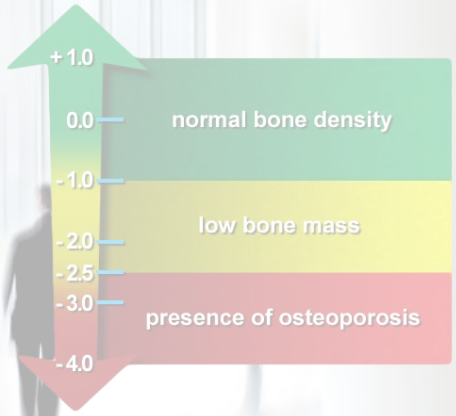
Technology Comparison

Bone Densitometry

The Diagnosis of Osteoporosis, in the absence of bone density testing, is currently not possible before the patient suffers a low energy fracture. Since Osteoporosis shows no symptoms in its early stages, the illness is not diagnosed for several years. The bone strength is primarily dependent on Bone Mineral Density (BMD). Bone densitometry refers to the process of testing bone density at the reference axial sites: Lumbar vertebrae and the femoral neck. A low BMD is an indication of potential fracture risk and, according to the guidelines of World Health Organization, the results of BMD testing are used to determine osteoporosis: based on a standard scale (T-Score) patients are classified into normal, osteopenic, and osteoporotic categories. BMD also serves to determine the effect of medical therapy, and to predict the individual future fracture risk. The major techniques available for the diagnosis of Osteoporosis can be separated into two categories, one class based on ionizing radiation (radiological), and the other on non-ionizing radiation.

Osteoporosis is diagnosed when a person's BMD is equal to or more than 2.5 standard deviations below this reference measurement. Osteopenia is diagnosed when the measurement is between 1 and 2.5 standard deviations below the young adult reference measurement.



The gold standard technique is called dual-energy x-ray absorptiometry (DXA). This technology has been introduced in 1987 as a successor of Single-energy x-ray absorptiometry (SXA) that took over Dual-Photon Absorptiometry (DPA) and previously over Single-Photon Absorptiometry (SPA) used for axial and peripheral skeletal sites respectively. During a DXA test, a x-ray tube exposed to 80-100 kV energy is passed over spine and hip and the information is evaluated by a computer program that determines how much bone mass the patient has expressed in g/cm2. DXA scanners use an X-ray beam composed of two different photon energies. In order to compensate for the different attenuation coefficients of mineralized bone and soft tissues encountered along the target path within the human body: the intensities of high-energy and low-energy photons that passed through the body are analyzed separately by a dedicated algorithm, which subtracts soft tissue attenuation and provides only bone attenuation values. These values are then compared with reference measurements in phantoms of known composition to obtain bone mineral content (BMC, in grams), which is finally divided by the projected area of the considered bone (in cm2) to obtain the BMD value (in g/cm2).

These principles are used to obtain BMD measurements mainly on axial skeletal site, namely hip and lumbar spine, even if other peripheral sites could be measured too. DXA is focused only on the average quantity of bone minerals and not on the bone microarchitecture quality. The potential impact of widespread testing of BMD on the burden of fractures is less than optimal also for the limited availability of bone densitometers due to the high cost of the devices, ionizing radiation exposure, certified operator needed for operations and only secondary care procedure. The measurement of bone mineral density (BMD) by dual x-ray absorptiometry (DXA) has been acknowledged as the gold standard for the diagnosis, treatment evaluation, and prognosis of osteoporosis due to the possibility to scan vertebra and femoral neck areas. Because of these reasons, international guidelines typically recommend DXA scans for osteoporosis diagnosis only in people aged 65 and older if no other specific risk factors are present. Nevertheless, physicians are unable to assess the risk of bone loss due to the limitations of DXA in patients above 65 years of age and the only way to overcome this is by performing a QCT (Quantitative Computer Tomography) which exposes otherwise healthy people to even higher radiation exposure.

The actual effectiveness of DXA systems has been critically assessed taking into account the factors that can restrict its employment and/or affect its accuracy and precision levels. These factors have been scientifically investigated and literature results are briefly reviewed and summarized in the following paragraphs. First of all, because DXA scanners use two X-ray energies in the presence of three types of tissue (mineralized bone, lean tissue and adipose tissue), measurement errors due to non-uniform distribution of adipose tissues have been reported in literature (*Tothill P, et al. J Clin Densitom. 2014;17:91-96; Tothill P, et al. Br J Radiol. 1994;67:71-75; Svendsen OL, et al. J Bone Miner Res. 1995;10:868-873; Lee DC, et al. ASBMR 2007;W514; Kuiper JW, et al. Osteoporos Int. 1996;6:25-30; Griffith JF, et al. Radiology 2006;241:831-838*). The typical uncertainty level associated to both hip and spine BMD measurements is around 0.060 g/cm2, which roughly corresponds to a relative error in the range 5-10% and this should be considered in evaluating the accuracy of DXA scanning.

Secondly, DXA outcome is strongly influenced by patient positioning, which should be carefully assessed by the technologist and double-checked by the clinician that interprets the test

For instance, for correct hip positioning, the patient should keep the femur straight with the shaft parallel to the image edge and an internal rotation of 25°, obtained by the use of apposite positioning devices. A very recent paper (*Messina C, et al. Eur Radiol. 2015*) retrospectively reviewed 793 DXA reports, including both spine and femur investigations, and documented the presence of patient positioning errors in about 9% of femoral acquisitions and in about 8% of spinal ones. A further source of inaccuracy in DXA scans is represented by possible post-acquisition analysis errors. Actually, DXA software typically provides an automatic identification of the regions of interest (ROIs) within the target bone district, but the technologist should make manual adjustments in order to obtain a reliable outcome.

In the case of spine, the ROI consists of the vertebrae L1-L4 and the correct placement of "spine box" and "intervertebral lines" is critical to avoid errors in BMD measurement, especially in patients with scoliosis (*El Maghraoui A, et al. Q J Med. 2008;101:605-617*). Analogous manual adjustments are routinely required for femoral investigations.

The above referenced paper (Messina C, et al. Eur Radiol. 2015) reported a very high rate of data analysis errors affecting the final BMD value: 64% for lumbar examinations and 48% for femoral ones. Therefore, proper DXA employment requires well-trained personnel, since incorrect patient positioning, data analysis errors and interpretation mistakes can easily affect diagnosis and subsequent therapeutic decisions (*Watts NB. Osteoporos Int. 2004;15:847-854*).

Recent literature has also questioned the intrinsic DXA suitability for osteoporotic fracture risk assessment, since, although BMD is one of the major determinant of bone strength, considerable overlaps in BMD values have been reported between individuals that develop fractures and those that do not (Hordon LD, et al. Bone 2000;27:271-276).

In order to try to overcome this important issue the trabecular bone score (TBS) based on DXA images has been recently introduced. It consists of a novel parameter, still under validation, based on a gray-scale textural analysis of spine DXA images, which uses variograms of 2D projection images to provide a quantitative estimate of trabecular microarchitecture status. However, TBS scores are provided through an additional installation software module in the DXA systems with the consequent cost increasing of the final examinations.

Quantitative ultrasound (QUS) is an alternative method introduced to evaluate skeletal integrity at easily accessible peripheral sites and currently it is performed on the calcaneus (heel), wrist, phalanx and tibia. Over the past decade many studies have examined the use of ultrasound in bone for investigation of Osteoporosis. There is now a widespread consensus that ultrasound as a proven role in the assessment of Osteoporosis fracture risk. Quantitative ultrasound has a number of intrinsic advantages over established DXA method, namely low cost, lack of ionizing radiation exposure, minimal regulatory requirements, portability and bone micro-architecture properties provided alongside bone density. From a technology point of view, QUS techniques typically involve the generation of US pulses in the frequency range between 200 kHz and 1.5 MHz, which are transmitted through the bone under investigation. Some devices transmit US waves parallel to the axis of the target bone (axial transmission): the same US probe contains both the pulse emitter and the pulse receiver, and this approach is adopted to investigate forearm, tibia and radius. Nevertheless, the most common clinically-available QUS devices send US pulses perpendicularly with respect to target bone axis (transversal transmission): there are two separate probes for sending and receiving US pulses, with the investigated bone (usually the calcaneus) placed between them. Most of literature-available papers focused on the assessment of QUS diagnostic effectiveness involved calcaneal applications. In fact, calcaneus is composed almost entirely of trabecular bone, is a weight-bearing bone and has the advantage of having two flat, parallel lateral surfaces that are very suitable to achieve a satisfactory transmission of US pulses through the bone. As a result, calcaneus is the only validated skeletal site for the clinical use of QUS in osteoporosis management. Nevertheless, despite the huge amount of published data, the ISCD restricted the actual clinical diagnostic usefulness of validated calcaneal QUS devices to patients aged 65 and older, and only in combination with clinical risk factors, in order to identify patients with very low fracture risk, requiring no further investigations. Ultrasound technique has recently been added to the diagnostic toolbox for the diagnosis of Osteoporosis but the major disadvantage and the highest barrier to the market and widespread clinical use of current ultrasound technology is the impossibility to perform scans at the spine and hip, the reference sites for Osteoporosis diagnosis.

The innovative R.E.M.S. (Radiofrequency Echographic Multi Spectrometry) method overcomes all main DXA mentioned limitations related to tissue modeling approximation, patient positioning and image manual segmentation by providing highly accurate measurements. In fact, patient positioning does not affect the BMD measurements, since inclination between incident US beam and target bone depends only on probe placement. In EchoS this operation is supported, firstly, by on-screen markers to facilitate the proper alignment between US beam and bone surface and, secondly, by the fully automatic selection of the frames with a suitable signal-to-noise (SNR) ratio. Furthermore, the numbers of frames needed for a correct diagnosis is 1/25 of the actually acquired data: excess acquired data improve diagnostic reliability. This assures that diagnostic calculations are performed only on correctly acquired data, while the "noisy" frames are discarded: in case, the system could ask the operator to repeat the acquisition, but "noisy" frames will be never used to provide an unreliable diagnostic output. Finally, once data acquisition is complete, the whole process is fully automatic and there are no further sources of error that can affect measurement reproducibility. The R.E.M.S. technology has been developed to take into account only Region of Interest belonging to the targeted skeletal site and then tissues and processing models do not affect the diagnostic performances. From the following table reported below, a direct comparison of main reference parameters reported in literature of DXA versus EchoS show how EchoS present always and by far (in some cases with a higher order of magnitude) and for all references parameters a superior reproducibility and precision.

QUANTITATIVE ASSESSMENT	VERTEBRAE	FEMORAL NECK
SMALLEST DETECTABLE DIFFERENCE (SDD) [g/cm^2]	0.010	0.005
INTRA-OPERATOR REPEATABILITY (RMS-CV) [%]	0.35%	0.25%
INTER-OPERATOR REPEATABILITY (RMS-CV) [%]	0.54%	0.41%
DIAGNOSTIC AGREEMENT WITH DXA	93.1%	94.2%

Certifications

Echolight has successfully secured ISO 13485 certificate of Quality Management System and has obtained CE mark approval for EchoS, EchoStation and EchoStudio products by KIWA CERMET. These are important milestones for Echolight, which support our mission to provide value creating innovative solutions in healthcare to simplify, ease and protect the life and well-being of patients and caregivers. It also gives us the ability to complete the validation of the results of EchoS system through clinical trials to demonstrate the accuracy of our breakthrough technology developed. In addition the process for FDA 510(k) is started in order to obtain the certification by the end of 2016.

In collaboration with CNR –National Research Council – Echolight made a multicenter study for the clinical validation of the innovative technology in comparison to the gold standard technique DXA. This validation involved the most important centers and the most important personalities for the diagnosis of osteoporosis in Italy and Europe. Thousands of patients were acquired in order to create the reference curves and the database is already completed. The study is still underway and several scientific publications have been published in the most important scientific journals.

In compliance with the standard:

UNI CEI EN ISO 13485:2012
ISO 13485:2003
UNI EN ISO 9001: 2008
Medical Device Class IIa
CE Mark

ISO 13485

CE

National Research Council of Italy

CERMET
Certificazione e ricerca per la qualità

ITALIAN PATENT

"Apparato ad ultrasuoni per valutare lo stato della struttura ossea di un paziente"
(Patent N. 0001405771, filed date 16/05/2011 and granted date 24/01/2014).

INTERNATIONAL PATENT APPLICATION (PCT)

"Ultrasound apparatus for assessing the quality of a patient's bone tissue" (WO2012156937)
- Europe (EP2709533)
- South Korea (KR20140035932)
- Cina (CN103648401)
- USA (US2014155748)

Europaisches Patentamt
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COMPARISON	DXA	QUS	REMS
Radiation Exposure	YES	NO	NO
Axial Sites	YES	NO	YES
Bone Density Assessment BMD (g/cm2)	YES	NO	YES
Bone Quality Assessment	NO	??	YES
FRAX Index	YES	NO	YES
Body Composition Index	YES	NO	YES
Operator Independent	NO	NO	YES
Patient Positioning Influenced	YES	YES	NO
Soft Tissue Influenced	YES	YES	NO
Operator Certified Needed	YES	NO	NO
Dedicated Shield Room	YES	NO	NO
Maintenance Costs	YES	NO	NO
Diagnostic Tool	YES	NO	YES
Prevention, Monitoring and Follow-up	NO	NO	YES

Contact

Echolight is a high-tech biomed company for the development of the very first non-invasive and office-based solution for the Early Diagnosis of Osteoporosis. In compliance with the standard: UNI CEI EN ISO 13485:2012; ISO 13485:2003; CE Mark Medical Device Class IIa.

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We see different things.
ECHOLIGHT