A Comparative Study of Current Methods and Recent Advances in the Diagnosis and Assessment of Osteoporosis

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ABSTRACT

Osteoporosis is an abnormality that is manifested by a decrease in bone density. People with light skin, fine skeletons, a family history of osteoporosis, smokers, sedentary people and postmenopausal women are more likely to develop the disease. Early diagnosis of this disease can be of great help to improve one’s future life course and prevent potential risks. There are currently ways to diagnose the disease that is discussed below. But what is important in this study is how to diagnose the disease further in this study and to use the tools that are least risky for the individual. In this case, almost all people in the community, including children and sick people, can also be tested. The person with the disease will receive early treatment.

Keywords: Osteoporosis, Bone Function, Quantitative Ultrasound Method, Reference Point Indentation Technique, Magnetic Resonance Imaging

INTRODUCTION

Bone as a connective tissue performs the essential functions of protecting vital organs such as the bone marrow, mechanical support as a stimulant member, and regulating the metabolism of minerals such as calcium and phosphate, and maintaining blood serum homeostasis. Bone repair and formation are regulated precisely by cells, local and systemic cytokines, and bone matrix (mineralized matter) hormones.

Basics of Bone Science

Bone is a combination of nanomaterials and real nanocomposites. Bone is an interconnected set of complex materials that make up the bones of the human skeleton. Bone is a living tissue that has the ability to Reassemble itself without leaving an extra or injured part of its life. The trauma of accidents has increased the need for bone grafts over the years. In the United States alone, there are more than six million bone fractures that require at least 55,000,000 bone grafts. The need for bone grafting depends on the complexity of the bone defect. If the defect is small then the bone itself is capable of rearrangement within a few weeks and no surgery is required [1, 2].

Bone Construction

Bone is basically formed in one of two ways:

1. Intramembranous Ossification: During which osteoblasts differentiate directly from the mesenchyme and begin secretion of stenoids.
2. Endochondral Ossification: During which the pre-existing hyaline cartilage matrix is scratched and replaced by osteoid-secretion osteoblasts. In both processes above, bone tissue that first appears is primary or immature. Primary bone is a temporary tissue and will soon be replaced by a permanent secondary blade bone. During bone growth, areas of primary bone, areas of bone resorption and areas of secondary bone are all seen together.

**Bone Macroscopic and Microscopic Structure**
There are many bones in the human body in many different forms. The shape of each bone is directly related to what it does. There are five types of bones found in the human body: long, short, broad, irregular and sesamoid. The long bones are made up of an almost cylindrical trunk called the diaphysis, with prominent articular surfaces at its two ends called the epiphysis. The wider portions of the diaphysis end, which is in contact with the growth plates, are metaphyses. The short bones have a cubic shape and an irregular form which are covering only with a thin layer of compact bone, like the bones of the wrist and toes. The details and structure of long bone is presented in Figure 1.

The broad bones have a wide surface compared to their narrow thickness and are covered by parallel layers of compact bone, such as the skull, scapular and sternum. Irregular bones do not belong to any of the above groups. The shape of these irregular and complex bones is like the hip and spine bones. The sesamoid bones that are inside the tendons, which hold the tendons, play an important role in joint movement, such as the patellar bones and the Pisiform.

The bones structurally are divided in two types: compact bone or cortical bone and spongy bone or trabecular bone. The compact bone is the hard outer layer of bone with the least hollow space and cavities (see Figure 2). The spongy bone consists of a network of needle-shaped or flat bones that causes and creates bone marrow spaces to be placed inside it. The Figure 3 shown the spongy bone tissue diagram.

The outer part of the bone is covered by the periosteum with a fibrous layer on the outside and an osteogenic layer on the inside.

![Figure 1: The bone structure and composition [3].](image-url)
Bone tissue is made up of cells called bone cells. Unlike many other tissues, bone cells are far apart. The gap between these cells is filled by the intercellular material. This material is also called the Matrix. The matrix fills up like a covering between the bone cells, and in fact, the bone is stiff and firm because of it. Therefore, most of the bone is the inter-bone material that is very strong and causes bone strength. However, this material is not fixed but is constantly changing. Parts of it are regularly absorbed and replaced by other parts, which results in bone strength.

This ability of bone and intercellular material is due to the presence of bone cells. These cells manage the matrix. The matrix consists of two intertwined parts. A scaffold and three-dimensional lattice made of a special protein called collagen as well as specific sugars. On this scaffold precipitated calcium salts. These
calcium salts are mainly made of a substance called Hydroxyapatite. Osteoblasts are bone maker mononuclear cells and are derived from Osteoprogenic cells. These cells are located on the surface of the osteoid and are responsible for secreting a protein matrix that converts the osteoid into minerals to form bone tissue. Osteoid usually consists of type I collagen. Calcium hydroxyapatite is the major inorganic component of the bone mineral. Bone cells that are osteocytes originate from osteoblasts and are trapped in the bone matrix and surrounded by this matrix. The space where this cell is located is called Lacunae. Osteocytes regulate and respond to mechanical stresses as a mechanical sensor by maintaining calcium homeostasis. The smallest unit in lamellar or dense bone structures, Osteon (Haversian system). The Haversian is the Canal in the center of Osteon.

At birth, there are about 270 bones in the body, with some of these bones clinging to age and eventually producing 206 bones for an adult. The largest bone in the body is the femur and the smallest in the middle ear [6].

**Bone Function**
Bone as a connective tissue that is part of the skeletal system has three general functions:

1. The mechanical role that the muscle attaches to and supports its movements.
2. The protective role that protects vital organs and bone marrow.
3. The role of metabolism as a source of ions, especially calcium and phosphate, to maintain homeostasis.

The basic components of bone include the extracellular matrix (ECM) and the cells. ECM This tissue is composed of an organic and inorganic phase generally composed of collagen filaments (type I collagen) that make up 90% of the ECM protein volume, and the ten remaining percentage is assigned to other non-collagenous proteins including proteoglycans, glycoproteins (osteocalcin, osteonectin and osteopontin) and a number of growth factors that make up the organic matrix.

These proteins are incorporated into the matrix to form a collagen matrix. Their function is not fully understood, but we know that they play important roles in regulating mineral deposition, controlling the activity of osteoblasts and osteoclasts (cells producing bone matrix and bone resorption) and cell adhesion. The inorganic phase is mainly composed of calcium and phosphate, which form fusible or plate-shaped hydroxyapatite crystals.

Bone tissue can maintain its optimal shape and structure through a continuous renewal process throughout its life. According to this process, in the event of any change in the bone mechanical situation, the bone utilizes a regeneration mechanism to respond to these changes and achieve proper loading and maintain optimal balance between function and diagnosis. Bone as a living tissue must be constantly provided with oxygen and nutrients, and the presence of defects or fractures limits the ability of the bone to return to its original state. In addition, the bone may be pathologically involved, such as cancer, or may be damaged due to age or disease, such as osteoporosis, in all of which bone function returns to its original state only by surgery [7].

**Osteoporosis Examination**
Osteoporosis is an abnormality that is characterized by a decrease in bone quality and density, which eventually results in the skeletal body becoming frail and frequently fractured (see Figure 4). According to the 1993 Consensus conference, osteoporosis is a skeletal disease associated with reduced bone mass and microscopic changes in bone tissue and the risk of fracture [8, 9].
It is noteworthy that forty-five-year-old women who are affected by osteoporosis spend more time in hospital than women affected by other disorders, such as diabetes, myocardial infarction and breast cancer [11].

In this condition, the bones become so weak that they can be fractured by bending or even slight pressure, such as bending. Osteoporotic fractures generally occur in the buttocks, hip, wrist or vertebral column. Osteoporosis occurs when the creation of new bone is incompatible with the removal of old bone [11].

General epidemiology shows that fractures caused by osteoporosis are at the top of the list of fractures in Asia. Pelvic fractures are a major concern as they cause some abnormalities such as chronic pain, poor quality of life, premature death, and disability that initially manifest fracture. About 20% of people die within a year, another 20% require long-term care, and about one-third of them fail to return to their previous jobs, and those who remain lead a low-quality life [12]. The treatment of fractures is expensive. Asia is a continent lagging behind in the treatment and diagnosis of osteoporosis. The situation is far worse in the backward rural areas. In rural areas, the hip fractures are often treated at home and without surgery because of the high cost of DXA (Dual-energy X-ray absorptiometry) and its inaccessibility [12]. Osteoporosis can have many different causes, but it may be different for each person. Some people may develop osteoporosis for a number of reasons; they are actually people prone to the disease. Several factors are associated with an increased risk of osteoporosis, including [12]:

- Elderly; more than 50% of women and 30-40% of men over 50 have osteoporosis.
- People with estrogen deficiency.
- People with testosterone deficiency.
- Those with a family history of osteoporosis.
- Women are more at risk (impact of gender factor).
- White people are more at risk (the effect of skin color factor).
- People exposed to calcium and vitamin D deficiency in nutrition.
- Sedentary people.
- Smokers and alcoholics.
- People who are overweight.
- People with hyperthyroidism.
- People who are exposed to insufficient sunlight.
- Low body mass index.
- High intake of sodium, protein and caffeine.
- Pharmacological and medical factors such as prolonged use of corticosteroids, diseases such as arthritis.

Osteoporosis Diagnosis
Osteoporosis diagnosis is based on bone mineral density measurements. Bone density tests are performed using X-ray (DXA) of the backbone, hip or arm. The DXA or DEXA (dual-energy X-ray absorptiometry) tests are presented in Figure 5 A and B.

The National Osteoporosis Foundation in the United States of America recommends a bone density test for all women age sixty-five, as well as men aged 70 and over.

Bone density tests for people with fracture risk factors such as low weight, previous fractures, family history of osteoporosis, smokers, overuse of alcohol, or long-term use of some medications should be performed sooner (at about age 50). The incident fractures range by skeletal site in the US which recorded in 2005 is shown in Figure 6.
According to the World Health Organization (WHO) definition, osteoporosis is diagnosed on the basis of a patient’s BMD (bone mineral density) comparison [8, 9]. In BMD method, the lumbar spine and pelvic area are evaluated and compared with standardized criteria and compared with normal specimens [12]. In this method, three factors are generally measured that are reported by specific criteria:
1. The amount of density, in gr/cm.
2. T-score, which is a high and low standard deviation of the patient's bone mass compared to a healthy 30-year-old person in the same sex.
3. The Z-score, which is a high and low standard deviation for the patient's own bone mass by age and sex.

The Figure 2-3 shows that people with a T-Score of 1 to 1 do not have osteoporosis; people with a T-Score of -2.5 to -1 have a bone mass of Normal condition is less and these people are prone to osteoporosis and eventually people with T-Score less than -2.5 have osteoporosis. T-Score Criterion for Diagnosis of Osteoporosis in the DXA Method is demonstrated in Figure 7.
Study of Osteoporosis in Other Countries

Osteoporosis is a major public health problem that is increasing. In Canada, nearly 25 percent of women and 12.5 percent of men have osteoporosis, and it is estimated that 25% of Canada’s population is over 65 by 2018, with the incidence of osteoporosis rising in the near future. Osteoporosis is also referred to as latent disease because it is not diagnosed until fractures occur according to estimates for hip, vertebral and wrist fractures [17].

Around the world, every 3 seconds happens one fracture because of osteoporosis and every 22 seconds one fractures occur in the lumbar spine. Thus, out of every 2 women over 50 years in their life a woman has a fracture of the spine and out of every 3 men in 50 years experiencing a hip fracture that both of them lead to disability and there is considerable mortality [18].

Proper treatment of the disease has reduced injuries and disabilities and increases the quality of life along with lowering social costs because, for example, the total cost of England and Wales and the United States following these fractures The order was 6.4 million £ and 18 billion $ [8, 19].

Examination of Osteoporosis in Iran

In Iran, there have been several studies of osteoporosis that have led to different findings. In the study of Mojibian and colleagues in Yazd in 2001-2002, 502 women had the condition, the highest prevalence was osteoporosis in the femur (43%), which was 28.6 times the prevalence in a study that year 2004-2005 in Bushehr were carried out by Eqbali et al. On 588 women with mean age 60.8 ± 05.05 with the least prevalence reported in femur (1.5%) [12, 20]. Also in a study carried out in Kashan by Zamani et al. on 87 women with a mean age of 66-71 years (2005-2006), the highest prevalence of osteoporosis was found in the spine (51.3%). It was equal to the prevalence in a study carried out by Eqbali et al. In 588 women in Bushehr in 2004-2005 that had the lowest prevalence (3.2%) [20]. In a comprehensive study conducted by Tehran University of Medical Sciences in Tehran, the prevalence of osteoporosis in the age group of 69-60 years was 32.4% in women and 9.4% in men [21]. In another study conducted in Iran, the total number of years lost to osteoporosis in the Iranian population in 2001 was 36026, of which 18757 belong to men and 17270 to women [22]. Like other countries, Iran will have a significant population of older people in the next 50 years so that 11 million people (50 years and older) and 6 million (70 years and older) and about 34 million of the Iranian population will be 50 years or older and till 2050 [23]. Recent studies have shown that osteoporosis in Iranians over 50 years of age is 22.2 to 59.9% in women and 11 to 50.1% in men. This rate is 33% of women and 31.6% of men less than 50 years of age [24].

METHODS FOR DIAGNOSIS OF OSTEOPOROSIS

As the prevalence of osteoporosis in human society is increasing and some people are at greater risk due to family history, race, skin color, and gender, it is important to identify early prevention (at an earlier age). On the other hand, some people will not be able to use X-rays for various reasons. For example, in pregnant women, children, people who have received high amounts of X-rays due to previous illnesses. For this reasons, it may be useful to use other new methods to diagnose osteoporosis, which will introduce some of them in this paper.

Quantitative Ultrasound Method

Quantitative ultrasound has many advantages over X-ray and CT scans (computed tomography scanning). Not just for low cost or easy access, but for its ability to provide comprehensive information on the mechanical and structural properties of bone [25, 26]. The ultrasound method quantitatively measures bone properties using ultrasonic waves with central frequencies in the range of 0.5–1.25 MHz In this method, two key parameters of speed of sound (SOS) in bone tissue and ultrasound attenuation bandwidth (Broadband ultrasound (intensity) attenuation or BUA) are commonly measured. The speed of sound in bone tissue depends on the properties of bone material such as elastic modulus and compressive strength. Ultrasound attenuation bandwidth is essentially dependent on bone density. Other parameters such as quantitative stiffness index (SI), quantitative ultrasound index (QUI), Amplitude- dependent speed of sound (AD-SOS) [27].
Different parts of the skeletal system such as heel bone, toe bone, radius bone and tibia have been tested by using quantitative ultrasound. Among these, heel bone has been frequently studied because it is readily available. It also has high bone trabecula, high metabolic volume, and high resemblance to spinal cord tissue. Although quantitative ultrasound has been shown to be as effective in predicting the risk of fracture in people with osteoporosis, the diagnosis of osteoporosis is used not only by using quantitative ultrasound. However, a quantitative ultrasound may be used as a pre-test for patients at risk for osteoporosis. Pre-screening is more affordable for patients who may not be able to use X-rays [26]. The quantitative ultrasound method is presented in Figure 8.

![Figure 8: Quantitative ultrasound measurement techniques. A) Through transmission: contact method; B) pulse-echo method; C) through-transmission: substitution method. s1, s2 and t1, t2 are the thicknesses of the soft tissue and the transit times through them, respectively. s is the heel thickness, s_b is the thickness of the calcaneus and t_b is the transit time through the heel [28].](image)

**Reference Point Indentation Technique**

Reference point indentation (RPI) technique is a new microscopic-scale method that is able to measure bone properties in both in-vivo and ex-vivo under different conditions (for example under conditions of bone pathology) and can also be used to diagnose osteoporosis and manage osteoporosis patients in the future [8, 19, 32]. This method measures the length of indentation based on the response of the bone to fracture resistance. In human specimens, the test section is usually the smooth surface of the tibia because it is easily accessible. The indentation in this method pierce the bone up to a few microns according to a predetermined protocol [8]. After local anesthesia and bone marrow removal, each cycle is performed at a predetermined point for twenty cycles, and the average value of the parameters in this procedure is calculated from five or more sites, each at least two millimeters apart. Injuries to this procedure are minor and do not appear to harm the patient. The RPI technique is shown in Figure 9.
Figure 9: Indentation procedure for measuring material properties of bone in vivo and SEM (Scanning electron microscope) imaging of an indent on a human bone sample. A) Illustration of the method for obtaining indentation measurements, B) SEM image of an indentation, C) the microcracks created during the repetitive loading cycles at a constant force obtained from SEM [29].

Parameters of the indentation method include the following and calculated directly:
- TID (Total Indentation Distance)
- IDI (Indentation Distance Increase)
- CID (Creep Indentation Distance)

Recent studies have found that increasing dentition distance at the end of all cycles is inversely correlated with the stiffness measured in the three-bone bending method. The indentation length of the first cycle is strongly dependent [30]. A small-scale clinical trial showed that this method can distinguish patients with fracture-related osteoporosis from others. The total distance traveled by the dentition and the increase in the dentition distance per cycle in patients with history of fracture increased with control. In another study with a small group of patients, similar results were observed [31].

**Fourier Transform Infrared Spectroscopy and Raman Spectroscopy**

Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy (see Figure 10) have been identified as important aids to understanding bone quality and fracture risk in patients with osteoporosis [32]. These techniques have only been used in small-scale laboratory studies and mainly as microscopic techniques, because there are currently no noninvasive methods to obtain bone osteoporosis measurements in clinically relevant departments. Raman spectroscopy for bone has been reported in vivo for animals, but has not yet been investigated in humans [33]. Both spectrometers are for evaluating quality-relevant bone parameters, such as mineral to matrix ratios, carbonate to phosphate ratios, mineral crystallization, or collagen (maturation or growth) [34, 35].
FTIR studies show bone marrow biopsy (iliac crest) in general, between collagen (maturation, maturation) and a history of fracture [37-39]. In women with osteoporotic fractures, higher collagen maturation is seen. A lower mineral-to-matrix ratio and heterogeneity of ratio is seen in females with femoral fractures compared to non-fractured females [40]. Furthermore, heterogeneity of carbonate to lower phosphate and crystalline variation have been observed in fracture cases. Studies are under way to find the correlation between bone material and mechanical properties using spine biopsy from elderly patients [41].

Short-term and long-term treatment with nonabsorbent drugs reduces the rate of crystallization and collagen grafting ratios more than any bisphosphonate (BP) and Alendronate (ALN). A tendency to increase the ratio of mineral to matrix with treatment has been found during both ALN and risedronate (RIS) [42]. In a research study, patients with unusual femoral fractures (abnormal femoral fractures) with longer BP intake had higher mineral-to-matrix ratios and reduced mineral heterogeneity compared to age-matched matrices [43].

**Magnetic Resonance Imaging (MRI)**

MRI is a medical imaging technique which used in several domains in medicine [44-46]. Unlike X-ray imaging, which is based on the quality and quality of images that produce more bone density than soft tissue, MRI scans protons in the bone marrow and adjacent soft tissues. Under normal imaging conditions, bone signals are close to the background density. From a number of close-up image cut-outs, one can build a three-dimensional grid of bone trabecular, as well as scale representation, geometrical parameters, and orientation parameters.

Alternatively, structure analysis is eliminated in all directions, and a three-dimensional volume model is generated from MRI data, read into a finite element analyzer, and quantifies the predicted mechanical properties of the bone, such as stiffness and provides the elastic modulus or fracture strength [47].

Numerous studies of patients’ MRIs have been published in recent years, demonstrating the potential of this method for obtaining structural and mechanical concepts in response to interventions. It is possible to detect and quantify using time-echo and ultrasound imaging techniques that allow the capture of proton signals from bone water. While it has been shown to be clinically unrelated to the creation of bone body water, its
evaluation is complicated due to the presence of water in many spaces (see Figure 11). Recent MRI studies on human truncated bone have shown that the water slits in the bones represent a type of collagen matrix of 60% - 80% hydrated environment and that occupy the pore structure of the Haversian system [48, 49].

Figure 11: MRI of a cadaveric forearm. Cortical bone produces a signal void on a conventional fast-spin echo (FSE) sequence, while signal is detected from cortical bone with the use of an inversion recovery ultrashort echo time (IR UTE, TR/TI 300/120 ms) pulse sequence [50].

Different lifetimes of the MRI signal of water in the two micro environments allow quantification of the pore water gap in the intact membrane and in vivo. However, measurements have not been clinically available so far. Such advances give the measurement of the pore volume gap. MRI is likely to have a major impact on the evaluation of bone marrow fat (adiposity), as this is a method of choice for determining the composition of soft tissue water and fat. There is a growing interest in this area because of the relationship between fat formation and bone formation. Stem cells (mesenchyme) can specialize in both adipocytes and osteogenic cells [51]. These observations have been confirmed in studies by MRI spectroscopy of vertebral bone that also have low BMD (bone mineral density), effectively correlating with saturated fatty acid [43, 52, 53]. Finally, MRI may be a specific selective technique in the diagnosis of osteoporosis and patient management applications.

CONCLUSION

Osteoporosis is an abnormality that is manifested by a decrease in bone quality and density, which eventually results in the skeletal body becoming fragile and repeatedly fractured. This trend increases with age and the prevalence of osteoporosis in the elderly increases sharply. So we have to predict and diagnose osteoporosis in people who are or will be at risk for osteoporosis. This is essential in people who are prone to osteoporosis and can be implemented at an early age. For example, people with delicate bones, people with a family history of osteoporosis, and smokers. As we know at present, the most common way to diagnose osteoporosis worldwide is to use X-rays which are very harmful to the body. Surely, there are also people in the community who cannot receive X-rays. For example, pregnant women or people who may be treated differently may receive radiation when they are ill. As a result, researchers and scientists have been looking for less risky methods for the diagnosis of osteoporosis, and success in this will serve the human community immensely. Because most people will develop this disorder at an early age, and almost everyone in middle age should evaluate their skeletal density. A low risk and low cost method instead of the DXA method may encourage more people to do the test. In this study we have discussed methods and therefore it can be said that non-invasive and standard methods can have a pre-examination or a pre-X-ray diagnosis. For example, people at high risk for early onset osteoporosis can be diagnosed and treated using methods such as ultrasound or MRI. These methods are also safe for children because they are safe. After examining and diagnosing osteoporosis, if the doctor thinks X-rays are needed then this method can be used and a thorough and accurate diagnosis can be obtained.
REFERENCES