Osteoporosis : New Biomedical Engineering Aspects

Kanika Singh, Sung Hak Lee, Kyung Chun Kim*
MEMS/Nano Technology Centre,
School of Mechanical Engineering, Pusan National University,
Busan 609-735, Korea

There is tremendous interest of research which surrounds the concept of "osteoporosis," as shown by the intense and growing research activity in the field. The urgency to advance knowledge in this area is motivated by the need to understand not only the causes, diagnosis and treatment but also need for early identification or detection of this silent disease. Despite the various researches work is going on, important issues remain unresolved. In this paper, Osteoporosis has also been discussed with respect to biological, engineering, biochemical and physical aspects. The diagnostic and therapeutic techniques have been described for osteoporosis, for better health care. The novelty of the review paper lies in clarifying several myths, explaining the disease in details with biomedical engineering aspects and focuses on the several detection techniques, providing a new direction for early diagnosis of this deadly disease and gives new directions for the POCT device for Osteoporosis.

Key Words : Osteoporosis, Bone, BMD, MEMS, Early Detection

1. Introduction

Osteoporosis is a bone disease. There is a need to understand the phenomenon of bone. The human bone has been constantly being built and rebuilt. Internally, bone is being eaten away itself and new bones are built. When this balance of modeling and remodeling of the bones is hampered or disturbed, the bones become thin or porous. Generally, after the menopause, in women, the women start loosing bone mass at higher rates. Such a problem is called Osteoporosis (www.medinfo.co.uk).

Osteoporosis (OP) is a disorder characterized by abnormal rarefaction of the bone occurring most frequently in postmenopausal women. It is called a silent epidemic or a silent disease (Arnaud, 1996 ; Deal, 1997 ; Korkia, 2002). Thus, it is a bone disease, in which bone tissue is normally mineralized, but the amount of bone is decreased and the structural integrity of trabecular bone is impaired. Cortical bone becomes more porous and thinner. This makes the bone weaker and more likely to fracture. Osteoporosis can be classified as primary or secondary. There are several risk factors for e.g. malnutrition, prolonged immobilization, weightlessness with space travel, lack of sunlight, excessive caffeine consumption etc.

Normally, the disease like Osteoporosis is associated with the Asian population for years. But now with the present research, it was found that the Osteoporosis is not only a Causation population's disease but the osteoporotic patients are found all around the world as proved by the research paper on Epidemiological Aspects of Osteoporosis in Brazil (Carneiro, 2001), Argentina, Pueroto Rico, United States, Peru (Becerra, 2001) Europe, Canada (Faulker, 1996) etc. There is a danger for the world with this serious disease. Therefore, it is important to understand that bone is not a hard and lifeless structure ; it is, in fact, complex, living tissue. The bones provide struc-

* Corresponding Author,
E-mail : kckim@pusan.ac.kr
TEL : +82-51-510-3947; **FAX** : +82-51-512-9835
School of Mechanical Engineering, Pusan National University, Busan 609-735, Korea. (Manuscript **Received** May 16, 2006; **Revised** October 25, 2006)

tural support for muscles, protect vital organs, and store the calcium essential for bone density and strength. The abnormalities of which may cause serious diseases (Rapado, 2001 ; Raiz, 1997).

The present study describes, in brief, various methods prevailing to detect OP and bone conditioning, with special reference to biomedical engineering aspects. Development of biomedical indicators using bone for the osteoporotic fracture detection is also given. New detection techniques are given for the bone abnormalities.

2. The Bones and their Characteristics

2.1 Bone as a biomaterial

Bone is a special form of connective tissue. The basic unit of bone is the Haversian system, which is called osteon (Fig. 1). Osteon consists of a series of concentrically parallel lamerlace. The lamerllae have irregularly arranged bone layers, which are designated intertitial lanrellac centre of the Haversian system canal consist of interstacing tissue, osteoblast osteocytes and osteoclast are three bone cells (Eastell, 1998), viz., a) osteoblasts which are bone-forming cells derived from normal cells, and they secrete collagen ; b) osteocytes are rounded cells surrounded by bone matrix that are found in bone ; and c) osteoclasts which are multinucleus cells that erode and resorb previously formed bone (Zaidi, 2006).

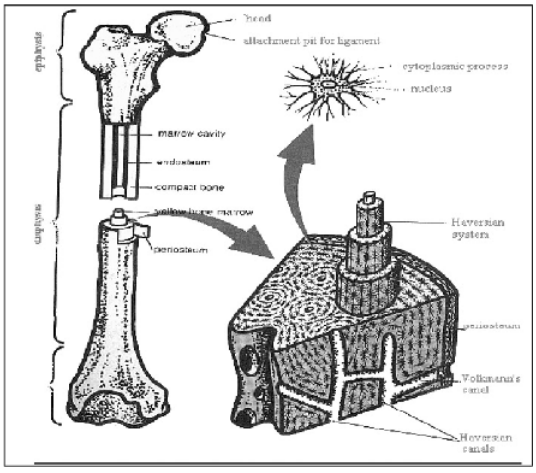

Fig. 1 Structure of bone (www.botany.uwc.ac.za/.../grade10/mammal/bone.htm)

Bone acts as a biomaterial with the reserves of collagen and Calcium phosphates. The bone structure is very unique with a hard outer covering, called cortical bone and smooth spongy inner core, called cancellous bone. Calcium helps in provide the strength to the bone. The bone has a honeycomb like structure which is interconnected with the help of blood vessels and bone marrow. Hence the unique structure adds to the bone strength.

2.2 Biocomposition of bone

Bone supports the skeletal structure of the human body. Bone is heterogeneous in nature. The characteristics of the bone consist of the high strength, light weight and flexibility. The bone consists of the organic and inorganic part. The strength comes mainly from a mixture of collagen (35%) and minerals (65%). The trabecular bone is characterized by the lacy network of interconnecting rods, while cortical bone has a solid matrix with few spaces. Cortical and trabecular bone do not change with age in a similar manner and the difference is due to the differing environments of the respective bone cells. During menopause, bone loss is accelerated, especially from the spine (Recker, 1994 ; Zaidi, 2006), Fig. 1.

2.3 Biochemistry of bone

Bone consists of organic, inorganic materials and water in percentages composition of organic 25%, inorganic 65%, water 10%. Organic components are further subdivided into bone cells, which constitute 4%, and intercellular matrix, which is 21%. The bone cells are derived from the mesenchymal precursor cells that differentiate into osteoblasts, osteocytes and osteoclasts. The organic matrix (21%) is constituted by collagens, proteoglycans, protein, peptides and lipids (Jeal et al., 1997). The inorganic portion of 65% consists of crystalline material - hydroxyapatite, amorphous calcium phosphate, trapped ions like citrate, fluoride, sodium, magnesium and potassium. The water content of 10% is either cellular or extracellular or in bone crystals (Zaidi, 2006). The The mechanical study of bone will give a

better view of the complexity and severity of the disease (Smith, 1993).

2.4 Biomechanics of bone

The most important factor for bone is the bone strength and bone stiffness.(Turner, 2002) These are generally dependant on the bone mass, shape, morphology of bone and intrinsic properties (density, matrix mineralization, collagen traits, microdamage) of the bone. The mechanical properties of the bone are dependant on the direction, magnitude of loads applied to it. The bone and the resulting deformations characterized by the structural behavior or structural properties, of the whole bone. Several studies with the compression and tension force test of bone have been made. A comparative analysis of the decalcified bone and the normal bone is made. It was found that stiffness and strength of the bone is related to density in non-linear fashion. The change in strength is disproportionate than the change in density. Another factor which affects the biomechanics of bone is the micro architecture (like the porosity and the mineralization of the matrix) and the histological structure (like collagen content, orientation of collagen fibers, extent and nature of collagen fibers, collagen cross-linking) of the bone.(Singh, 2005 ; Bouxsein, 2005)

2.5 Biomechanism of bone growth

2.5.1 Bone turnover

When the skeletal growth is complete, continual remodelling occurs in cortical and trabecular bone, as part of normal bone maintenance. The control of physiology of Calcium metabolism and remodeling is controlled by hormones e.g. estrogen, PTH, calciton. In women bone loss accelerates after menopause when ovaries stop producing estrogen (Korkia, 2002). The Vitamin D levels fall with age and become lower in the winter months. The Vitamin D deficiency elevates the hormone named, PTH release and hence extracts the calcium from the bones.

2.5.2 Bone modelling (Smith. 1993)

Modelling and remodelling change the structure and shape of the bone continuously. Modelling takes place during foetal life and goes on till the second decade and stops when the longitudinal growth of the skeleton is completed. Bone is formed at locations in such a way as to change the shape and microarchitecture of the skeleton. There is great importance of epiphyseal growth plate which helps in the longitudinal growth of bone based on the differentiation of these cartilage cells. Bone is also reabsorbed at the endosteal surface which results in a stimulation of periosteal new bone formation by apposition. This periosteal bone apposition increases with aging and is more pronounced in men than in women and thereby the endosteal bone reabsorption is partly offset (www.fpnotebook.com).

2.5.3 Bone remodelling (Smith. 1993)

Bone remodelling is a continuous process. This includes bone formation and resorption, there is structural change in the shape of the bone. Importance of skeleton biomechanical integrity and strength is due to result of remodeling. It also permits the skeleton to be the major source of calcium and phosphorus. This is particularly true when absorption of calcium does not keep pace with urinary excretion. This remodelling occurs at focal or discrete areas. The morphological dynamic structure of turnover is the basic multicellular unit (BMU), also called the bone remodelling unit (BRU). The morphological entity formed when the process is terminated is called bone structural unit (BSU). The BSU corresponds to the 'packer' in cancellous bone and to the osteon in cortical bone (Franasco, 2001 ; Gillespy, 1991).

The remodelling process is primarily initiated by osteoclastic activity resulting in bone erosion and this is followed by osteoblastic activity which refills the areas where resorption has taken place. The remodelling process is controlled by various hormones. When osteoporosis occurs due to sex hormones deficiency or primary hyper parathyroidism or hyper thyroidism, this phase of bone resorption exceeds bone formation and this is also true when there is exposure to steroidal hormones (Eastell, 1997).

2.6 Biophysics of bone

Bones are now considered as a well accepted series of piezoelectric materials. Several researchers have used the bone material to develop piezoelectric sensors for the measurement of pressure, force, acceleration and other such parameters. However, with the advancement of technology in sensor systems, micro and nano-scale devices are now being developed by using semiconductor or biological materials, all over the world. Bio-chips based on DNA, and Bio-MEMS, etc are some of the examples. In the present research, new bone chips have been developed for various sensor applications like nano and microscale systems (Singh, 2004).

3. Osteoporosis : A Silent Epidemic

3.1 General aspects

Osteoporosis is known as a progressive systemic disease having low bone density. Osteoporosis is a disease in which bones become fragile and more likely to break. It is defined as a state of micro-architectural deterioration of the skeleton predisposing that skeleton to fragility (Korkia, 2002 ; Arnaud, 1996 ; Deal, 1997 ; Gillepsey, 1991 ; Gluer, 1997 ; Isenberger, 1997 ; Raisz, 1997 ; Melton, 1992 ; Sambrook, 1994). The Osteoporosis disease travels painlessly within the body leading to breaking of the bones, fractures. Therefore it is important to get the treatment at the right time. The osteoporosis fracture sites are hip, joints and spine. These areas are the most important part of the body which may lead to the immobilization. It can impair a person's ability to walk. These fractures may also lead to death. The hip fractures can only be cured by surgeries. Spinal or vertebral fractures also have serious consequences, including loss of height, severe back pain, and deformity.

The women have higher risk for the disease as compared to men, though men also suffer from osteoporosis. Bones are constantly changing, with the natural aging process of the body the bones become weaker as they lose the capability to store and absorb Calcium. The efficiency of the bones is till the age of 30 (www.cleavelandclinic.org).

It is a silent epidemic and is asymptotic in nature with gross deformity or acute fracture occurs. But there are several myths regarding the disease. Protection measures are given in Fig. 2, along with the status of osteoporosis is shown in the following diagram. The hip and spines bones are more prone to fracture. The fracture in hip and spine many make the person bed ridden, may cause

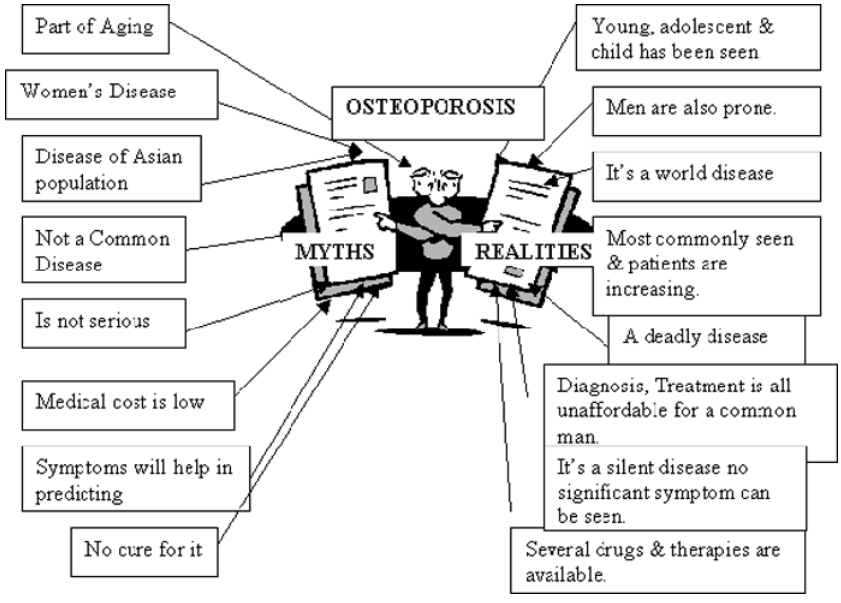

Fig. 2 Protection measures for OP

prolonged or permanent disability or even death. They have serious consequences.

3.2 Diagnosis with BMD

The WHO suggested four diagnostic categories: normal, osteopenia, osteoporosis and established osteoporosis. These categories depend primarily on bone density and presence of fractures. The WHO definition involves standard deviations, which are statistical units of variation (Samsioe, 1996).

Osteoporosis has a bone density between 1 standard deviation and 2.5, standard deviation below the average for young people (Hernanalez, 2003). Established osteoporosis has a bone density lower than 2.5, standard deviation and has a fracture. The bone density in osteopenia of the hip is estimated to be between 0.664 and 0.826 gm/cm^2. There are ethnic, cultural and racial variations. For example, a Caucasian female and male have a lower bone density than individuals of African descent. The Asian group falls between the Caucasian and African group. Bone mass is expressed as bone mineral density (BMD (g/cm^2)) or as bone mineral content (BMC (g)) (Danielson, 1999). The definition of OP is based on a measurement of bone mass because it can be used to predict long-term fracture risk fairly precisely and it is known that about 75-90% of the variance in ultimate bone strength is linked with BMD (WHO report), Table 1.

3.3 Causes of osteoporosis

Some of the risk factors are given as follows (Korkia, 2002 ; Melton et al, 1992 ; Bagur, 2001) (Fig. 3):

3.4 Osteoporosis : age and sex

Recent researches have shown that osteoporosis is found in men, women and children. The disease is not only limited to older women but also easily found in younger women. A research study has shown the osteoporosis is becoming common in adolescents (Gordon, 2000). Men start out with a greater bone mass to begin with, so they have a greater reserve against loss comparatively. But they may acquire the disease (Fig. 3).

Osteoporosis in children is considered to be for the unique cases. OP in children occur with some underlying disease like asthma, hormonal disorder, arthritis etc. these are treated with corticorteroids showing loss in bone mass (Faulkner, 1996). These conditions limit the physical activities reducing bone formation and interrupting the calcium metabolism. Sometimes OP in children may occur due to gentic conditions conditions of the bone called osteogenesis imperfecta (Bianchi, 2005 ; www.hmc.psu.edu) (Table 2)

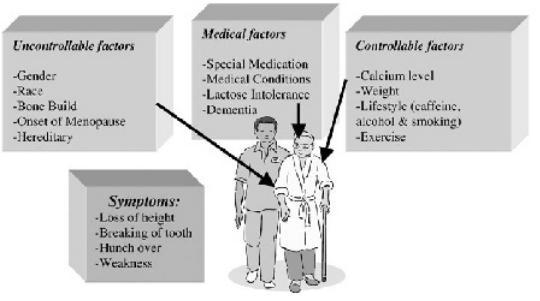

Fig. 3 Causes of OP

Table 1 Four general diagnostic Categories for osteoporosis (WHO)

BMD or BMC	RANGE
Normal	no more than 1 SD below the mean for young adults
Loss bone mass	more than 1 SD below the young adult mean (osteopenia) but not less than 2.5 SD below this mean
Osteoporosis	more than 2.5 SD below the young adult mean
Severe osteoporosis	more than 2.5 SD below the young adult mean in (established the presence of one or more fragility fractures osteoporosis) BMD : bone mineral density ; BMC : bone mineral content ; SD : standard deviation

BMD : Bone Mineral Density ; BMC : bone Mineral Content ; SD : Standard Deviation

3.5 Inflammatory bowel disease

Osteoporosis can be called as an inflammatory bowel disease, due to low bone density. In general the treatment or the medication of Inflammatory Bowels Disease hinders with the development and maintenance of healthy bones. Other way to treat this disease is by using surgical method. But the patients who have undergone surgery loose the capability to absorb Calcium and Vitamin D which are the main components of the strength of the bone (Vermeer, 1996 ; Hosking, 1998).

3.6 Asymptotic nature of osteoporosis

The bone fragility is achieved in the OP disease. The Osteoporosis disease may be divided into primary OP refers to the postmenopausal women and senile and secondary OP. Secondary OP refers to bone loss as a result of a specific clinical disorder, such as hyperthyroidism.

Primary OP is divided into two distinct types because their cause and effect on bone is different. Type I OP signifies loss of trabecular bone following menopause in response to decreased estrogen levels and type II OP refers to the loss of both cortical and trabecular bone as a result of age-related bone loss. Losses which occur due to age-related bone loss are reduced bone remodelling efficiency, adequacy of dietary calcium and vitamin D, intestinal mineral absorption, renal mineral handling and parathyroid hormone (PTH) secretion. The lower the peak bone mass, PBM the bones reach the fracture threshold, earlier in life. This leads to extended bed-ridden status, eating disorders or inadequate food consumption, menstrual irregularity during the adolescence or prevailing illness at the growth years may reduce the bone mass (Sortis, 1996).

It is a commonly held view that OP is a consequence of bone loss (Jean et al., 2003 ; Delmas, 2002 ; Dermers, 1997) is abnormalities in bone acquisition as a basis leading to bone fragility. This approach highlights the importance of PBM, which is influenced by sex hormones, diet and exercise.

3.7 Gross deformities of osteoporosis

Histologically the normal and Osteoporotic bones are the same but in composition and microscopic structure, they are very different (Fig. 4). The osteoporosis fragile or porous bone is more prone to fractures with trauma, even minor trauma. As discussed earlier, mostly the fracture areas for OP

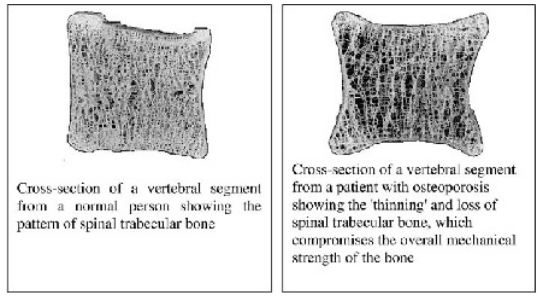

Fig. 4 Consequences (source : www.uthscsa.edu)

Table 2 Risk factors for osteoporosis

WOMEN		MEN	MEN AND WOMEN
Young	Old (<45 yrs)		
-Due to heredity -Abnormal Life style -Chronic Disease -Medications -Imbalance in hormone -Premature ovarian failure -Organ transplantation -Hyperthyroidism -Eating disorder	-Lack of estrogen due to early, menopause -Early hysterectomy or oophorectomy -Amenorrhoea caused by over-dieting or exercise	-Low testosterone levels	-Long-term corticosteroid use -Maternal history of hip fracture -Mal-absorption, inflammatory bowel disease and gastric surgery -Long-term immobility -Heavy drinking -Smoking

patients are hip (femoral head and neck), wrist and vertebrae.

The details about the different types of OP fractures occurring are like -hip fractures that occur, they may occur minor falls, can be disabling and an elderly person to a wheelchair or bed (Korkia, 2002). The only treatment left for the patient is surgery. The wrist fractures are common with falls forward with arms extended to break the fall, but the wrist bones break too. The vertebral fractures are of the compressed variety and may be more subtle. They may result in back pain. Another consequence is shortening or kyphosis (bending over or hunch over) of the spine which may lead to respiratory problems (library.med.utah.edu). Hospitalization and immobilization for the patient suffering from fractures will have a higher risk for death.

3.8 Women and osteoporosis

Osteoporosis is due to accelerated bone mass loss at old age. This is higher in women than in men of the same age (Table 3). The bones in older persons become inefficient with age as the slow resorption process takes 8 months. This may affect the osteoblastic activity, release of the growth factors and may finally affect the bone density (Bal et al., 2002 ; Khovidhunkit, 1999 ; McClung, 2001). The post menopausal women have lot of bone loss which is hard to compensate (Bal, 2002)

Table 3 Status of OP in different age groups (Source : National Institutes of Health Consensus Panel, Optimal Calcium Intake, 1994)

Age	Sex	Daily Calcium intake
7-12	Children	800
13-19	Teenagers	1000
20-60	Men	1000
20-45	Women	1000
	Pregnant & nursing women	1200
	Pregnant & nursing teenager	1500
>45	Women	1000
>60	Women	1500

3.9 Fracture risk, bone mass and quality

Osteopenic men and women are considered to be at increased relative risk of fracture as a consequence of a fall (Table 3). It is important to recognize that bone strength depends not only on its mass but also its size and geometry. Studies have shown that there is considerable overlap in the bone mass of people with and without OP fractures, which points to the importance of other aspects of bone quality besides BMD (Bal, 2002). In addition, factors such as surrounding soft tissue strength, impact level when falling, impact angle and position of the femoral bone also affect the outcome of a fall. These factors may be increasingly important in protecting the hip joint in the elderly, as most will have already lost sufficient bone for the hip to fracture (Sortis, 1996).

4. Pathophysiology of Osteoporosis

4.1 General

The sole clinical manifestation of osteoporosis results from the fractures that arise. The pathogenesis of fracture is multifactorial and includes the liability to falls, the force of the impact as well as the strength of bone. In turn, there are many determinants of each of these factors. In the case of bone strength, the geometry of bone, microarchitectural deterioration and skeletal losses all contribute to bone strength (Ferretti, 2003 ; Eastell, 1998). An understanding of the mechanisms of bone loss permits an appreciation of the expectations of pharmaceutical interventions in osteoporosis. The healthy skeleton is normally maintained by the ordered cellular sequence of events termed 'bone remodelling' (www.osteofound.com). Bone remodelling comprises the excavation of an erosion cavity by osteoclasts and the subsequent deposition of new bone within the erosion cavity. When the skeleton is neither gaining nor losing bone the volume of new bone formed matches that resorbed. In health, 10-15% of the bone surface at cancellous sites is occupied by remodelling activity (Sortis, 1996). Osteoporosis is characterized by an increase in remodelling activity. Osteoporosis is characterized by an increase in remodelling activity. The increase in the number

of bone remodelling units decreases skeletal mass since resorption always precedes formation. In addition, the greater amount of younger bone present is hypomineralised. Over and above this many forms of osteoporosis are associated with an imbalance between the amount of bone resorbed and that formed within each remodelling sequence, in favour of net bone resorption. This may be variously due to an increase in the depth of erosion or a decrease in the volume of new bone formed. For this reason, inhibitors of bone resorption used in therapeutics induce a small increment in bone mass, which may thereafter stabilise or increase or decrease, depending upon the ultimate effect of remodelling balance. The major course for osteoporosis is the gonadal deficiency that occurs in women at the time of the menopause. This does not, however, explain the current increase in age and sex specific incidence of osteoporosis (Demas, 2002; Ferretti et al., 2003). This may be related to changes in habitual exercise or due to secular trends in the environment. Understanding the causes will help in the development of global interventions, whereas currently therapeutic intervention of individuals at high risk is the preferred option.

4.2 Genetics

The osteoporosis is called the multifactorial disease with the involvement of many genes. Genetics is another important factor which influences the bone mass and PBM. Results have been inconsistent and, at times, contradictory. According to Roux, 2001, the most conclusive finding is the association linking the Sp1 polymorphism of type 1 collagen to bone mineral density and osteoporotic fractures. Polymorphisms of other genes either have very little influence. In all likelihood, the best predictive value is obtained by using a combination of several gene polymorphisms (Roux, 2001).

5. Diagnostic Techniques of OP

The Figure 5 depicts various diagnostic techniques of OP.

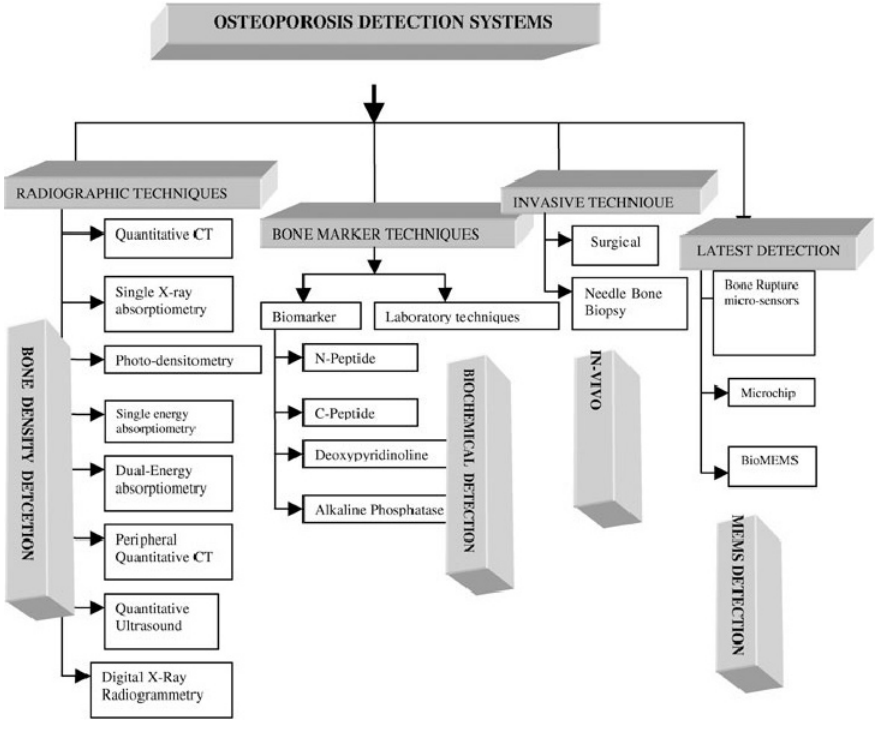

Fig. 5 Types of detection method

5.1 Radiographic diagnosis

Radiogrammetry, a technique that has been in use for more than 30 years, relies on the measurement of the cortical thickness of bones in the hand (metacarpals) to estimate bone mass. This technique suffers from relatively poor accuracy and reliability and has largely been supplanted with new techniques.

The following diagnostic techniques are generally used for the detection of osteoporosis (Arnaud, 1996 ; Deal, 1997 ; Easteall et al., 1997 ; Gillgespy, 1991 ; Gluer, 1997 ; Hosking et al., 1998 ; Yates et al., 1995 ; Faulkner et al., 1996 ; Sartoris, 1996 ; Osteoporosis Canada).

Bone Mineral Density Technique (BMD) is an effective approach for detection of Osteoporosis. A decrease in the amount of bone, resulting in thin, weakened bones that are susceptible to fractures. Several techniques are available for BMD testing. For example ; Dual-energy X-RAY absorptiometry (DXA) remains the standard for testing the BMD. Dual energy absorptiometry measures the bone density within a given area of bone (g/cm^2). This technique offers the advantages of higher precision, minimal ionizing radiation exposure, rapid scanning time and the ability to access cortical and trabecular bone mass at appendicular and axial sites. Limitation, include equipment expense, the need for certified X-Ray technician and non-portability. In addition, DXA scans of the spine may show a false increase in spinal BMD in patients with osteophyes, aortic calcifications and degenerative arthritic changes.

The conception of osteoporosis relates bone health to bone strength, rather than mass. A bone's health implies that it should have enough strength to keep voluntary loads from causing spontaneous fractures. Thus, the diagnosis of osteoporosis would be a biomechanical matter concerning both bone strength and muscle strength (Martin et al., 1998) This supposes two kinds of problems, namely : (a) to properly assess bone material properties, structural design and strength ; and (b) to correlate the respective indicators with suitable indicators of muscle strength. As standard densitometry is unsuitable to assess muscle strength or bone strength, it should use of other, preferably cross-sectional analyses of bone structure as those provided by quantitative computed tomography (QCT), peripheral quantitative computed tomography (pQCT), MRI, or similar procedures. The value of pQCT lies in the ability of the software to account for all the 'mass', material and architectural factors in whose-bone strength and to provide data on muscle cross-sections.

5.1.1 Quantitative CT

This provides the evaluation of trabecular bone density of the lumbar spine based on bone volume. Quantitive Computed Tomography, CT may be less practical than DXA because of the lower precision, higher cost and increased radiation exposure.

5.1.2 Peripheral bone densitometry

These devices used for many devices single-energy X-ray absorptiometry, peripheral DXA and peripheral CT. these device have the advantages of less expense, portable equipment, reasonable precision, and low radiation exposure. The use of quantitative ultrasonography for screening of osteoporosis and assessing fracture risk has increased. Using the speed of sound and broadband ultrasonic attenuation measurements, ultrasonic densitometry provides on bone elasticity and structure in peripheral sites. Advantages of this method, is low cost and lack of ionization radiation.

5.1.3 Single-energy absorptiometry

Single-energy absorptiometry measures bone mineral at peripheral sites such as the wrist and heel. Single photon absorptiometry (SPA) used a radioactive energy source, usually iodine125 to estimate the amount of bone mineral at peripheral measurement sites. In recent years, Single-energy X-ray absorptiometry (SXA) has supplanted SPA for measurements of the peripheral skeleton (heel and wrist) because of its better reproducibility and ease of use. SXA avoids the necessity of obtaining and disposing of radioactive energy sources. It requires immersion of the part in water bath and hence can measure bone mass in peripheral bones like bones of forearm

and legs (Jaunanny, 1995).

5.1.4 Dual-energy absorptiometry

Bone density tests are painless, non-invasive and safe. Dual-energy absorptiometry was developed to measure bone in parts of the skeleton (lumbar spine, hip, and total body) that could not be measured with single-energy devices. Currently dual-energy X-ray absorptiometry (DXA) is the most widely used technique for measuring bone at these sites. DXA devices also are capable of measuring bone at the heel and wrist with high accuracy and precision, with very low exposure to radiation (Kanis, 2002).

5.1.5 Peripheral quantitative CT (pQCT)

Quantitative computed tomography (QCT) measures the density of vertebral trabecular bone, the spongy bone in the center of the vertebra. pQCT devices are QCT instruments that have been adapted for measurements at peripheral sites such as the wrist.

5.1.6 Quantitative ultrasound

Quantitative ultrasound devices measure bone at several skeletal sites, including the heel, hand, finger, and lower leg. The heel measurement it is composed of primarily trabecular bone, similar to the composition of the spine. Ultrasound devices based on the changes in the speed of sound (SOS), as well as specific changes in sound waves (broadband attenuation or BUA) as they pass through bone. QUS measurements provide information on fracture risk by providing an indication of bone density and possibly also information on the quality of the bone. Ultrasound devices do not expose the patient to ionizing radiation. Ultrasound devices do not expose the patient to ionizing radiation (Marsh, 2003).

5.1.7 Digital X-ray radiogrammetry

Recently, the computer technology has renewed interest in this old technique. The Pronosco X-posure system estimates forearm bone mass from measurements of the cortical width of bones in the hand using computerized digital x-ray radiogrammetry from a single plain radiograph of the hand and wrist. The BMD estimate, referred to as DXR-BMD, is corrected for cortical porosity and striation. The results indicate that this technique is highly reproducible and appears to be at least as good as other peripheral bone assessment techniques in its ability to discriminate among patients with low bone mass at the spine and/or hip and osteoporotic fractures (sartoris, 1996).

5.1.8 Photodensitometry

Previously, Radiographic absorptiometry (RA) uses standard X-ray images of the hand and distal forearm are taken with a graduated aluminum reference. The radiographic image of the hand and wrist is captured by a video camera and the levels of grey seen on the hand image are quantified and compared with the grey levels of the reference standard, resulting in an estimate of bone mineral density (BMD). The cortical thickness of the bones can also be measured. Radiographic Photo Densitometry comprises of comparing the optical density of bone X-ray with standard calibrative. Aluminium-Step-Wedge. Although inexpensive and easily accessible, this method had poor reproducibility. Computer-assisted methods have reduced these errors and several commercial systems have been developed in recent years. Although RA is generally less precise than DEXA, radiographic absorptiometry holds promise as a cost-effective method to screen cases of osteoporosis. Further research is needed to evaluate its effectiveness in predicting fracture and monitoring therapy (Sartoris, 1996).

5.1.9 Double photon absorptiometry

The principle of dual photon absorptiometry (DPA) is the use of a photon beam that has two distinct energy peaks. One energy peak will be more absorbed by soft tissue and the other by bone. The soft tissue component then can be mathematically subtracted and the BMD thus determined (Sartoris, 1996, book).

5.1.10 Neutron activation analysis

A limb is bombarded by slow neutron from a generator. This is taken up by the soft tissue to convert it into thermal neutron. This thermal neu-

tron is captured by the nucleus of calcium ion. The nucleus becomes radioactive. Decay of the nuclei emits photon which can be measured by a Geiger counter, giving an idea of bone mass. This is reduced in osteoporosis (source : www.iupac.org/publications/pac/1995/pdf/6711x1929.pdf).

5.2 Biochemical techniques

Biomarkers are substances found in an increased amount in the blood, other body fluids, or tissues and which can be used to indicate the presence the presence of osteoporosis. Biomarkers of bone remodeling (formation and breakdown), such as alkaline phosphatase and osteocalcin (serum markers) and pyridinolines and deoxypyridinolines (urinary markers), help in evaluating risk for osteoporosis (Pedra, 1997). The research studies show that biomarkers correlate with changes in indices of bone remodeling and may provide insights into the mechanisms of bone loss which may give a basic detection method. The method may not be precise or accurate but it is quick, early, cheap and non-invasive way of detection. This method gives an indication of the onset of the disease (Demers, 1997 ; Eastell, 1998)

5.2.1 Bone markers

There is a need for the development a non-invasive and repeated measurement of bone turnover which demands precision, accuracy and specificity (Jourdon, 2002). These kind of independent measurements of bone formation and resorption are done at organ or tissue level (Clemens, 1997). The validated biochemical markers are Urine and Serum (see Table 4).

Methods of Analysis : The two main biochemical markers for bone formation are serum alkaline phosphatase and serum osteocalcin. Markers for bone resorbtion include urinary calcium and urinary hydroxyproline : Alkaline phosphatase, which reflects osteoclast activity in bone, is measured in serum, (Takao, 2004) but it lacks sensitivity and specificity for osteoporosis, because it can be elevated or decreased with many diseases. It is increased with aging.(See Table 5)

Urinary calcium can give some estimate of resorbtion (loss of) bone, but there are many variables that affect this measurement. Urinary hydroxyproline is derived from degradation of collagen, which forms extracellular bone matrix. However, hydroxyproline measurement is not specific for bone, because half of the body's collagen is outside the bony skeleton. It is also influenced by many diseases, as well as diet. Several ELISA kits are developed by Osteomark Company for detection of Osteoporosis (www.osteomark.org).

5.2.2 Laboratory methods

There are several premilary tests to identify the loss of bone mass. A number of laboratory tests may be performed on blood and urine samples.

The most common blood tests evaluate :

- blood calcium levels
- blood vitamin D levels
- thyroid function

Table 4 Urine and serum markers (Sartoris, 1996)

S.No	Osteoblastic Activity	Osteoclastic Activity
1.	S-alkaline phosphatase -Total alkaline phosphatase (S-tAP) -Bone alkaline phosphotase (S-bAP)	U-Hydroxyproline (U-OHPr)
2.	S-osteocalcin (S-BGP)	U-collagen crosslinks -Pyridinoline (U-Pyr) -Deoxypryridine (U-D-Pyr)
3.	S-carboxyterminal propeptide of human type I collagen (S-PICP)	S-C Terminal pyridine crosslinked telopeptide domain of type I collagen (S-ICTP) S-Tartrate-resistant acid phosphatase (S-TRAP)

Table 5 Comparison of the radiation detection techniques of OP

S.No	Diagnostic Techniques	Working Principle	Benefits	Limitations	Source
1.	Quantitative CT (Q-CT)	A type of X-ray that uses a computer. It reflects three-dimensional bone Mineral density.	-painless, noninvasive and accurate -fast and simple	-Low Precision -Increased radiation exposure -early detection not Possible. -expensive	Hernández, 1995
2	Peripheral quantitative computed tomography (p-QCT)	Measures bone density in the appendages	-Latest technology -good for spine, wrist and heels	-expensive -early detection not possible -Installations are very complicated	Hernández, 1995
3	Dual Energy X-Ray Absorptiometry. (DXA)	A type of X-ray that is used to measure the mass of bone and bone density scanning	-most accurate -widely used -fast -high resolution	-expensive -early detection not possible -Not portable -expensive -limited use	Yates and Ross, 1995
4	Single X-ray absorptiometry (SXA)	assess bone density	-density of figures, wrist and heels can be found -good general indicator	-expensive -early detection not possible -Not portable -results phase out for hips and spine.	Yates and Ross, 1995
5	Peripheral DXA (p-DXA)	DXA test used to assess bone density in the forearm, finger, and heel.	-Heel measurement is unique -Do not expose to ionizing radiation -density	-expensive -cannot measure bone density in the hip or spine -density. Limited to peripheral sites.	Gluer, 1997
6	Quantitative Ultrasound (QUS)	A test that uses sound waves to measure bone density in the heel, shinbone, and kneecap.	Measurement of forearm and legs.	-nor can it discriminate between cortical and cancellous bone.	Marsh, 2003
7	Single Energy Absorptiometry (SPA)	Single energy gamma source which measures cortical bone in the peripheral skeleton	-accurately determine the concentrations of bone	-expensive -early detection not possible	Yates and Ross, 1995
8	Neutron Activation Analysis	A limb is bombarded by slow neutron	-Latest Technique -Accuracy in some parts of the body	-early detection not possible -Harmful for the body -requires immersion of the part in water bath -very expensive -rarely used -early detection not possible	Sartoris, 1996

Table 5 Comparison of the radiation detection techniques of OP

S.No	Diagnostic Techniques	Working Principle	Benefits	Limitations	Source
9	Photodensitometry	Measurement of the degree of darkening of X-ray film by means of a photocell which measures light transmission through the film.	-results are highly reproducible	-early detection not possible -Very expensive	Sartoris, 1996
10	Digital X-ray Radiogrammetry	Computerized digital X-ray radiogrammetry	-simple -easy	-Very expensive -area under scan is large -Requires special technicians -reliability is low	Sartoris, 1996

· parathyroid hormone levels

· estradiol levels to measure estrogen (in women)

· follicle stimulating hormone (FSH) test to establish menopause status

· testosterone levels (in men)

· osteocalcin levels to measure bone formation.

5.3 Invasive detection technique

5.3.1 Needle bone biopsy

Needle bone biopsy is not a very common assessment technique of bone density. This test has limited availability, and is best utilized as a research technique for analysis of treatment regimens for bone diseases. The best clinical use of bone biopsy combines double tetracycline labelling to determine appositional bone growth and rule out osteomalacia. Doses of tetracycline are given weeks apart, and the bone biopsy is embedded in a plastic compound, sliced thinly, and examined under fluorescent light, where the lines of tetracycline (which auto fluoresce) will appear and appositional growth assessed.

5.4 Recent novel techniques

Osteoporosis is the disease which creeps into one's body silently without showing a significant symptom. The nature of the disease asymptotic until a gross deformity occurs in one's body. This is can be very serious and deadly for the patient. The time the patient realizes structural support of the body has totally deteriorated. The diagnosis and treatment is sometimes unaffordable for a common man. The patient has the control over prevention of this disease or is reliable, easy and cheap way is available for such deadly disease than proper care can be taken. There are several researches going on in order to achieve some cheap, easy early detection of osteoporosis (Takao, 2004; Yang, 2004). The latest trend is in miniaturizing the device which make it portable, useful for homecare, user-friendly, cheap, Non-invasive and provides a kind early indication for OP. This technique is based on MEMS based technique.

5.4.1 Bone fracture detection micro-sensors

The method for detection or investigation of Osteoporosis is with the help of a micropump (Yung, 2004). The micropump has been designed using the electromagnetic principle to actuate the piston in two directions. A closed loop system is used for circulating the fluid with the pumping device. This is kind of pump is useful for blood sampling or drug delivery. Here the oscillating micropump is used to study the mechanosensitivity of bone cell for better investigation of Osteoporosis.

There is another research which has proposed an Implantable, telemetry-based MEMS bone sensor with the capability of determination of bone stress via wireless RF interface. The bone

stress is detected using the embedded piezoresistive strain gauges with polysilicon layer and CMOS chip.

Another design of micro-fabricated strain gauge array is used to monitor bone deformation in vitro and in vivo for detection of osteoporosis. These kinds of microsensor provide a map of distributed strain data over the area of interest on the surfaces of bone to monitor the structural integrity of bone. This type of strain membranes are wireless and implantable embedded in flexible membrane. A simulation experiments are conducted to develop such micro-strain gauge for study of osteoporotic bone.(Yang et al., 2004)

A bone sensor has been used for the Piezoelectric bioMEMS. An attempt has been made to develop bone-based piezoelectric sensors to detect the stress in bone (Singh, 2003). Another micro-scale sensor for bone surface strain measurement is discussed (Singh, 1997 ; 1998 ; 1998). This kind of sensor is used for studying the structural effects of osteoporosis. Designs and simulation using ANSYS finite element modeling tool of thin-film metal strain metal strain gauge. Metal films for electrical interconnection encapsulated in PDMS have been studied. The PDMS membrane was characterized to facilitate encapsulation designs. The basic fabrication steps like Silanization, PDMS preparation, Photolithography, PDMS metallization, wire bonding and finally device separation. With experiments were performed for optimizing and characterizing the device like mechanical testing, electrochemical testing and adhesion testing (Yang et al., 2004), and there is a new design which has been discussed here.

Another latest technology is detecting osteoporosis with the study of the brittleness of the bone. The bone mass and bone density play an important role in bone strength. It is important to measure the brittleness or fragility or the bone mechanics. Certain walking studies are done and it is found that as the heel strikes the ground it creates force pulse, energy that passes up through the body and it is absorbed by bone. The osteoporosis reduces the quality of the bone so by attaching the skin-mounted sensors for measuring the electrical pulses of the muscles which is an active part of the skeletal system. If the person has osteoporosis the energy which passes up to the body is disrupted due to porous nature of the bone (http ://www.uc.edu/news/NR.asp?id=3280).

5.4.3 Microfluidic channels-detection by biomarkers

The total Alkaline phosphatase is the mostly widely used bone marker in the clinics and hospitals. AP have physiological substrates which splits the inorganic phosphatase with organic phosphatase, increasing the calcium-phosphatase product and enabling mineralization.AP is essential for normal mineralization of the bone. Bone AP(bAP) constitutes approximately 50% Serum AP and the serum has the half-life of 24-48hrs. Though the half-life is relatively large but it may differ on cardiac rhythm, with peak levels in afternoon and night. The exact metabolic pathway is unknown.AP is measured with the help of spectrophotometer using p-nitrophenylphosphate as substrate. The bone and liver AP may be separated by electrophoresis but this method is time consuming and gives semi-quatitaive results. The concentration of bAP concentration may be measured using two antibodies with small differences in affinity toward the isoforms.

MEMS based detection with alkaline phosphatase: A microfluidic device has been used for enzyme assay. The measurement of enzyme-substrate reaction will to do the substrate consumed. A lab-on-chip device is developed for controlling the flow containing small volumes of liquids in microchannel which can speeed up and simplifies sample preparation steps in lab-on-chip which offers high throughput, low version of traditional research. The microfluidic device is fabricated by the casting process with PDMS. It consists of three parts part I is the injection system, part II is the reaction chamber and part III is the microchannel. This particular microchannel measures the ALP activity using a micro-plate reader. Microfluidic mixing for single enzyme assay was applied and with mathematical prediction the enzymatic activity was studied. The table Fig. 6 shows the Biochemical indices which help in early

Table 6 Biochemical indices

BONE FORMATION	BONE RESORPTION
· Osteocalcin (OC)	· Pyridinoline (Pyr)
· Bone-specific alkaline phosphatase (BAP)	· Deoxypyridinoline (dPyr)
· Amino terminal propeptide of type I collagen (PINP)	· Amino terminal telopeptide of type I collagen (NTx)
· Carboxy terminal propeptide of type I collagen (PICP)	· Carboxy terminal telopeptide of type I collagen (CTx)

detection of OP.

5.4.4 BioMEMS-based sensors

BioMEMS using electrochemical immunoassay with microfluidic system (Heineman, 2001) help in blood sample analysis using the heterogeneous immunoassay. Two concept of immunoassay is studied in this research. First is based on analogous microcapillary immunoreactor and other combines the reaction and detection chamber within the area of electromagnet. Both are MEMS based system for alkaline phosphatase study.

Another MEMS microvalve with PDMS diaphragm and two chambers with thermo-pneumatic actuator for integrated blood test system with silicon have been suggested for Point of Care device. The blood test system can be reduced to reasonable cost with MEMS technology.(Takao et al., 2004) The microvalve with long stroke has been fabricated with two chamber thermo-pneumatic actuator.

6. Discussion

6.1 Bone density testing

There is several bone density measurement testing techniques which have been discussed with their working principles. The recent developments in the instruments for BMD measurement have also been discussed. But there are several limitations in these devices. The testing with these devices is very expensive, early detection is not easy, these are invasive measurement, errors in magnification may occur, accuracy is not achievable, scan time is high, harmful radiation may cause problems in the body, home care is not possible and the instruments are not portable. Specially trained persons are required to operate such sophisticated equipments.

Though BMD measurement is the most accurate method for detection of Osteoporosis but it is unable to help in early detection and is very expensive. Early detection of such a silent and deadly disease is important for the mankind. Hence there is a need for new, novel, portable, cheap detection systems to be developed for point of care testing.

6.2 Invasive technique

The invasive technique has several risk involved like skin is punctured. There is a slight chance that the needle may cause fracture the bone being sampled or injure one of the nerves, blood vessels, or organs near the biopsy site. If complications occur, another surgery may be needed to treat the problem. After a bone biopsy, there is a slight chance that the bone may become infected, osteomyelitis or not heal properly. In rare instances, the bone from which the biopsy sample was taken may become weak and break, fracture at a later time. This type detection is only good for extreme severe cases.

6.3 Biochemical measurements

There are several bone markers or the biomarkers available for the early detection of the osteoporosis which control the osteoblastic and osteoclastic activity. The biochemical detection is not accurate detection but it gives the indication for onset of osteoporosis detection.

6.4 MEMS based techniques

The MEMS-based techniques are portable, handheld, easy to use, can be used for home care and point-of-care testing. But the accuracy of the detection may be achieved by using bone mineral

density testing (BMD).

The Radiographic techniques are needed for the accurate detection of Osteoporosis as they give precise data for detection of the deadly disease. Generally, the patients are just unaware of the disease as Osteoporosis creeps silently within a human body. Osteoporosis is a silent killer and is a very progressive disease. The time the person realizes the detection and treatment becomes unaffordable for patient. This research paper focuses on the urgent need for the development on early, non-invasive, cheap, and handheld POCT device for such a dangerous disease. These characteristics can be achieved by using a micro-size (MEMS/Nano based techniques). There have been several attempts in this direction as mentioned in the paper above. But this area needs more of research and deep studies as see in Figure 6.

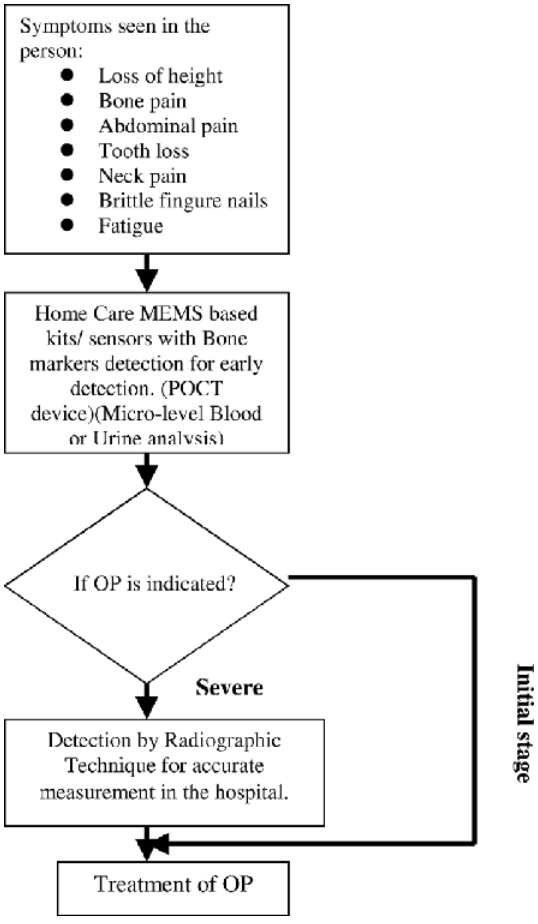

Fig. 6 New Model for better, early and inexpensive detection of OP

7. Challenges-Future Research Needs

New type of biochemical markers of bone reabsorption have been identified for early detection of Osteoporosis (Piedra et al., 1997). However, there is a need for an early, portable, cheap pocket device for the detection of osteoporosis. This new type of sensor will measure bone loss (e.g., in osteoporosis) in different bone marker fluids. There is also a need for a microfluidic chip to help in home health care for the patients. Main emphasis is to be placed on NTx (Clemens et al., 1997, osteomark) and CTx (osteomark) for early detection of osteoporosis. Thus, all pathological laboratories have to study the NTx and CTx for early detection of the osteoporosis. There is an urgent need to design and develop such systems in future.

8. Conclusions

Osteoporosis has been discussed with respect to biological, engineering, biochemical and physical

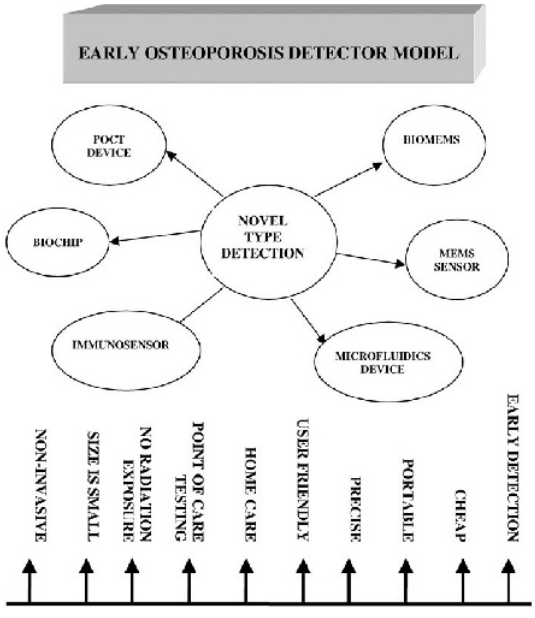

Fig. 7 Trends for latest detection technique for OP

aspects. Diagnostic and therapeutic techniques have been described for osteoporosis, for better health care. Protection measures have been highlighted to avoid such disease. New bioengineering techniques have been described for the diagnosis of the osteoporosis.

According to the Fig. 7, the emphasis is given on the development of new novel type early indicator for silent and deadly disease ; Osteoporosis. Combining the MEMS based technology with Biomedical Engineering has been the latest trend in the recent research papers. The focus is on the MEMS based biochip. A new direction of research has been introduced which may bring a new revolution in the detection of Osteoporosis.

Acknowledgments

"The authors would like CIBST for providing their support. This study was supported by a grant of the Korea Health 21 R&D Project (02-DJ3-PG6-EU05-0001), Ministry of Health & Welfare, Republic of Korea and by Korea Science and Engineering Foundation Grant R01-2006-000-10742-0. One of the authors, Kanika Singh would like to thank for the financial assistance by Korea Research Foundation Grant Funded by the Korea Government (KRF-2005-211-D00203)."

References

Arnaud, C. D., 1996, Osteoporosis : Using 'Bone Markers' for Diagnosis and Monitoring. Geriatrics, 51, pp. 24～30.

Bal, S. K. and McCloskey, E. V., 2002, *Menopause and Bones*, Current Obst & Gynaec. 12, pp. 354～357.

Becerra-Rojas, F. and Jupari, M., 2001, Epidemiology of Osteoporosis in Peru Bone, Volume 29, Issue 3, Page 297.

Bagur, A., 2001, Epidemiology of osteoporosis in Argentina Bone, Volume 29, Issue 3, Page 298.

Bianchi, M. L., Cimaz, R., Bardare, M. et al., 2000, "Efficacy and Safety of Alendronate for the Treatment of Osteoporosis in Diffuse Connective Tissue Diseases in Children : A Prospective Study," Arthritis & Rheum 43, 1960.

Bianchi, M. L., 2005, How to Manage Osteoporosis in Children? Bone Prac. & Res Clinical Rheumatology, Vol. 19, Issue 6, Dec, pp. 991～1005.

Bouxsien, Mary L., 2005, Determinants of Skeletal Fragility, Best Practice & Research Clinical Rheumatology, Vol. 19, No. 6, pp. 897～911.

Carneiro, R. A., 2001, Epidemiological Aspects of Osteoporosis in Brazil Bone, Volume 29, Issue 3, Page 298.

Clemens J. D. et al., 1997, Evidence That Serum NTx (collgen-type I N teolopeptides) Can Act as Immunochemical Marker of Bone Resorption, Clin. Chem, 43 : pp. 2058～2063.

Danielson, M. E., Cauley, J. A., Baker, C. E., Newman, A. B., Dorman, J. S, Towers, J. D. et al., 1999. Familial Resemblance of Bone Mineral Density (BMD) and Calcaneal Ultrasound Attenuation : the BMD in Mothers and Daughters Study, J Bone Miner Res 14, pp. 102～110.

Deal, C. L., 1997. Osteoporosis : Prevention, Diagnosis, and Management, Am J Med. 102 (1A), pp. 35S～39S.

Delmas, P. D., 2002. Treatment of Postmenopausal Osteoporosis. The Lancet. 359, pp. 2018～2026.

Demers, L. M., 1997. Clinical Usefulness of Markers of Bone Degradation and Formation, Scand J Clin Lab Invest. Suppl 227, pp. 12～20.

Eastell, R., 1998, Treatment of Postmenopausal Osteoporosis, N Engl J Med. 338, pp. 736～746.

Eastell, R. and Blumsohn, A., 1997, The Value of Biochemical Markers of Bone Turnover in Osteoporosis, J Rheumatol. 24, pp. 1215～1217.

Faulkner, R. A., Bailey, D. A., Drinkwater, D. T. et al., 1996, Bone Densitometry in Canadian Children 8-17 Years of Age. Calcif Tissue Int 59, pp. 344.

Ferretti, J. L. et al., 2003, Etiopathogenesis of osteoporosis. Mechanism of Ageing & Development. 00, 1-11.

Francisco, Diez, DC., 2001, Review of the Literature : Guidelines for the Diagnosis of Osteoporosis by Densitometric Methods, J. Manipulative and Physiological Therapeutic, July/Aug, Vol. 25, Number 6, pp. 403～412.

Gillespy, T. and Gillespy, M. P., 1991, Osteo-

porosis. Radiol Clin North Am. 29, pp. 77～84.

Gluer, C. C., Jergas, M. and Hans, D., 1997. Peripheral Measurement Techniques for the Assessment of Osteoporosis, Semin Nucl Med. 27, pp. 229～247.

Gordon, C. M., 2000, Mini Review-Bone Density Issues in the Adolescent Gynecology Patient, J Pediatr Adolesc Gynecol, 13, pp. 157～161.

Heineman, W. R., Thomas, J. H., Wijayawardhana, A., Brian Halsall et al., 2001, BioMEMS : Electrochemical Immunoassay with Microfluidic Systems, Analytic Sciences, Vol. 17, Supplement pp. i281～i284.

Hernández, E. R., Seco-Durban, C., Revilla, M., González-Riola, J. and. Rico, H., 2003. Evaluation of Bone Density with Peripheral Quantitative Computed Tomography in Healthy Premenopausal, Perimenopausal, and Postmenopausal Women, Age and Ageing, Volume 24, Number 5, pp. 447～450.

Hosking, D., Chilvers, C. E. D., Christiansen, C. et al., 1998. Prevention of Bone Loss with Alendronate in Postmenopausal Women Under 60 Years of Age, N Engl J Med. 338, pp. 485～492.

Isenbarger, D. W. and Chapin, B. L., 1997, Osteoporosis. Current Pharmacologic Options for Prevention and Treatment, Postgrad Med. 101, pp. 129～132.

Jeal, W., Barradell, L. B. and McTavish, D., 1997, Alendronate : a Review of its Pharmacological Properties and Therapeutic Efficacy in Postmenopausal Osteoporosis, Drugs. 53, pp. 415～434.

Jean Hodson and Jen Marsh, 2003, Quantitative Ultrasound and Risk Factor Enquiry Comparative Study in Primary Care Osteoporosis : as Predictors of Postmenopausal. doi : 10.1136/bmj. 326.7401.12502003 ; 326 ; pp. 1250～1251 BMJ, 2003 Jean.

Jourdon, K. M., 2002. Epidemiology of Osteoporosis, Best Practice & Res Clin Rhe. 16, pp. 795～806.

Jouanny, P., Guillemin, F., Kuntz, C., Jeandel, C. and Pourel, J., 1995 Environmental and Genetic Factors Affecting Bone Mass. Similarity of Bone Density among Members of Healthy Families, Arthritis Rheum 38, pp. 61～67.

Kanis, J. A., 2002, Diagnosis of Osteoporosis and Assements of Fracture Risk, The Lancet. 359, pp. 1929～1936.

Khovidhunkit, W. and Shoback, D. M., 1999 Clinical Effects of Raloxifene Hydrochloride in Women, Ann Intern Med. 130, pp. 431～439.

Korkia, P., 2002. Osteoporosis : Process, Prevention and Treatment, J. Bodywork & Movement Theparies. 6, pp. 156～169.

McClung, M. R., Geusens, P., Miller, P. D. et al., 2001, Effect of Risedronate on the Risk of Hip Fracture in Elderly Women, N Engl J Med. 344, pp. 333～340.

Melton, L. J. D., Chrischilles. E. A., Cooper, C., Lane, A. and Riggs, B. L., 1992, Perspective : How Many Women Have Osteoporosis? J Bone Miner Res 7, pp. 1005～1010.

Osteoporosis Society of Canada. 2, The Use of Bone Density Measurement in the Diagnosis and Management of Osteoporosis, Can Med Assoc J. 155, pp. 924～929.

Pedra C. de la et al., 1997, New Biochemical Markers of Bone Resorption in the Study pf Postmenopausal Osteoporosis, Clinical Chimica acta, 256, pp. 225～234.

Raisz, L. G., 1997, The Osteoporosis Revolution. Ann Intern Med. 126, pp. 458～462.

Rapado, A., 2001, Epidemiology of Osteoporosis in Spain, Bone, Volume 29, Issue 3, Page 299.

Recker, R. R., 1994, Bone Biopsy and Histomorphometry in Clinical Practice, Rheum Dis Clin North Am 20, pp. 609～627.

Roux, Sophie, 2001, The Genetics of Osteoporosis, Jt Bone Spine, 68, pp. 482～486.

Sambrook, P. N., Kelly, P. J., Morrison, N. A. and Eisman, J. A., 1994. Genetics of Osteoporosis, Br J Rheumatol 33, pp. 1007～1011.

Samsioe, G., 1997. Osteoporosis-an Update, Acta Obstet Gynecol Scand, 76, pp. 189～199.

Singh, Kanika, 1997, "Electronic Bone Fracture Detector," Proc IEEE- EMBS Int Conf, Chicago (USA), Oct 29 to Nov 3.

Singh, Kanika, 1998, "Portable battery operated bone fracture evaluator," Proc IEEE- EMBS Int Conf, Hong Kong, Oct 28 to Nov 3.

Singh, K. and Kim, K. C., 2005, Biomechanics

of Bone, Proc. 7th Cross Straits Symposium on Materials, Energy and Environmental Sciences, CSS7, pp. 35～36.

Singh, K., 2004, A Bone- Based Sensor, 26th Annual International Conference for Attending IEEE-EMBS conf., San Francisco, USA, 1-5th Sept.

Singh, Kanika, 1999, "Development of a Dynamic Bone Micro-Sensor for Biomedical Applications," Proc. IEEE-EMBS Int. Conf., Atlanta, USA, Oct 29-Nov1.

Smith. R., 1993, Bone Physiology and the Osteoporotic Process, Respir Med. Feb ; 87 Suppl A : 3-7.

Sortis, D. H., 1996, Osteoporosis Diagnosis and Treatment Edited by David J., Copyright by Marcel Dekker, Book, Printed in USA.

Sturtridge, W., Lentle, B. and Hanley, D. A., 1996, Prevention and Management of Osteoporosis : Consensus Statements from the Scientific Advisory Board of the.

Vermeer, C., Gijsbers, B.L., Cracium, A. M. et al., 1996, Effects of Vitamin K on Bone Mass and Bone Metabolism, J Nutrition 126, 1187S.

Takao, H., Miyamura, K. et al., 2004, A MEMS Microvalve with PDMS Diaphragm and Two -Chamber Configuration of Thermo-Pneumatic Actuator for Integrated Blood System on Silicon, Sensor and Actuators A 119, pp. 468～475.

Turner, C. H., 2002, Review Article : Biomechanics of Bone : Determinants of Skeletal Fragility and Bone Quality. Osteoporosis Int (2002) 13 : pp. 97～104 2002 International Osteoporosis Foundation and National Osteoporosis Foundation.

Yates, A. J., Ross. P. D., Lydick, E., Epstein, R. S., 1995, Radiographic Absorptiometry in the Diagnosis of Osteoporosis, Am J Med. 98(2A), pp. 41S～47S.

Yang, G. Y, Vasudev, J. B. et al., 2004, Design of Microfabricated Strain Gauge array to Monitor Bone Deformation In Vitro and In Vivo, Proc. of the Fourth IEEE Symp on Bioinformatice and Bioengineering (BIBE'04).

Yang, G. Y., Bailey. V. J., Wen, Y. H., Tang, W. C. and Keyak, J. H., 2004, Fabrication and Characterization of Microscale Sensors for Bone Surface Strain Measurement, IEEE, pp. 1355～1358.

Zaidi Mone, 2006, Edited, Skeletal Development and Remodeling in Health, Disease and Aging. Boston Mass, Blackwell Pub on Behalf of New York Academy of Sciences, 2006.

Net References

www.nof.org/osteoporosis/images

www.osteomark.org

www.osteofound.org

www.who.org

http ://www.iupac.org/publications/pac/1995/pdf/6711x1929.pdf

http ://www.uc.edu/news/NR.asp?id＝3280

www.niams.nih.gov/bone/osteoporosis

www.activella.com/2_3_2.asp

www.medinfo.co.uk

www.fpnotebook.com