear and good explanation about the complexity of matter, we mension it here, with almost no change. The first generation commercial dual-energy X-ray absorptiometry (DXA) system became available in 1987 after its initial progress in the late 1960s and 1970s. The three main companies, introduced three X-ray-based absorptiometry systems (approved by the Food and Drug Administration): QDR-1000W3 (Hologic Inc., Waltham, MA), DPX (Lunar Radiation Corp., Madison, WI) and XR-26 (Norland Corporation, Fort Atkinson, WI). Each system uses a source- that generates X-rays at two different energies- a detector and an interface with a computer system.

These three DXA systems operate in different ways. The QDR-1000 and QDR- 1000W systems produce two X-ray beams of different energies by using an X-ray tube alternately pulsed at 70 and 140 kVp peaks. The DPX system uses a constant potential generator and a Cerium K-edge X-ray filtration to generate photons at two energies (40 and 76 keV). The Norland XR-26 unit also employs a constant potential X-ray generator, but it operates at 100 kVp and employs a Samarium filter (K-edge = 46.8 keV). Unlike the DPX and XR-26 systems, the QDR-1000W system has an internal calibration system that consists of a rotating filter wheel composed of three sections (two sections of epoxy-resin-based material consistent with the densities of bone and soft tissue and one section of air). In the QDR system, photons of only one energy are present at any one time, and the detector measures the intensity of the transmitted photons without energy discrimination. An integral line single detector is used in the Lunar DPX system. The XR-26 detector consists of thin and thick sodium iodide crystals (low intensity X rays are stopped by the thin crystal, and high intensity photons are trans mitted and detected by the second thick crystal).

An important advantage of the DXA systems is the increased photon flux emanating from the X-ray sources in comparison to the photon flux from the radioisotope source used in dual-photon absorptiometry. The increased photon flux improves the resolution and precision of the image and reduces the time for a scan. To assess soft tissue composition, the DXA systems use different forms of external calibration. The QDR and XR-26 systems rely on external standards, which are wedges made of aluminum and ucite (polymethylmethacrylate) calibrated against stearic acid as 100% fat, and dilute saline solution as 100% fat-free mineral free tissue. The DPX systems use a plastic polyoxymethylene (Delrin), as 40% fat equivalent and water (~5% fat) as standards (Lukaski, 1993). Recently, the name of Medi-link brand is added to list of machines in FRAX software. Fan beam models are added to DXA machines family and have different beam geometry from pencil beam models. They are explained later.

BMD devices are popular machines, because they are low X-ray radiating, don't need especial preparation for patients and they are not invasive but as it mentioned before, these instruments are not widely distributed in the world, and the expensive cost of these machines is a main reason for it. Properties of these devises that make them expensive are:

- Safety
- The Hardware
- The Software

3.2 Safety

The special method used in these devices, make them low X-ray radiating. They don't need special shielding. We can evaluate the safety of DXA by the radiation dose that each patients or subjects receive. The average skin dose is 1-3 mrad per scan. The radiation dose of DXA is less than other radiologic methods, such as single-photon absorptiometry, dualphoton absorptiometry and quantitative digital radiography, conventional chest x-ray and many others. For example, skin exposures from environmental background are ~3.5 mrad/wk; from dental bite-wing posterior films, 334 mrad and from chest X-ray films, ~8-10 mrad. Thus, we can conclude; for routine measurement of human body composition and bone mineral status , DXA may be noticed a relatively safe method. Manufacturers suggest that it is safe from 1 meter (Lukaski, 1993).

3.2.1 Dose reduction techniques for patients

Damilakis et al, remind us that the system for patients protection against radiation is based on 2 principles: (a) justification and (b) optimisation. Clinically justification of all X- ray exposures used for bone densitometry is very important. Examinations that do not influence patient care, must be avoided.

Preparing patients before bone densitometry is very important. For example metallic things such as jewelry or coins can cause artifact and careful checking for the presence of these items and proper positioning of patient before bone densitometry, will optimize the imaging quality and there will be no need to repeat imaging with additional radiation exposure. In pediatric examinations, proper interaction with the children and parents is essential. All actions should be taken to avoid movement of the child during imaging and to avoid repeating measurement. The duration time of DXA should be minimize and should take into account patient's body size, if possible (Damilakis et al., 2010).

3.2.2 Occupational radiation doses and shielding

Although the annual occupational doses from DXA is very lower than standard occupational radiation dose, but for a pregnant employee that declares pregnancy, special dose reduction should be applied. As Damilakis et al. suggest, The ICRP and European Commission recommend that pregnant individual be protected by the application of a dose up to 1 mGy. Of course, as they emphasize, the exclusion of pregnant workers from DXA examinations on the basis of radiogenic risks from occupational DXA exposure cannot be justified on scientific grounds. Because the scatter radiation can increase the exposure limits for pregnant workers, especially for fan-beam systems. Radiation protection measures should always be taken to ensure that the conceptus dose will be kept below 1 mGy during the declared pregnancy. For monitoring radiation dose, it is recommended to use personal radiation meter at waist level.

Correcting design of the room in which the imaging device has been installed, can influence in limiting the risk of radiation exposure in the workplace. Measurements performed by Larkin et al. as cited in Damilakis et al., 2010, showed that the scatter from fan-beam DXA systems can increase the limits for public exposure i.e. 1 mSv/year. In these cases, additional structural shielding might be required, especially when the distance from the imaging table to the adjacent wall is less than 1 m. They say, parameters like the workload, the material of the walls, the location of the operator and the location and use of rooms that adjoin the imaging room must also be remembered as important factors (Damilakis et al., 2010).

3.3 Hardware

3.3.1 Basic principles of dual-energy X-ray absorptiometry (DXA)

The proportion of beam of X- rays weaken (attenuating) during transporting through a complex material depend on composition of material, the thickness of material and any of its components. Soft tissues, which contain principally water and organic compounds create limitation to the flux (number of X-rays per unit area) of X-rays, and of course, this limitation is lesser than the limitation creates by bone tissue. The un-weakened or un-attenuated energy, in the form of X-ray radiation, is detected by an external detector. In dual-energy X-ray system, there is a source that emits X-rays, which are collimated into a beam (there is a shutter that can turn on and turn off the beam, also). The source lies beneath the patient and the beam transports in a posterior-to-anterior direction, through the body of patient (bone and soft tissue), and goes upward to be detected by a detector, above the patient, lies in the arm of machine (Lukaski, 1993).

3.3.2 Specific technology of dual energy X-ray absorptiometers scanners (DXA)

Before using dual x-ray absorptometry (when single-photon or single-x-ray absorptiometry used), the ROI (region of interest) of scanning, should be immersed in a water bath for densitometry (Fig. 3.). By use of water bath, the water and soft tissue (with almost the same attenuation), make a single compartment of attenuation (on the other hand, the influence of soft-tissue in the measurement significantly reduces and soft tissue don't contributed to measured absorption). They make one compartment and bone makes another compartment with its specific attenuation (than is very different and very higher that other compartment). This can lead to calculating of density of bone, because the attenuation of energy of x-ray beam is related to density of tissue. The density of soft-tissue (and water) is known and constant in almost all humans. The density of bone is not constant and changes one by one. By comparing the attenuation of energy of bone compartment of anyone to attenuation of energy of his soft tissue, machine can calculate the bone density. Without water bath, there is 3 compartment (air, soft tissue and bone), that machine can't separate them exactly and so can't differ between their density, and there is not single reference for comparing density of bone. So finding the exact density of bone would be impossible. Using of water-bath was a development for bone densitometry. But some big practical problems remained. It is practically, impossible to immerse whole body in water bath to measure the bone density of e.g. Spinal region or neck of femur. Water bath was useful for testing BMD of forearm. Remember spine and femur are most important parts of densitometry, because the important or fatal pathologic fracture occurs in these regions and measuring the BMD of e.g. forearm is not a good predictor of BMD or fracture in these important parts. The creating DXA methods, came helpful in solving this big problem. Imagine, using Dual x-ray absorptiometry (using 2 different energy beams) works as water bath in creating two distinguished compartment from compartments that were previously three different compartments of air, soft tissue and bone. The DXA (Dual X-ray absorptiometry) method depends on the differential absorption of two distinct beam energies - a high and low energy beam. When measuring bone, bone will normally have air and soft tissue around it. The high and low energy photons don't change in soft tissue, but the lower energy photon will be significantly reduced by bone tissue (high energy photon don't changes significantly). This difference in reduction of low energy beam, in two different tissue-bone and soft-tissue- can be used for measurement of bone density. On the other hand, the soft tissue component becomes the reference for determining the bone component (Royal Adelaide Hospital, 2009). When two different beams, pass from body compartments, the difference between their intensity before and after passing the soft tissue (and air), don't change (so, the air and soft tissue around the bone create a single compartment). This constant difference can be considered as 1 unit of difference. When two different beams, pass from bone tissue, the low energy beam attenuates significantly after passing bone, it means there is big difference in the intensity of low energy beam before and after passing bone. So the difference between intensity of two high and low energy beams increase significantly and may be multiple times of 1 unit difference reported for soft tissue (and air). This increase in difference is a result of attenuation of low beam energy in bone tissue and relates to bone density. If we have the density of soft tissue compartment, now we can calculate the density of bone. As mentioned before, the density of soft tissue is known and constant and is used as reference for determining bone density in DXA method. It means use of DXA, makes bone densitometry possible, without need to water bath that was needed in single x-ray absorptiomtery. Dual x-ray absorptiometry, makes axial bone densitometry in the conventional form that is performing now, possible (with patient lying on a table in normal atmosphere of an imaging room with no special preparation).

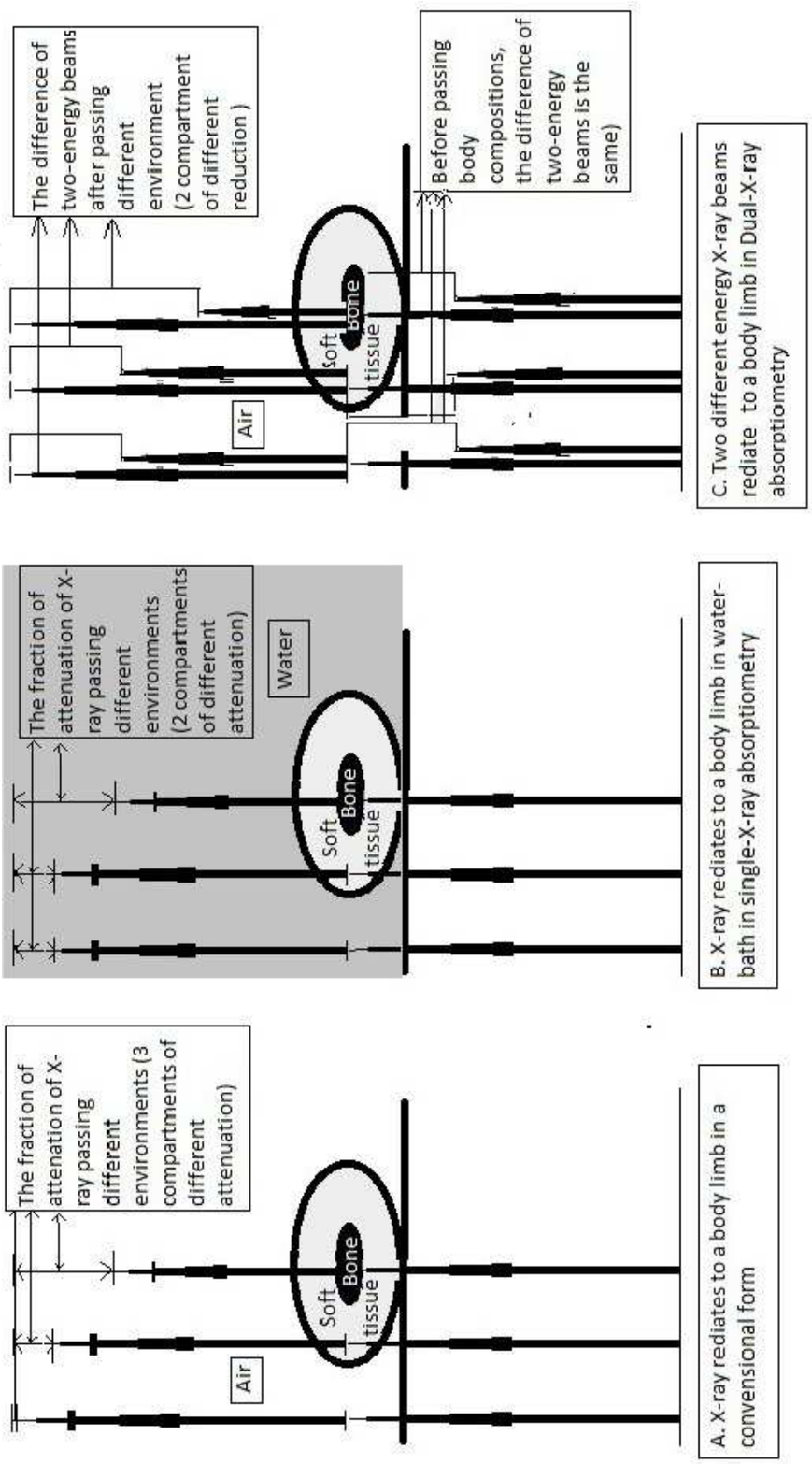

Fig. 3. Different methods of bone densitometry

3.3.3 Quality control

For diagnosing longitudinal changes, assessment of precision error in bone mineral density (BMD) testing is very important (Leslie et al., 2007). Lukaski emphasizes that one parameter of quality control in the use of DXA is the precision of the measurements. Precision is generally reported as the coefficient of variation (CV), which is the standard deviation of repeated measurements expressed as a percentage of the mean of the measurements. The precision of DXA has been assessed for short-term (in vitro and in vivo) and for long-term (in vitro) (Lukaski, 1993).

The International Society for Clinical Densitometry (ISCD) has a standardized methodology for performing an in vivo precision study and recommends that this be performed by each densitometry center. Leslie at al., explain the ISCD procedure as gaining precision error from an assessment with 30 degrees of freedom (df; e.g., 30 subjecs with 2 scans each or 15 subjects with 3 scans each) drawn from the patient of referral population and using the root mean square (RMS) approach (RMS is not explained there) (Leslie et al., 2007).

Lukaski, reports that in first studies, short-term precision and long-term Precision, in different period times and different devices studied. Wahner et al. (1988), as cited in Lukaski; 1993, reported a short-term precision (repeat measurements on the same day) of 0.2 and 0.5% for BMC and BMD, respectively, and a long-term precision (for up to 6 mo) of 0.4% for BMD in lumbar spine phantoms made of hydroxyapatite. Duplicate scans performed on the same day in patients showed a difference of <1% between scans for BMC and BMD. Kelly et al. (1988), as cited in Lukaski; 1993, also observed high reproducibility (CV = 0.23%) of BMD measurements in spine phantoms measured over 6 months. Rencken et al. (1991), as cited in Lukaski; 1993, evaluated the precision of DXA measurements using six different QDR instruments at separate locations. Nine consecutive scans were performed on a single spine phantom at each site. The investigators reported an average precision for BMC and BMD of <1% (range: 0.3-0.6%). The average of the highest and lowest mean values was 1.1% for BMC and 1.07% for BMD. Mazess et al. (1989), as cited in Lukaski; 1993, reported a long-term precision in BMD measurements of 0.6% using a DPX system in a spine phantom over 6 mo. Estimates of 1.8 and 0.9% for the measurement of total body BMC and BMD, respectively, in 12 adults were also reported with a DPX instrument (Mazess et al. 1990, as cited in Lukaski; 1993). Johnson and Dawson-Hughes (1991), as cited in Lukaski; 1993, assessed long-term precision of BMD measurements in six volunteers scanned six times initially and at the same frequency 9 mo later. The short-term precision of BMD measurements in the spine, femoral neck and whole body were 1.08, 2.08 and 0.66%, respectively. The long-term precision was 1.01, 2.07 and 0.62%, respectively. The investigators also reported the precision in determining body composition variables; thus, the precision of whole-body BMC, fat-free mass and fat mass was 0.8, 1.1 and 2.7%, at the start of the study, and 1.2, 1.0, and 1.7%, respectively, after 9 months.

Another aspect of quality control is the accuracy of the DXA measurement. The extent to which DXA measurements represent true bone mineral status has been assessed by measuring the mineral content of cadaver vertebrae of known ash weights and volumes. Ho et al. (1990), as cited in Lukaski; 1993, measured BMC and BMD in lumbar vertebrae from 11 cadavers. The ash weights of 31 lumbar vertebrae and the DXA BMC values were significantly correlated ($r = 0.963$, SEE = 1.01 g; $P < 0.001$). The slope of the regression of ash weight as the dependent variable versus QDR-BMC as the independent variable was 1.0, but

the intercept was 0.59. Although the value of 0.59 was not statistically different from 0, the authors concluded that DXA under estimates ash weight (Lukaski, 1993).
Before to 2000, DXA measurements were conducted with a pencil-beam instrument (Lunar DPX, GE Lunar, Madison WI), and after that a fan-beam instrument was used. As Leslie et al suggested in 2011, instruments were cross-calibrated using anthropomorphic phantoms and 59 volunteers. They say there was no clinically significant differences (T-score differences <0.2). Densitometers showed stable long-term performance [CV<0.5%] and satisfactory in vivo precision (CV 1.7% for L1–4 and 1.1% for the total hip) (Leslie et al., 2011)

3.3.4 The long-term performance of DXA bone densitometers

Monitoring the performance of DXA after long time utilization is very important because any deterioration could change bone mineral density (BMD) measurements and affect clinical management. The importance of DXA in longitudinal trials of new osteoporosis therapies also need constant performance over years to confirm that any altration in bone density is real and not due to machine shifts or fluctuation. In this way, Wells and Ryan, assessed the performance of a 6-year-old bone densitometer (a Lunar DPX alpha), which has undertaken 1500 scans/year over this period. They concluded that the machine performs extremely well over a long period and after 6 years of Performing, measurements is very suitable to be fit for clinical use. It may be can be generalized to all main DXA devices in market (Wells & Ryan, 2000).

3.3.5 Beam geometry

At website of department of nuclear medicine, PET & bone densitometry of Royal Adelaide Hospital (Australia), at section of "Bone Densitometry Equipment", beam geometry of "DXA devices" are explained so:

3.3.5.1 Pencil beam

First generation bone densitometers (isotope and x-ray) use this beam geometry. The photon beam is tightly collimated with one photon source and one detector (some scanners have two, usually photomultiplier tubes). The source and detector are rigidly coupled and moved together in a rectilinear manner to build an image of the bone being examined line by line. The disadvantage of this technology is the relatively slow scan speed (typically 2-4 minutes per scan site). However, the direct relationship between source and detector means that calculated bone and tissue masses are less likely to be artefactual.

3.3.5.2 Fan beam

The second generation of x-ray bone densitometer has a fan geometry, with a source which fans out in the short axis plane of the patient and is measured by an array of detectors in the same plane.
The bones are imaged in one pass along the long axis of the body (as illustrated at middle) providing an immediate advantage in scan speed which is typically about 1 minute on modern scanners.
The disadvantage of fan beam DXA is that the photon flux at the edges is lower than the middle of the image (due to the inverse square law). As a result, mass calculations may have some systematic error, although bone mineral density values have been shown to be unaffected.

3.3.5.3 Narrow fan beam

This is designed to overcome some of the limitations of the fan beam geometry. A small fan beam radiation (about 4cm wide at the detector) in the long axis is detected by an array of detectors. The beam scans the bones in the short patient axis on each individual sweep along the long axis of the patient with some beam overlap. Although slightly slower than a fan beam scanner (1-2 minutes per scan), the mass results should be more accurate as the photon flux has little variability in the area being measured (due to the beam overlap). You can see the schematic figure of different beam geometries in the Fig. 4, from mentioned website (Royal Adelaide Hospital, 2009).

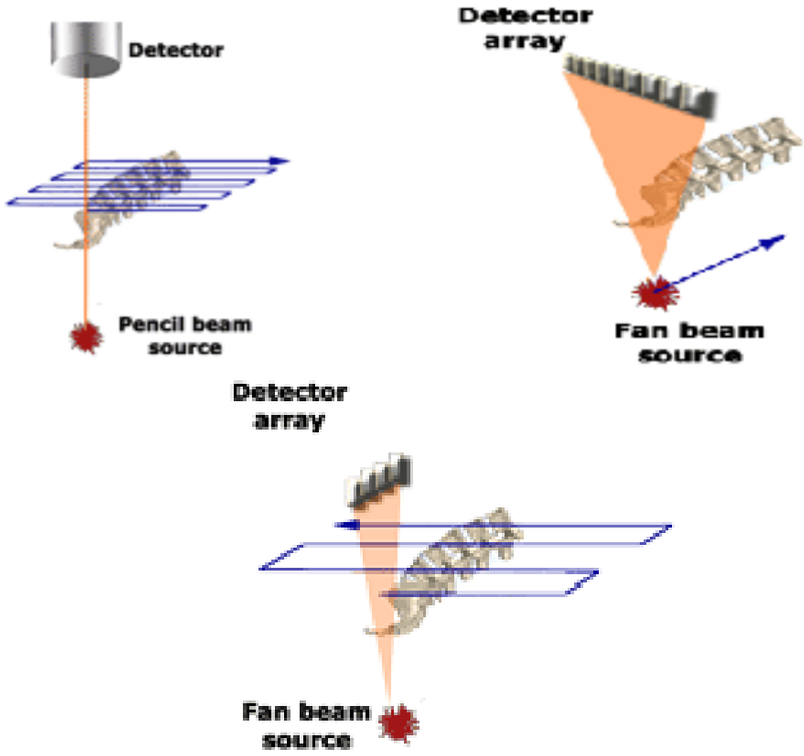

Fig. 4. Beam geometry of DXA mechines (from website of Royal Adelaide Hospital (Australia)

3.4 Software

The reference data of these machines, contain data of BMD tests of almost 5000 Caucasian white normal persons; around 20-80 y/o. Any brand of these machines has different reference data. It is clear that collecting such huge database, nowadays, seems impossible (especially due to cost and financial problems). This makes these method (DXA) and machines, unique. It seems impossible that any other method or brand can replace them in future, at least in near future.

Another ability of the software of this machines is, ability to calculate T-score and Z-score for patients (Shepherd &Blake, 2007):

$$\text{T-score}=\frac{\text{Measured BMD-Young adult mean BMD}}{\text{Young adult population SD}}$$

$$\text{Z-score}=\frac{\text{Measured BMD-Age-matched mean BMD}}{\text{Young adult population SD}}$$

It means after acquisition of absolute BMD of patients by Hardware, the software compute the difference between BMD of patient and young adult mean BMD (from reference data in the software). Then divide it on young adult population standard deviation, contained in the software, the result is T-score. When Z-score is under calculation, the software divides the difference between BMD of patient and age-matched mean BMD and divides it on age-matched population standard deviation. The ability of calculating T—score and Z-score is another interesting characteristic of software of these machines.
As the different brands, have different database, scientists tried to find ways to compare the results of deferent machines. Now we suggest some of these methods.

3.4.1 Providing sBMD

Genant et al, as inventors of sBMD, explained the methods of providing sBMD in their article, so.
We can t compare patient information between various DXA scanners, because there isn't any acceptable universal cross-calibration procedure or standard. Although operating on the same basic principles, normative databases, are specific and different for each scanner. The instruments show differences in scanner design, bone mineral calibration, and analysis algorithms. Lunar and Norland scanners rely on daily scanning of standards to provide a bone tissue equivalent calibration. Hologic uses an internal calibration system, which corrects for short-term instabilities. Also, the software used for analysis of the scans, is manufacturer specific (and unique), especially with regard *to* the edge detection algorithms used for separating bone and soft tissue regions. This implementation causes in variations in the defined bone area (cm2) and bone mineral content (BMC, g) and density (BMD) of the same subject on different systems. Genant et al, study was performed under the auspices of the International DXA Standardization Committee to establish appropriate cross-calibration parameters. Posteroanterior (PA) lumbar spine measurements of 100 women, ages 20-80 years (mean 52.6 ± 16, range of BMD = 0.4-1.6 g/cm2) were obtained on a Norland XR26 Mark II, a Lunar DPX-L, and a Hologic QDR 2000 densitometer using standard procedures (pencil beam mode for all three scanners). Area, BMC, and BMD results from the different scanners were compared for all patients. In addition, the European spine phantom (ESP) and the European spine phantom prototype (ESP prototype), as well as standard phantoms from all three manufacturers, were evaluated on the three systems. To reach universal scanner calibration, they used the intercept and slope of the patient's correlations and the value of the middle vertebra of the ESP as a reference point in a series of standardization formulas, and expressed the results as sBMD (mg/cm2). The correlations of the patients' spinal BMD values were excellent for each of the three scanner pairs. The average absolute difference in patient spinal BMD values (L2-L4) between Hologic and Norland was 0.012 g/cm' (1.3%); it was 0.113 g/cm' (11.7%) between Hologic and Lunar and 0.118 g/cm2 (12.2%) between Norland and Lunar. The phantoms' regression lines approximated those of the patient regression lines, and the phantoms with only one measurement point were very close to the patients' regression lines. After applying the standardization formulas, the average absolute variations for the 100 patients were 28 mg/cm2 (2.7%) for Hologich/Norland, 23 mg/cm2 (2.2%) for Hologic/Lunar, and 29 mg/cm2 (2.8%) for Norland/Lunar. Average BMD results for the patients before correction were 0.972 g/cm2

for Hologic, 1.100 g/cm2 for Lunar, and 0.969 g/cm2 for Norland. After correction, sBMD results for patients were 1045 mg/cm2 for Hologic, 1047 mg/cm2 for Lunar, and 1043 mg/cm2 for Norland. The standardization approach as performed in our study provided compatibility of DXA results obtained on different scanners. Finally the sBMD for different machines calculates as sBMD = 1.0761BMDnorland, sBMDl = 0.9522BMDlunar and sBMDh = 1.0755BMDhologic. (Genant et al., 1994).

3.4.2 Use of NHANES III

When the reference-data of different machines (the young-adult mean BMD), used for defining T-score of patient, the variability within these reference data of different brands, substantially impacts osteoporosis prevalence with using this T-score-based approach. Binkley et al, emphasize that ideally, all bone mass measurement devices would use the same population to define the young-normal mean BMD and SD, a process that cause obtaining of similar T-scores with instruments of different manufacturers. Although use of a single large sample population to develop a unique normative database for all densitometers has been suggested, this process has not been possible. To increase coordination between diagnostic classification, the International Committee for Standards in Bone Measurement (ICSBM) agreed on a universal reference database for the femur based on NHANES III, the only large standardized reference database ever published (Binkley et al., 2005). Looker et al., mention that this data were gathered from 14646 men and women aged 20 years and older, using dual-energy X-ray absorptiometry, and included bone mineral density (BMD), bone mineral content (BMC) and area of bone scanned in four selected regions of interest (ROI) in the proximal femur: femur neck, trochanter, intertrochanter and total. These variables are separated by age and sex for non-Hispanic whites (NHW), non-Hispanic blacks (NHB) and Mexican Americans (MA). They emphasize that the updated data on BMD for the total femur ROI of NHW have been selected as the reference database for femur standardization efforts by the International Committee on Standards in Bone Measurements (Looker et al., 1998). The ICSBM published formulae to convert measured BMD into standardized BMD (of total femur), thereby allowing use of the NHANES III database by other brands' densitometer. The NHANES III data were acquired using Hologic densitometers (Binkley et al., 2005).

4. General consideration in bone mineral densitometry

4.1 Recommendation about ROIs that should assess

Siminoski et al., have some recommendations about ROIs that are under measurement:

- In the lumbar spine, using a minimum of 2 valid vertebra is recommended (if there is problems in L1-L4 vertebrae that cause exclusion one or 2 of them).
- In the proximal femur, Ward's area should not be included in the report, as the small amount of bone yields measurements of poor accuracy and reproducibility.
- If either hip or spine is not valid, forearm BMD is recommended. Preferred site is 1/3 radius, 33% radius or proximal radius.
- When the final report includes a graph of the patient's BMD, it should be based on the same anatomic levels that were used for numeric results; for example if L3 and L4 were excluded from spinal analysis because of degenerative objects, the graph should be based on the combined value for L1 and L2(Siminoski et al., 2005).

4.2 What is the criteria for using other sites for densitometry? Calcaneus an example

For densitometry we can also use appendicular skeleton. Particularly the calcaneus is an excellent site for measurements by a range of techniques. So we use it as an example for describing the rules of choosing ROI for bone mineral densitometry. The calcaneus is easily accessible with little overlying soft tissue. It is not a common fracture site but remember that in the spinal region, the most susceptible sites for fracture are at T7_ T8 and T11_L1, but we measure bone mineral content to L1_L4 because of less overlying soft tissue.

The remodeling of trabecular bone is more active than cortical bone. It means trabecular bone is more active metabolically and more sensitive to metabolic bone changes. Calcaneus is made up, almost entirely of trabecular bone and may provide a more sensitive measurement site for finding early signs of diseases that affect mostly metablism. A number of studies suggested that bone mass of calcaneus may contribute to fracture risk in other sites and that its predictive power is not very different than that of spine and hip. The study by Cummings et al. as cited in Kang and speller; 1999, confirmed this in 65 years old women and over.Interestingly, many early single energy measurements of bone mineral were made in the calcaneus, because it is a peripheral site that can be immersed to water. The arrival of dual energy techniques changed the focus. Earlier studies validated a highly significant correlation between the ashed bone mass of cadaver calcanei and the measured BMC values of calcaneus by densitometry (r=0.97). Kang and Speller, describe calcaneus as a site with excellent accuracy that it's measurements can be made quickly and easily and with portable instruments. (Kang & Speller, 1999)

4.3 Operators, the heart of a BMD center

Correct positioning among other factors is very important to ensure an optimal scan. Simonoski et al., emphasize that correct and consistent positioning and labelling of hip and lumbar spine (as the main job of operators), are important when evaluating serial assessments (monitoring of patients). It is important to follow manufacturer-specific protocols to ensure appropriate comparisons with normative reference data.

Structural abnormalities and artifacts can significantly influence the results. Independent factors, like body weight, may affect BMD results. However, in interpreting the results of a scan, first of all, it must be described whether the scan is valid with regards to positioning, artifact, and analysis, or not (Siminoski et al., 2005)

Fuleihan et al, assessed the effects of the machine, operator and subjects on error of measurements of bone density. They explained their technique for this assessment as an analysis applied to data from a prospective study of BMD measurements on spine phantoms and on pre- and postmenopausal women. Scans performed on the same day or up to 4 weeks apart with DXA (QDR IOOOW, Hologic). Their model assessed (or suggested) that : operators' and subjects' variability were the most causes of errors in measurements rather than machine performance (Fuleihan et al., 1995). Subjects are not changeable or controllable, but operators job can be under quality control and its quality develops by time (and experience). These machines, are not very extensively distributed, and any machine is unique in its way (the data of a second scan of a patients, can be compared to data on the same machine that first BMD is performed, only). These make finding expert operators for these machines, not very easy. What mentioned above, is the cause that operators are called "the heart" of BMD centers. So some-ones believe in this sentence "Never change your operators (in BMD departments) and if the change is inevitable, never change them again."

4.4 Material of a standard BMD report

Shimonoseki et al, recommend that , a standard BMD report should include:

- Patient identifiers.
- DXA scanner identifier.
- BMD results expressed in absolute values (g/cm2; 3 decimal places) and T-score (1 decimal place) for lumbar spine; proximal femur (total hip, femoral neck, and trochanter); and an alternate site (forearm BMD preferred: 1/3 radius, 33% radius or proximal radius) if either hip or spine is not valid.
- A statement about any limitations due to artifacts, if present.
- The fracture risk category (low, moderate, or high). It must be included major clinical factors that modify absolute fracture risk probability (with an indication of the corresponding absolute 10-year fracture risk of <10%, 10-20%, or >20%).
- A statement as to whether the change is statistically significant or not for serial measurements. The BMD centre's least significant change for each skeletal site (in g/cm2) should be included (Siminoski et al., 2005)

4.5 Discordance

Discordance makes difficulties in diagnosis of osteoporosis and management of osteoporotic patients. Moayyeri et al, explain, discordance in diagnosis of osteoporosis that is defined as presence of different categories of diagnosis based on T-score (osteoporosis, osteopenia, and normal) in two skeletal sites of an individual patient. They mansion that discordance has been divided into two groups: major and minor . When the different sites results, are close; i.e., normal in one site and osteopenic in the other site, or, when patient is diagnosed as osteopenic in one site and osteoporotic in the other site, minor discordance happens. When patient diagnosed normal in one site and is osteoporosis in another site, major discordance happens. (Moayyeri et al., 2005). In a clinical study, BMD measurements performed at lumbar spine both for baseline risk assessment and for monitoring purposes. Leslie et al. discuss a difficulty that clinician are confronted with highly discordant measurements and at the same time lumbar spine is worse than femoral neck and about how this should be integrated into the decision-making process. They discuss about different guideline recommendations in this situation. They say under NOF guideline, if t-score in lumbar spine is in osteoporotic range without consideration to estimated risk -by special soft-wares-, treatment should be recommended. In other national guideline such as those from the UK, till a 10 year fracture risk prediction from the femoral neck does not reach the intervention threshold, don't recommend any treatment for patients with osteoporotic lumbar spine. Canadian guidelines have attempted to show the issue of site discordance (in femur) by recommending use of the minimum T-score, in femur for diagnosis and treatment of osteoporosis. However, Leslie et al. suggest that this may systematically overestimates fracture risk and does not consider site-specific differences in fractures or the way BMD declines with age. They suggest that as lumbar spine and hip measurements are both performed for clinical purposes, using a procedure that accurately reflects the contribution of each measurement site to fracture risk, is clearly preferred, so they propose a a procedure for adjusting FRAX probability, based upon the T-score difference between the lumbar spine (LS) and femoral neck (FN). This procedure is termed "offset". They furmulated following rule: "Increase/decrease FRAX estimate for a major fracture by one tenth for each rounded T-score difference between LS and FN." (Leslie et al., 2011)

4.6 Pediatric consideration

4.6.1 Low bone mass in pediatrics

New investigations show prevalence of low BMD in children is very high and it is higher than expected range. Genetic, environmental and iatrogenic factor are 3 most important factor that lead to bone disorders in children.

Bogunovic et al., name causes of pediatric osteoporosis as idiopathic juvenile osteoporosis and heritable connective tissue disorders like osteogenesis imperfect and Ehler–Danlos. They also name a long list of factors as secondary causes of pediatric osteoporosis that include neuromuscular disorders (cerebral palsy and Duchenne muscular dystrophy), childhood cancer, endocrine disorders (Turner Syndrome and juvenile diabetes mellitus), and inborn errors of metabolism (Gaucher disease) and Chronic diseases like thalassemia. Anticonvulsants, glucocorticoids, and various forms of chemotherapy may adversely affect normal skeletal maturation (Bogunovic et al., 2009).

4.6.2 Problems with DXA in pediatric

Bone mass densitometry by dual X-ray absorptiometry (DEXA) of the lumbar spine and femoral neck is recommended as one of the most reliable and non-invasive technique for the assessment of bone mass (Hamidi et al., 2008). This method is very common around the world and many pediatric studies about bone densitometry and body composition have been published by using this method. (Van Kuijk, 2010).WHO osteoporosis diagnostic criteria should not be applied to children. We can't use T-score because children have not reached PBM, yet. Instead, in children, Z-score must be noticed, that it is a comparison of BMD of child to pediatric normative data. If the z- score is below -2 , we can use the term 'low bone density for chronologic age" (Daniels et al., 2003). DXA is reliable and accurate for adult but in children there is a challenge for it. As it is known, true bone density is a result of dividing BMC(g) by volume(cm3). In DXA , BMD is determined by dividing BMC by 2 dimensional area of a three dimensional objective (bone). By the use of these criteria smaller bone appear to have a lower BMD than larger bones. (Bogunovic et al., 2009). Bone size does not change, in adults, over time. On the contrary, bone size changes in growing children in 3 dimentions. When we screen children with DXA and follow them over time, we actually measure their growth instead of measuring actual changing in BMD.(Van Kuijk, 2010). It must be remembered that wide variation of height, and bone size in children makes interpretation of BMD difficult, especially in short children. Bogunovic et al., mention that longitudinal evaluation of a given patient over time is affected by the ever-changing size of the growing skeleton and the rates of skeletal growth vary with each bony dimension (Bogunovic et al., 2009). All this problems, cause to ask a question: Is it right to use DXA for measuring bone density and fracture risk in children or not? In response we emphasize some useful points about DXA. First it has fewer radiation than other methods, that is very important in radiology of children, 2) it is not a fearful (less noisy with no tunnel) method for children densitometry, 3) It is used worldwide and many pediatric studies, have been published in the field of bone densitometry and in the field of body composition studies, by using DXA method also 4) Studies about the relationship between bone density and fractures in healthy children, suggested that bone mass may contribute to fracture risk in childhood (Van Kuijk, 2010). So may be the answer is that performing DXA for measurement bone density and fracture risk in children, is a helpful method yet. However

we should emphasize that bone fragility in children extends beyond single BMD measurement, and bone geometry and body size influence it and in the diagnosis of osteoporosis, the presence of both a clinically significant fracture history and low bone mass, must be noticed (Bogunovic et al., 2009).

4.6.3 Special consideration of comparison of normal children and children with chronic disease, some points in BMD of chronic ill children

The measurement of BMC (g/cm) and BMD (g/cm2) are not only dependent on the mineral density of cortical and spongious bone, but also depend on the bone geometry. Lower BMD or BMC in shorter children may not describe a mineral deficiency or mineralization disorder, as is often thought, because the smaller bone may show lower BMD because of properties of DXA methods (Schonau,1998). BMD measurement in children is more affected by the wide variation of age at onset and progression of puberty. This leads to a wide variation in the age at reach of peak bone mass. It is thought the presence of a chronic disease, like juvenile arthritis, cause delay in pubertal onset and development. It has been estimated that one-third to one-half of the total mineralization in the lumbar spine in adult women is occurred during the 3 years around the onset of puberty. Therefore, we can t compare the BMD of a well-grown 13-year-old girl who is in mid-puberty with that of a small pre-pubertal 13-year-old with juvenile arthritis. Rabinovich remembers us that a DXA scan is not needed to tell who has the lower BMD. The question then is, is the BMD result in this small pre-pubertal girl normal? (Rabinovich, 2004).

As van Kuijk suggests, children with chronic disorders or medication, should never be compared with age-matched reference (normal) values. They should be compared with children with the same maturation status (skeletal age) (Van Kuijk, 2010).

5. Geometry (Another use of dual x-ray absorptiometry)

Some important factors such as the shape and structure of bone and the risk of falling, affect susceptibility to fracture so BMD alone cannot exactly predict who will have fracture. As Gregory and Aspden emphasize, the geometry of the proximal femur is a vital component in determining a person's risk of hip fracture. When a trauma occurs, such as a fall, the shape and structure of the femur determines how the forces are passed through the bone from the point of impact and whether they surpass the inherent strength of the bone and result in a fracture or not. Geometry component is seen in the picture from Gregory and Aspden article (Fig. 5.)

They explained any of these components

- Hip axis length: The distance from greater trochanter to inner pelvic brim, shown between points A and C in Fig. 5
- Femoral neck axis length (FNAL):

Femoral neck axis length is the linear distance measured from the base of the greater trochanter to the apex of the femoral head. It is illustrated by points B to C in Fig. 5. Confusingly, it is also sometimes referred to in the literature as hip axis length.

- Femoral neck width (FNW):

The narrowest distance across the femoral neck, often constrained to being perpendicular to the neck axis. The distance between points F and G in Fig. 5.

- Neck-shaft angle:

Usually defined as the angle between the femoral neck axis and the shaft axis (angle at point H in Fig. 5).

- Other geometrical measures: In addition to the most common measures of geometry discussed above, a number of other measures have also been related to fracture; including a thinner femoral shaft cortex , a thinner femoral neck cortex , a smaller calcar femoral (a dense, vertically orientated bone present in the posteroemedial region of the femoral shaft under the lesser trochanter of the femur) , a narrower trochanteric width and smaller inner and outer pelvic diameters. In contrast, an increased femoral head diameter has been related to increased bone strength.

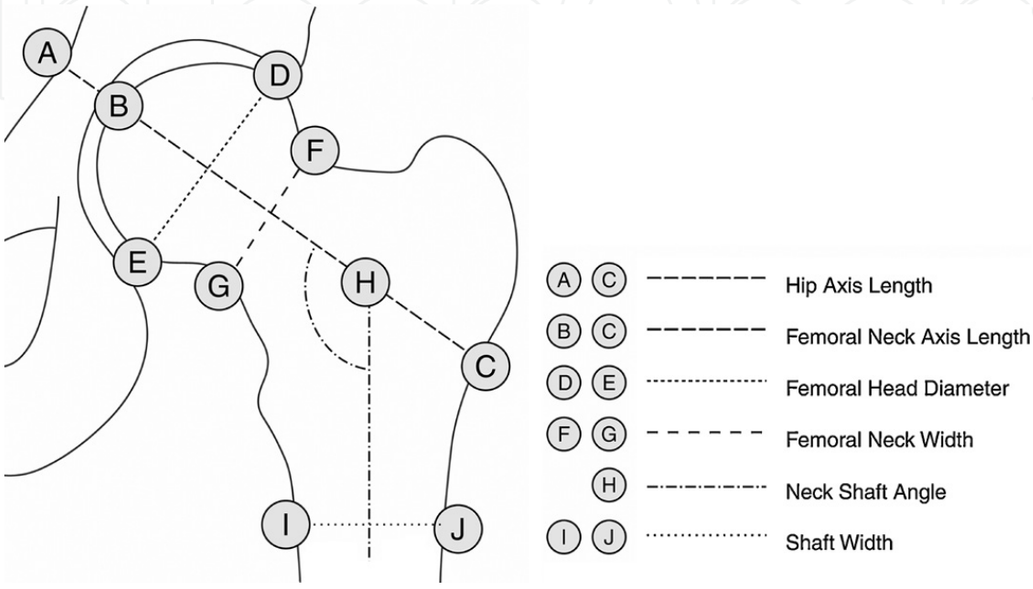

Fig. 5. Diagram illustrating some of the most common geometrical measurements made from the proximal femur (from Gregory and Aspden, 2008).

Two methods are must commonly used for assessing bone geometry, radiography and dual energy X-ray absorptiometry (DXA) (fan beam devices, more provide this service). Each of them; has its own advantages and disadvantages. Femoral geometry is important in determining both bone strength and fracture risk. The strongest associations with both outcomes appear to be a longer (Hip axis length) HAL and larger NSA (Neck-shaft angle) (Gregory & Aspden, 2008).

6. Finite element (An helpful method for better understanding of bone)

Need to a mathematical tool for solving complex mathematical problems, is answered by inventing Finite-element modeling (FEM). It helps to understand patterns of stress, strain, deflections, heat transfer, fluid flow, etc., in computer models of organic structures. Ross, emphasize that FEM provides a method for addressing a range of questions that are otherwise intractable, or very difficult to solve -in vivo or in vitro- and is potentially one of the most powerful tools in the methodological tool of vertebrate biomechanics. For example, clarifying functional consequences of the remarkable histological and morphological diversity of the vertebrae, is one of the important aims of vertebrate biomechanics. Many of researches on various disorders or diseases of the bone, are relied on this structure-function relationship. Skeletal health during long term space flight, as well as interpretation of skeletons found in the fossil and archeological records, are benefitted from these researches. Ross mentions that form-

function relationships of the skeleton are therefore of concern to bioengineers, clinicians, biological anthropologists, and paleontologists, and FEM provides a method for studying them. He also suggests that the availability of increasingly powerful computers at progressively more affordable prices has made FEM an accessible tool for biomechanists and the wide use of FEM in clinical research is now imitating many basic science researches (Ross, 2005). Finite element can be helpful in femoral characteristics finding as helpful as is in spinal vertebrae and finding the mechanisms and risk factors for fracture.

7. Recent progress in bone imaging for osteoporosis research

Development in bone imaging techniques have provided tools for analyzing bone structure at the macro-, micro- and nano-level. Ito, provided a list of recent progress in bone imaging as

- High-resolution CT (HR-CT) and high-resolution magnetic resonance (HR-MR). They are in vivo quantitative techniques for assessing the microstructure of trabecular bone non-invasively and non-destructively. Compared with MR imaging, CT-based techniques have the advantage of directly visualizing the bone in the axial skeleton, with high spatial resolution (of course, disadvantage of delivering a considerable radiation dose remains).
- Micro-CT (μCT) and Synchrotron μCT (SR-CT). The farmer provides a higher resolution of the microstructure and is principally applicable in vitro, has undergone technological advances such that it is now able to elucidate the physiological skeletal change mechanisms associated with aging and determine the effects of therapeutic intervention on the bone microstructure. In particular, synchrotron μCT (SR-CT) provides a more detailed view of trabecular structure at the nano-level.
- DXA-based hip structure analysis (HSA) and CT-based HAS. DXA-based HSA is a convenient tool for analyzing biomechanical properties and for assuming cross-sectional hip geometry based on two-dimensional (2D) data. CT-based HSA provides these parameters three-dimensionally in robust relationship with biomechanical properties, at the cost of greater radiation exposure and the lengthy time required for the analytical procedure.

The author, suggests that further progress in bone imaging technology is promising to bring new aspects of bone structure in relation to bone strength to light, and to establish a means for analyzing bone structural properties in the everyday clinical setting (Ito, 2011).

8. Conclusion

Tanner in his article reminds us the Bonnick suggestion (noted in the preface of the most recent edition of the author's book on bone densitometry in clinical practice)". . . as strange as it may seem, the technology itself is in danger of becoming so devalued that improvements in accessibility and advances in applications may be lost." (Bonnick SL. as cited in Tanner, 2011 from book "Bone densitometry in clinical practice: application and interpretation"(current clinical practice series). 3rd ed. Totowa, New Jersey:Humana Press; 2010). The future of DXA bone density testing is challenged by reimbursement, complicated guidelines, and the controversy over the monitoring of treatment. Nevertheless, bone health assessment and fracture risk prediction rely on quality bone density measurement using DXA (Tanner, 2011).

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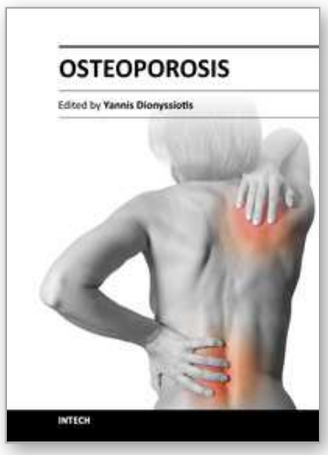

Osteoporosis

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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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