"THE EFFECT OF ZOLEDRONIC ACID IN PATIENTS WITH CHRONIC BACK PAIN ASSOCIATED WITH VERTEBRAL OSTEOPOROSIS: A PROSPECTIVE STUDY"

By

Dr. UMESH M. MBBS

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In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

IN

ORTHOPAEDICS

Under the Guidance of

Dr. PRABHU E MBBS M.S. ORTHO

Associate Professor

SDUAHER

Sri Devaraj Urs Academy of Higher Education and Research

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Date:

Place: Kolar

Signature of the Guide

Dr. PRABHU E,

Associate Professor,

Department of Orthopaedics,

Sri Devaraj Urs Medical College,

Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, TAMAKA, KOLAR, KARNATAKA

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Date:

Place: Kolar

Dr. ARUN. H.S

Professor & HOD,

Department of Orthopaedics,

Sri Devaraj Urs Medical College,

Tamaka, Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, TAMAKA, KOLAR, KARNATAKA

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Date:

Place: Kolar

Dr. SREERAMULU P.N

Principal,

Sri Devaraj Urs Medical College,

Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA

ETHICAL COMMITTEE CERTIFICATE

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Dr. UMESH M

Post-Graduate student in the subject of ORTHOPAEDICS at Sri Devaraj Urs Medical College, Kolar to take up the Dissertation work entitled

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SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, TAMAKA, KOLAR, KARNATAKA,

Date:

Place: Kolar

Member Secretary

Sri Devaraj Urs Medical College,

Tamaka, Kolar-563101

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DATE:

PLACE: **Dr. UMESH M**

LIST OF ABBREVATIONS USED

AOA	American Orthopaedic Hospital
WHO	World Health Organization
DEXA	Dual Energy X Ray Absorptiometry
BMD	Bone Mineral Density
FRAX	Fracture Risk Assessment Tool
PTH	Parathyroid Hormone
PTHrP	Parathyroid Hormone Related Peptide
RANK	Receptor For Activation Of Nuclear Factor Kappa B
RANKL	Ligand For Receptor For Activation Of Nuclear Factor Kappa B
SERMS	Selective Estrogen Receptor Modulators
USA	United State of America
PBM	Peak Bone Mass
BMI	Body Mass Index.
DXL	Dual X Ray and Laser
ZA	Zoledronic Acid
ALN	Alendronate
GI	Gastrointestinal
JBJS(Br)	Journal Of Bone and Joint Surgery British
ECM	Extracellular Matrix
TGF-β	Transforming Growth Factor- β
BMP	Bone Morphogenic Protein
OPG	Osteoprotegerin
CBFA1	Co-binding Factor A1
DNA	Deoxyribose Nucleic Acid
M-CSF	Monocytes Colony Stimulating Factor
IL-1	Interleukin - 1
CaSR	Calcium Sensing Receptors
IGH-2	Immunoreactive Growth Hormone 2
IGF-1	Insulin Like Growth Factor - 1
SD	Standard Deviation
ERT	Estrogen Replacement Therapy
BPs	Bisphosphonates
ATP	Adenosine Tri Phosphate
GTP	Guanosine Tri Phosphate
PMO	Post Menopausal Osteoporosis
VAS	Visual Analogue Score
MODI	Modified Oswestry Disability Index
FU	Follow Up
AEs	Adverse Events

ABSTRACT

Back ground and objectives:

Osteoporosis is a chronic progressive systemic skeletal disease characterized by reduced bone mass and micro-architectural deterioration of bone tissue with consequent fragile bones, predisposing to increased risk of 'osteoporotic fractures' or 'fragility fractures'.[01, 02] This condition often remains asymptomatic and undiagnosed until it presents with fragility fractures. The condition is associated with significant socioeconomic burden with disability, morbidity and mortality.[07, 05, 08] Early diagnosis as well as treatment is needed for preventing fractures. Intravenous Zoledronic Acid infusion is potent and most compliant bisphosphonate, given at once yearly 5mg dose. The present study is an effort to early diagnosis of osteoporosis and efficacy of Zoledronic acid in treating chronic back pain.

Methods:

70 patients above 60 years age presented with complaint of chronic low back ache to outpatient, department of orthopaedics, RL Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College. The study period was between November 2016 and November 2018.

Result:

In all the patients found excellent clinical improvement following Zoledronic Acid infusion in early and long term follow up and the efficacy of Zoledronic Acid also found to be excellent with significant improvement in BMD, T-Score and Z-Score.

Conclusion:

Early diagnosis and treatment of such condition is most important factor in preventing fragility fractures. Zoledronic Acid being an antiresorptive drug with its better compliance, is very effective in ‘controlling low back pain’, ‘improving bone mineral density’ and preventing occurrence of atraumatic fragility fractures. With all above factors Zoledronic acid is most preferable bisphosphonate for treatment and prevention of osteoporosis.

Key words: Vertebral osteoporosis, bone remodeling, fragility fractures, Dual Energy X ray Absorptiometry, Bone mineral density, T-Score, Bisphosphonates, Zoledronic acid.

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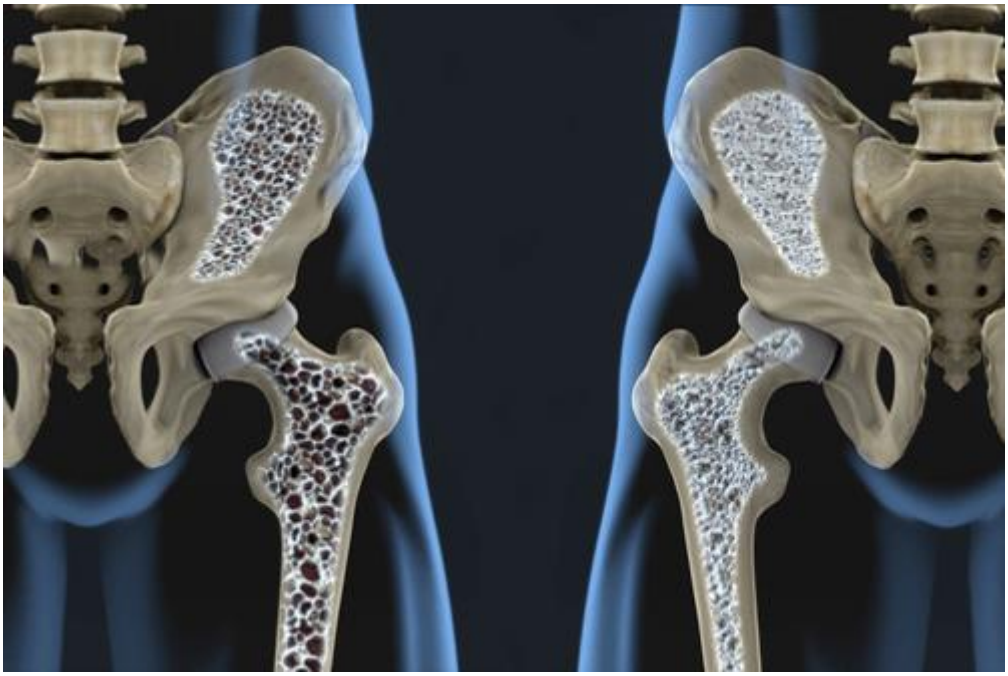
INTRODUCTION

Osteoporosis is a chronic progressive systemic skeletal disease characterized by reduced bone mass and micro-architectural deterioration of bone tissue with consequent fragile bones, predisposing to increased risk of 'osteoporotic fractures' or 'fragility fractures'.[01, 02, 03, 04] This condition often remains asymptomatic and undiagnosed until it presents with fractures involving hip, spine, proximal humerus, pelvis, also wrist as a result of trivial trauma which frequently leads to hospitalization.[05] Sometimes it also presents with severe backache or loss of height.

Picture No:01, Osteoporotic and Normal Hip Bone[06]



The condition is associated with significant socioeconomic burden with disability, morbidity and mortality.[07, 05, 08] Early diagnosis as well as treatment is needed for preventing these fractures. After introduction of 'Own the Bone' programme by American Orthopaedic Association (AOA), the orthopaedic surgeons gained a vital importance in managing osteoporosis beyond the acute fracture management, this has been proved useful in better management of patients in many studies.[09]

Since the dawn of history women population is being haunted by Osteoporosis.[10, 11] The word osteoporosis has come from 'osteon' meaning bone, 'por' means porous in Greek and 'osis' means condition in English.[02] The term was coined by Jean Lobstein in the 1830s to describe holes in bones which he found were larger in some patients compared to others.[12] Hippocrates in 500BC has written "the vertebrae of the spine when contracted into a hump behind from disease".[13]

Because of its insidious onset and silent nature, World Health Organization has recognized osteoporosis as second global health problem next to cardiovascular diseases.[14]

Osteoporosis is most common metabolic bone disease that affects all age groups mainly postmenopausal women and elder population. According to WHO published statistics one out of three women and one out of eight men in India are osteoporotic above 50 years of age. It is

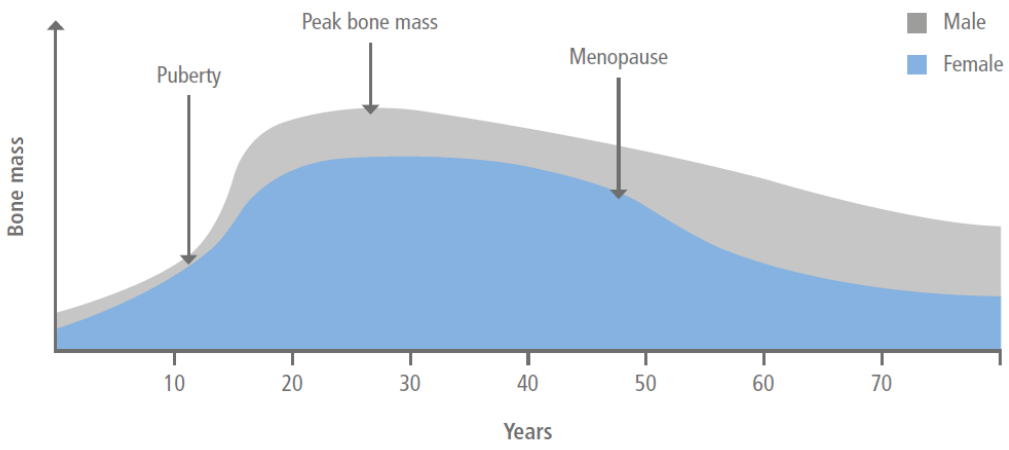
estimated in few studies that more than 61 million Indians are osteoporotic; of which, 80% are females.[07] Many small studies among women in India on prevalence of osteoporosis suggest that prevalence of osteoporosis is in rising trend due to increasing longevity and 23.5 crore of Indian women expected to be above 50 years of age, of which 20% are osteoporotic with prevalence of 8% to 62% in Indian women of different age groups.[15, 16] The disease prevalence has been rising at an alarming rate without being recognized as a 'national' as well as 'public health priority' by the medical fraternity, with lack of awareness among the general population, hence osteoporosis can be called as 'silent global epidemic'.[17] Worldwide around 20 crore people are affected by osteoporosis.

Earliest clinical feature of osteoporosis is usually chronic low back ache, but its not being noticed and diagnosed. Hence major number of cases are presenting to health system with osteoporotic fractures. Most common fractures seen in osteoporotic patients are vertebral compression fractures followed by hip fractures.[18] International Osteoporosis Foundation recently mentioned after the age of 50 years, 1 in 3 women and 1 in 5 men in their lifetime will experience osteoporotic fractures worldwide.[19] Each year worldwide approximately 16 lakh people will suffer from hip fractures and the number is expected to reach 45 to 63 lakh by 2050.[71] With significant morbidity even mortality is noted with rates up to 24% in the first year after hip fractures.[20, 21]

Bone tissue is metabolically active tissue. It undergoes continuous remodeling with balanced osteoclastic bone resorption and osteoblastic bone formation.[22]

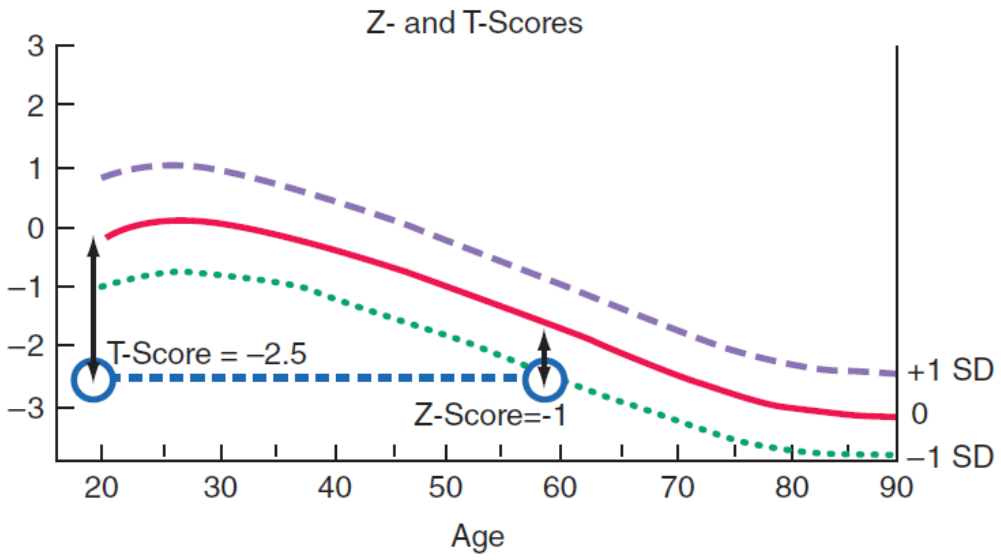
Bone mass achieves its peak at early adulthood i.e. 18-25 years and until menopause it will remain relatively stable. With age and after menopause sets the balance shifts resulting increased resorption than formation leading to decreased bone strength.[14] In women greatest bone loss happens during perimenopausal age due to estrogen insufficiency as a result of menopause and it continues in further life span.[07, 20] Pathogenesis of osteoporosis depends on both non-modifiable risk factors such as age, gender, race and ethnicity as well as modifiable risk factors such as diet deficient in calcium, insufficient exercise and activities, caffeine products, smoking, alcohol, deficiency of vitamin and inadequate exposure to sun.[17]

Graph No: 01, Peak Bone Mass and Trend of Bone Mass[21]



Osteoporosis is a silent disease which will present late usually with osteoporotic fractures. Evidence of a fragility fracture was necessary for diagnosis of osteoporosis before 1994.[22] After invention of dual-energy x-ray absorptiometry (DEXA), this has been recommended by WHO and has been internationally accepted as Gold standard test for Bone mineral density assessment and diagnosis of osteoporosis.[23] Because of strong correlation among bone mineral density (BMD), bone strength and fractures risk, WHO designed Fracture Risk Assessment Tool (FRAX) in February 2008 to help the practitioners to assess fracture risk.[24] It is a computer based algorithmic programme which assesses 10 year hip fractures or major osteoporotic fractures risk.[23]

Graph No:02, Relationship Between T and Z Score[25, 26]



Both anabolic and antiresorptive therapies are available to use separately or one after another and even in combination for osteoporosis.[27] Since 1960s after discovery of bisphosphonates, the management of osteoporosis has revolutionised.[12] These are basically pyrophosphate stable synthetic analogs that acts by suppressing bone resorption by osteoclasts and indirectly decreasing osteoblast activity. Teriparatide, an analog of parathyroid-hormone (PTH), Abaloparatide, an analog of parathyroid hormone–related peptide (PTHrP), Romosozumab is an investigational monoclonal antibody that inhibits sclerostin, Testosterone therapy and Calcitonin are anabolic drugs available. Nitrogen containing bisphosphonates, denosumab (a RANKL blocker), Estrogens and selective estrogen receptor modulators (SERMs) are main antiresorptive drugs available at present. Denosumab is credited with the most rapidly acting and potent antiresorptive properties.[27] Intravenous Zoledronic Acid infusion is potent and most compliant bisphosphonate, given at 5mg dose over 15 min.

As low back ache is earliest symptom of osteoporosis present study is intended for early diagnosis and treatment and to determine the efficacy of Inj Zoledronic Acid 5mg in patients with spinal osteoporosis in view of pain control and improvement in BMD in the rural population.

HISTORY AND EVOLUTION OF CONCEPTS ABOUT OSTEOPOROSIS

Even though osteoporosis evidences are available in Egyptian women mummies of 4000 years old, it is being recognized and quantified from 17th century. As early as in 1750 process of new bone formation and old bone is destroyed or resorbed in body called 'remodelling' was first described by John Hunter (1728-93) a famous Scots born anatomist and surgeon.[12, 28]

Age related decline in bone mineral density and increased fracture risk was recognized by Sir Astley Cooper (1768-1841). 'Osteoporosis' or 'porous bone' term was first described for explaining holes in bones in 1830 by a French pathologist Jean Lobstein (1777-1835).[12] In 1885 Pommer distinguished between osteoporosis and osteomalacia.

Kienbock in 1925 called osteoporosis as deficient nutrition of bone, but again in 1940 he reviewed it again and postulated as endocrine gland defect that governs skeletal growth and nutrition.[29]

Fuller Albright (1900-69) gave most important revolutionary facts about osteoporosis. Albright along with Bloomberg and Smith established deficiency of osteoblastic activity in osteoporotic bones a century after Lobstein's work. He also described the long bones, spine and pelvic bones as predominantly involving sites, its association with disuse and

senescence and is most common in postmenopausal women specifically those who had early menopause, proton pump inhibitors use, in Cushing's disease and on corticosteroids therapy, he also added the word 'senile osteoporosis' in 1940.[12, 30]

He postulated connection between bone atrophy and cessation of ovarian function resulting in postmenopausal osteoporosis in his 'estrogen hypotheses'. Ovarian secretion and osteoblastic activity relationship was studied by Albright because he thought administration of sex hormones influences the structure of bone. He found osteoporosis occurring around 9 years after menopause and hence he marked 65 years as upper age limit for 'postmenopausal osteoporosis' and called it as 'senile osteoporosis'.[30] After this he announced that in women estrogen deficiency but in men deficient androgens plays pivotal role in pathogenesis of osteoporosis. Soon after this gained importance Reifenstein measured pre-senile and senile individuals daily sex hormones excretion levels and showed rapid drop in excretion levels after female menopause and also in elderly males. He postulated that osteoporosis is related to adrenal gonadal imbalance rather than just sex hormones deficiency.[12]

During Albright era Meulengracht in 1939 thought insufficient diet and chronic disturbance of digestive system as reason for porous bones.[30]

Osteoporosis was defined as ‘a disease of inadequate bone formation from lack of matrix’ by Alaxender Cooke (1899-1999) in 1955. He noted lack of remodeling (reduced osteoblasts to replace osteoclastic erosions). He also identified benefits and adverse effects of androgens.[12]

Nordin in 1960 published his observations on osteoporosis related to chronic deficiency of calcium because of less mineral content in diet, scanty resorption of calcium or excessive urinary excretion. Experimental animal studies proved his statement calcium deficiency caused osteoporosis but vitamin D deficiency produced osteomalacia. Osteoporotic patients treated with calcium salts showed relief of pain partly and positive calcium balance. He distinguished clearly between osteoporosis and osteomalacia and demonstrated practically.[12]

In 1960s Herbert Andre Fleish (1933-2007) discovered bisphosphonates for treatment of osteoporosis which revolutionised its management. Bone loss detecting devices including densitometers were also developed during 1960s which helped in early diagnosis and management of the condition.[12]

In 19th century it was being measured by bone opacity in dental X ray as published by Dennis John in 1897. Even after all these inventions, early diagnosis of osteoporosis was a great challenge and diagnosis of Osteoporosis needed a fragility fracture. This was made easier by evolving

the concept of ‘bone mineral density’ and its measurement in 1963 when Cameron and Sorensen introduced single photon absorptiometry(SPA) which could be used only for peripheral skeletal sites.[32,33]

In 1976 Madsen introduced dual photon absorptiometry (DPA) which uses gamma rays of two different energy to measure BMD. After introduction of Dual Energy X-ray Absorptiometry(DEXA) around 1990 acquisition time was significantly shortened and accuracy and precision of BMD measurement was dramatically improved. In 1994 WHO announced DEXA as gold standard investigation for BMD measurement and diagnosis of osteoporosis.[32, 33]

REVIEW OF LITERATURE

There are very limited number of articles on prevalence of osteoporosis from many region of the world to calculate worldwide prevalence of osteoporosis, according to few studies available, prevalence of osteoporosis worldwide is more than 200 million with 9 million fractures reported yearly because of osteoporosis and 1 in 3 women and 1 in 5 men above 50 years of age suffer from osteoporotic fractures in their whole life.[34]

A review article in 2016 stated in USA about 10 million were diagnosed with osteoporosis and 34 million with osteopenia with 1.5 million osteoporotic fractures every year and same study quoted in USA and Europe 30% of post-menopausal women were found to be osteoporotic with prevalence among population aged above 50 years was 14% and 24% in women and 6% among men. In Japan it is estimated that 15 million are osteoporotic but of which only 20% are receiving treatment.[35] The study has given conclusion that osteoporosis is being dangerously neglected despite the severity of the condition and significant gap in knowledge is still existing.[35] The study also explains modifiable risk factors like Vitamin D deficiency, medication (glucocorticoid, anti-epileptic), life style (physical activity, diet, smoking, alcohol and caffeine consumption) and non-modifiable risk factors like elderly age, female sex, associated illness, genetic factors and regional factors).[35]

Many recent studies available among Indian population on osteoporosis prevalence and severity, a study conducted in Kozhikode, Kerala, the amount of population suffering from osteoporosis was estimated to be more than 61 million of which 80% are females and poor sunlight exposure, skin pigmentation and dietary Vitamin D deficiency are major risk factors leading to high incidence in both sexes. They have concluded that low back ache and combination of low back ache with knee pain are the predominant presenting symptoms. Osteoporosis and osteopenia are most prevalent in population of above 50 years. They have also found positive association of low BMD with elderly, female gender, menopause, education and hysterectomy status.[07]

In a cross sectional study done in 2018 in Bengaluru, it is mentioned that international osteoporosis foundation has noted in 2013 total 36 million were osteoporotic, young population is more affected in India compared to western side. Total burden of osteoporosis is 51.6% of which 88.8% are females.[17]

In an article published in 2011 about pathogenesis of osteoporosis, it is mentioned that attainment of peak bone mass (PBM) is most important factor in assessing risk of osteoporosis and fractures. Increasing PBM by 10%, reduces osteoporosis and fractures risk by 30%. Diagnosis is based on BMD measured by DEXA scan which is considered Gold standard. Best tool to measure fracture risk in osteoporosis is FRAX algorithm,

introduced by WHO in 1994. It includes age, sex, bone mineral density (femoral neck), body weight, height, history of previous fractures, smoking habits, alcohol consumption, glucocorticoid therapy, rheumatoid arthritis, risk of secondary osteoporosis, history of parental fractures for calculating risk of fractures.[36]

In a study done on 2014 in Vellore, it is observed that one in three osteoporotic fractures are occurring in men after the age of 50 years and that screening for osteoporosis in men is recommended after age of 70 years. The study has concluded that significantly larger proportion of healthy men are found to be osteoporotic and Vitamin D deficient in Indian population and men with high BMI had high BMD may to due to high physical stress or activity.[37]

In a study done in 2013 on correlation of vitamin D, BMD and PTH levels in adults with low BMD, they concluded that no evidences suggest relationship between serum Vitamin D and BMD, but significant association observed between Intact PTH levels and BMD at hip or lumbar spine, signifies the critical role of PTH on bone metabolism and bone health, the study also tells that elderly age, gender and BMI are other significant predictors of BMD.[38]

In a meta-analysis study on effect of parity on BMD in postmenopausal women in 2013, majority of studies suggested positive

effect by parity on BMD in postmenopausal women and reduced hip fracture rate and while some studies have shown negative or no correlation.[01]

In multiple studies on diagnosis of osteoporosis, it is mentioned that diagnosis of osteoporosis required a fragile fracture, but after WHO announced DEXA as Gold standard investigation for diagnosis of osteoporosis, the situation has changed. It involves very less exposure of radiation as it less time consuming, WHO recommends DEXA of hip and spine as standard site as they are more sensitive and helps in better assessment of fracture risk also.[02]

A review article published in 2016 has mentioned many identified confounding factors like degenerative changes, aortic calcification, interspinous ligament calcification, vertebral compression fractures artificially elevate BMD in lumbar. It has concluded that currently DEXA is considered as Gold standard for BMD measurement and fracture risk assessment.[13]

In a study on comparison between DEXA vs Dual X Ray and Laser(DXL) published in 2013 Muschitz et al. has concluded that BMD measurement at femoral neck using DEXA and at calcaneus using DXL are comparable in view of identifying fracture risk. Hence DXL is feasible, cheaper and portable alternative in place where DEXA in not available.[03]

In a multi-center comparative study in 2010 among US population between IV infusion of Zoledronic Acid(ZA) and Alendronate(ALN) by Orwoll et all. It was found that both ZA and ALN were found comparably effective and safe with comparable BMD improvement, ZA gave immediate more pronounced effect as well as better tolerated compared to ALN. Incidence of adverse events were comparable with ZA had post infusion symptoms and ALN had more of GI side effects.[39]

In a study done in 2010 on Belgium population by Boonen et al. ZA was found to be safe and effective in elderly females and advised as better mode for treatment of geriatric patients.[40]

In a study on frail seniors in 2015 by Greenspan et al. it is proved that ZA in single infusion dose is safe and improves bone density and reduce bone turnover for at least 2 years.[41]

In a study published on JBJS(Br) on 2004, done by Bobyn et al. They got evidences supporting that Zoledronic Acid cases enhanced bone growth into porous implants, when compared with control statistically significant better results were obtained in Zoledronic Acid group.[42]

In a study on US population by Benjamin proved and concluded that combinations of sequential anabolic and antiresorptive therapy (combination of Denosumab and Teriperatide) shows promising results and can be considered in patients at highest risk of fragility fracture.[27]

In a study on adverse effect profile of ZA by Kotian et al. in 2016 adverse events noted are pyrexia in 77%, myalgia in 65%, headache in 37%, influenza like symptoms in 12% and arthralgia in 12% patients and no patients had renal toxicity, osteonecrosis, atrial fibrillation and atypical femoral fracture.[43] In case reports it is noted that atypical femoral fractures, symptomatic hypocalcemia and thrombotic thrombocytopenic purpura with a fatal outcome has been reported.[44, 45, 46]

BONE BIOLOGY AND PHYSIOLOGY

Bone is an architectural masterpiece which is a special form of connective tissue and is unique from others in being physiologically mineralised.[47, 48] It is very strong, rigid and evolved for helping support and fast terrestrial locomotion.[48, 49] It is biochemically a distinctive admixture of inorganic component and organic matrix in 65%: 35% ratio. The inorganic element microcrystalline calcium hydroxyapatite $\{10Ca:6(PO_4) : (OH)_2\}$ is responsible for bone strength and rigidity.[49]

Bone as a tissue has five main tasks as function:

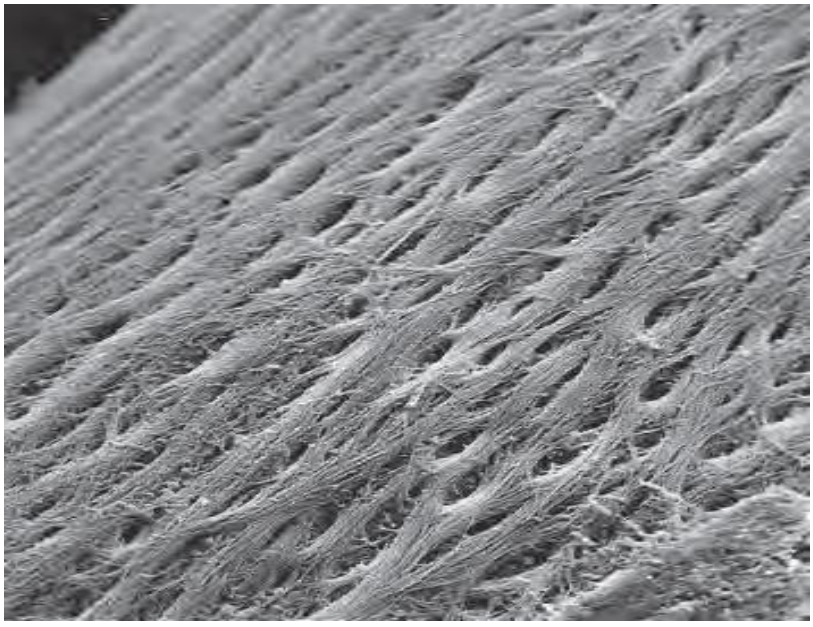
1. **Support, weight bearing** and **fast locomotion** of the body as a single unit.[48]
2. **Protection**: Internal organs like heart and lungs protected by rib shelter, Brain tissue by cranium and spinal cord by spine from external dangers.[48]
3. **Storehouse**: Bone is storehouse for minerals and matrix proteins. It is major site for mineral storage and store 99% of total body calcium, 85% of phosphate and 65% of sodium and magnesium. Bone matrix forms 30-40% of total bone mass, 90% of which is made of collagen type 1 and is secreted by osteoblasts.[48, 49]
4. **Endocrinal Function**: Through leptin and osteocalcin it regulates glucose level in serum and energy balance as well as

affects adiposity. Along with calcium homeostasis it also regulates many endocrine organs. It is noted in some studies that bone even has growth factors and cytokines.[48]

5. Space created by trabecular patterns provides a secure site for haemopoietic tissue and fat.

The unmineralised part of bone is called ‘Osteoid’ which consists of collagen fibre and ground substance. The newly synthesized osteoid will start getting mineralized by 5-10 days[94] and reaches 70-80% by 3 weeks and it slows over time.[49]

Picture No: 02, Electron Microscopic Picture of Collagen Fibre Arrangement In Bone[49]

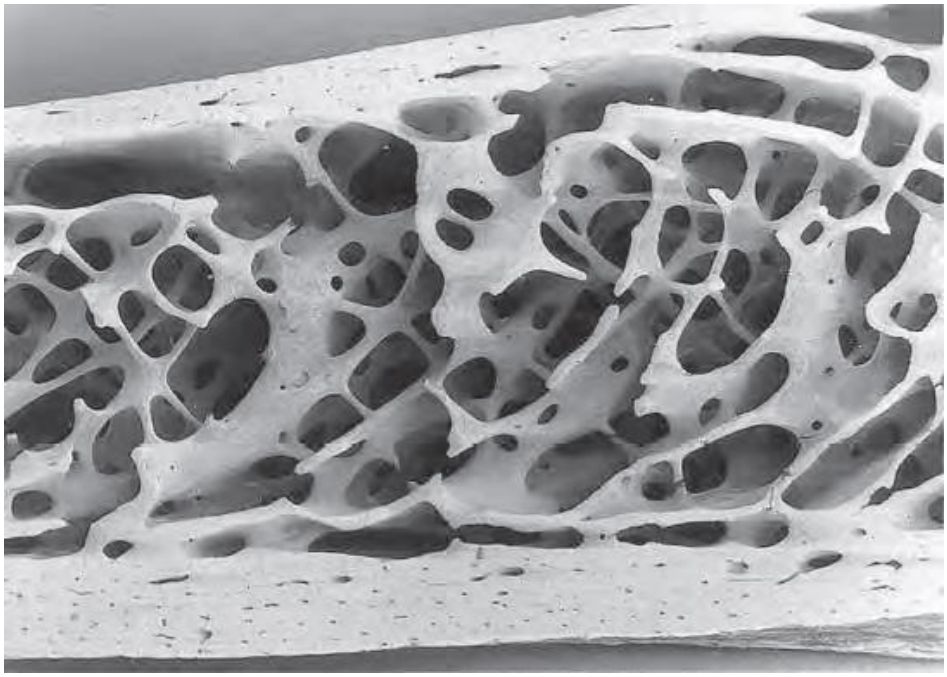


MACROSCOPIC ANATOMY OF BONE

Living bone is white in color and its texture is either dense like ivory (cortical or compact bone) or honeycombed with large cavities (cancellous, spongy or trabecular). Cortical bone usually seen in outer shell or cortex of mature bone where strong rigid bone is needed providing rigid articular surfaces.

In trabecular bone bony element is arranged in latticework of bars and plates pattern called as ‘trabeculae’ and gives bone lightness. Cancellous bone is usually present in weight bearing axial bones such as calcaneum, pelvis, spine, epiphyseal and metaphyseal part of long bones and also in the skull. It is metabolically more active than cortical bone. The proportion or cortical and trabecular bone varies between and within bones.[48]

Picture No:03, Macroscopic Appearance of Bone[48]



MICROARCHITECTURE OF BONE

Bone is made of mineralized collagenous extracellular matrix (ECM) which surrounds range of specialised cells with periosteum, endosteum and marrow closely related to it, The specialized cells are,[50]

- Osteoblasts
- Osteoclasts
- Osteocytes
- Cells of vascular and nervous supply

BONE ORGANIC MATRIX

Bone matrix is mineralized extracellular substance which is made of collagenous and non-collagenous proteins, glycoproteins and carbohydrates. The collagen found in bone is predominantly type 1 collagen arranged in paralleled branching fibre network. It is different from type 1 collagen found in other tissue by having stronger and chemically more inert internal cross links between component fibrils and larger spacing between collagen fibre molecules, which provides more space for mineral deposition. These properties of collagen give great cohesive mechanical strength to bone and makes it tough. A minimum amount of type 5 collagen also present in bone, probably helps in regulating fibrillogenesis. Non collagenous proteins are osteonectin, glycoproteins such as biglycan and decorin, sialoproteins like osteopontin

and thrombospondin which are secreted by Osteoblasts and also many growth factors, proteases and protease inhibitors, TGF-β synthesized by both osteoblasts and young osteocytes. TGF-β will get activated in acidic conditions and it might be a coupling factor for stimulating bone formation at resorption sites.[49, 50]

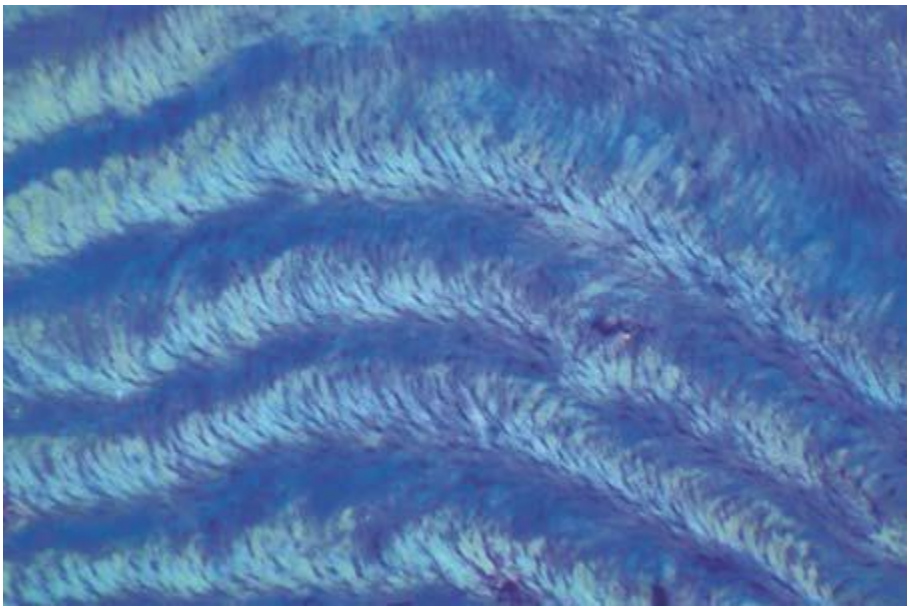
Bone matrix forms 40 to 50% of bone mass, of which 10 to 20% is water. Of its total dry weight bone,[49]

- 60-70% formed by inorganic (minerals)
- 30-40% by collagen predominantly type 1 but also type 5
- 10-20% by water
- 5% by non-collagenous proteins and carbohydrates

The proportions of all these components of bone varies with age, race, location and metabolic activity status. In a mature bone, the bone matrix is moderately hydrated.[47]

The bone matrix proteins are synthesized by osteoblasts. The newly synthesized tropocollagen gets polymerized to form fibrils which then gets associated to form fibres. In woven (non-lamellar) bone these are irregularly arranged in form of complex interwoven meshwork with strong numerous cross links. In lamellar bone these will be arranged in regular laminar arrays of parallel collagen fibres.[48, 49]

Picture No:04, Lamellar Arrangement of Collagen Fibres[48]



As described above metric composition as well as manner of organization of matrix constituents defines mechanical properties of bone. Woven bone is typically seen in young fetal bones, rapidly remodeling and fracture healing in adult bones. It is formed by extremely active osteoblasts. Whereas lamellar bone produced more slowly and is well organized and is seen in adult skeleton. Haversian canals are formed by concentric cylindrically arranged lamellae surrounding neurovascular channels in cortical bones producing interconnecting, three dimensional, laminated structure which increases toughness of lamellar bone.[49]

Pluripotent mesenchymal stem cells known as ‘Osteoprogenitor’ cells are present on all bone surfaces. The bone morphogenic proteins (BMP), are growth factors of TGF-β super family, stimulates stem cells to undergo division to produce cells that differentiate into osteoblasts. This process is

initiated and governed by Transcription Factor Core Binding Factor-A1, which activates expression of osteoblast- specific gene. This process of differentiation of Osteoprogenitor stem cells into bone forming osteoblasts is very important for growth, remodeling and fracture union throughout life.[48]

BONE MINERALS

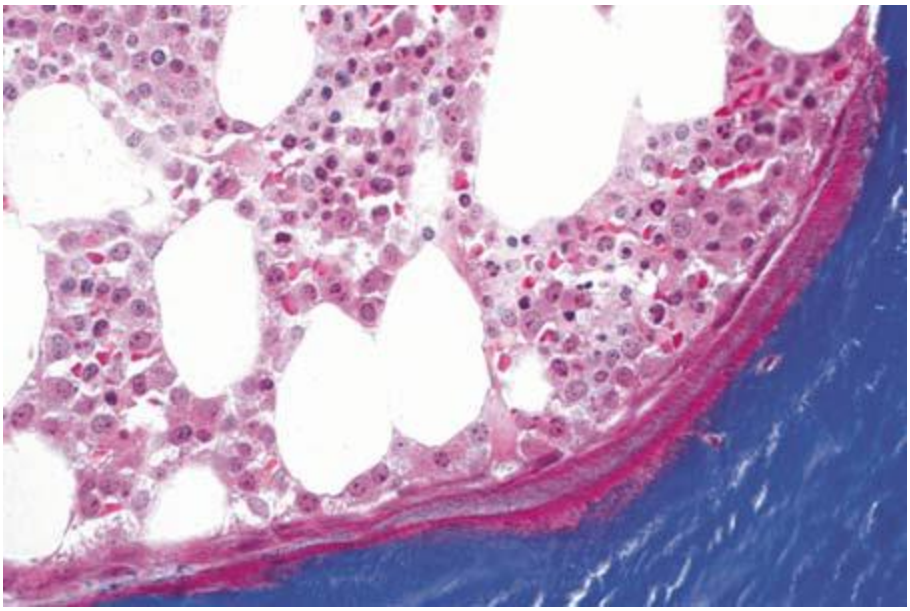
As mentioned earlier inorganic mineral salts in the form of microcrystalline calcium hydroxyapatite 60-70% of total bone dry weight. Bone crystals are too small and are packed closely together in the form of thin plates filling the space between matrix collagen fibre molecules with their long axis almost parallel to fibrils. The mineral part of bone is mostly acid soluble. In cortical bone the lamellae get mineralized in cylindrical osteon form and starting from inside to out. So the mineral concentration is highest in older peripheral lamellae. With aging bone matrix mineralization increases but the bone mass decreases.[26]

The bone mineral contains calcium, phosphate, hydroxyl and carbonate as major inorganic ions. Citrates, Mg^{2+}, Na^{+}, K^{+}, Fl^{-}, Fe^{2+}, Zn^{+}, Cu^{2+}, Al^{2+}, Pb^{+}, Sr^{+}, Si^{2+} and B^{3+} are present in traces.[26]

OSTEOBLASTS

Osteoblasts are basophilic, cuboidal, mononuclear cells containing bundles of actin, myosin and other cytoskeletal proteins which are needed for maintaining shape, attachment and motility of the cell. They are derived from mesenchymal originated Osteoprogenitor stem cells present in bone marrow. In adult bone they are located on endosteal surface where they are arranged in a mono layer rather than on periosteal surface. They play an important role in synthesis, deposition and mineralization of extracellular bone matrix. They become osteocytes and remain embedded in matrix.[47]

Picture No: 06, Flat osteoblasts and layers of newly formed osteoid on mineralized bone[48]



Osteoblasts show many plasma membrane extensions to neighbor cells to facilitate coordination of ground cells activities. Functionally and structurally osteoblasts are typical protein secreting cells. They synthesize collagen and many glycoproteins such as[26, 47, 48, 49, 50],

- **Osteocalcin** - It is needed for bone mineralization and it binds hydroxyapatite and calcium crystals, it can also be used as new bone formation marker.
- **Osteonectin** - It is a phosphorylated glycoprotein and it binds strongly to hydroxyapatite and collagen. It plays vital role in initiation of crystallization. It can also act as cell adhesion molecule.
- **RANKL** - Ligand on cell surface for RANK (Receptor for Activation of Nuclear Factor Kappa B). It is an osteoclasts progenitor receptor.
- **Osteoprotegerin (OPG)** - It restricts osteoclast differentiation being a soluble, high affinity decoy ligand for RANKL.
- **Biglycan and Decorin** - These are proteoglycans which attracts water. Decorin also binds TGF-β.

- **Bone Sialoproteins, Osteopontin and Thrombospondin** - These molecules binds to osteoclast integrins and mediate adhesion of osteoclasts to bone surface.
- **Proteases** (E.g. - Alkaline Phosphatase [ALP] and Pyrophosphatase) and **Protease inhibitors** - These are stored in the form of membrane bound vesicles and on release into newly formed osteoid, they initiate hydroxyapatite crystal formation. ALP is detected in blood in conditions with high bone turnover.
- **Growth factors (BMP and TNF-β)** - Acts as coupling factor and stimulates new bone formation at resorption site.

Osteoblasts play a vital role in the hormone regulated bone resorption. They express receptors for 1, 25- Dihydroxy Vitamin D_3 and parathyroid hormone (PTH) and get activated. Then they express RANKL which binds to RANK on immature osteoclasts promoting osteoclast differentiation in response to PTH and down-regulate Osteoprotegerin which deactivate RANKL. When bone deposition is favored osteoprotegerin is secreted and blocks RANKL, thus restricting Osteoclast numbers.[49]

Genetic studies on osteoblasts differentiation and function identified involvement of several key genes. Each key genes and their roles are as below,[26]

- **RUNX2** - It is classically described as ‘master regulator of osteoblastogenesis’. It’s plays key role throughout induction, proliferation and differentiation of osteoblasts and also regulates many genes expression. It is also known as ‘Core-binding factor A1(CBFA1)’. Its expression is regulated by many factors mainly BMPs. They are also seen on chondrocytes. It regulates many osteoblast proteins including osterix, osteopontin, sialoprotein, collagen type 1, osteocalcin and receptor activator of RANK ligand.[51]
- **Osterix** - Also known as Sp7, Osx, it is a zinc finger transcription factor. These are expressed on osteoblasts and Runx2 gene is believed to influence it. Mice with absent Osx die at birth as bones fails to mineralise.[51]
- **ATF4** – This being a substrate for RSK2 kinase, has a positive role in osteoblast formation. Recently it was found to also regulate energy metabolism also via osteocalcin and leptin pathway.[51]
- **SMADs** - SMADs interact with DNA and associated transcription factors in mesenchymal cells to direct them into osteoblastic lineage through Runx2 induction.[51]
- **NFATc1/Calcineurin** - It is a transcription factor and plays a key role in osteoclastogenesis. Few studies noted that Calcineurin inhibitors

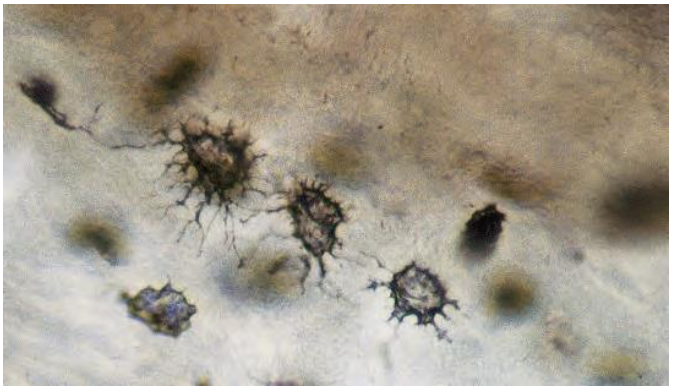
suppress resorption and increase bone mass resulting in osteopenia. Calcineurin also promotes T cell development.[51]

- **Twist** - Twist is a type of basic transcription factor for helix-loop-helix loop which regulates many cell type differentiation. It antagonizes osteoblastogenesis by binding and inhibiting Runx2 DNA.[51]
- Many other genes such as AP-1, Tcf7, zinc finger proteins also regulate osteoblastogenesis and thus bone formation[51].

OSTEOCYTES

Osteocytes are predominant cell type arranged in complex cellular network formed by numerous interconnecting dendritic processes and are distributed uniformly throughout the matrix of mature bone. These are products derived from osteoblasts enclosed within rigid matrix. They don't have ability to multiply or to secrete new matrix. But these osteocytes retain contact with neighbor cells and cells at surface of bone throughout their lifespan.[51]

Picture No:07, Osteocytes In Lacunae[95]



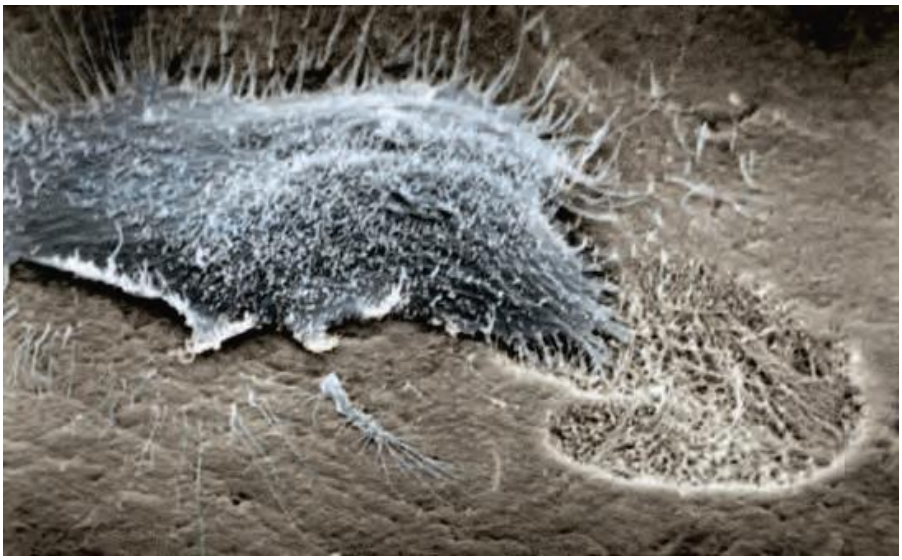
The mature and relatively inactive osteocytes are ellipsoid in shape and are arranged with long axis parallel to surrounding lamellae. At the tip of dendritic process, they possess numerous fine branching which forms gap junctions with adjacent cells to maintain electrical and mechanical continuity. They respond to PTH and 1,25$(OH)_2$ Vitamin D3. The average lifespan of osteocytes is measured in years and varies depending on the metabolic activity of bone. Dead osteocyte might form matrix which might get resorbed by osteoclast activity or they often get mineralized. They are also responsible for mineral exchanging between adjacent bone matrix.[47]

OSTEOCLASTS

Osteoclasts are large polymorphic cells with closely packed nuclei up to 20 in number. Osteoclasts are differentiated by macrophage colony forming unit originated from myeloid stem cells. The key factors regulating this differentiation are macrophage colony stimulating factor synthesized by osteoblasts and RANKL expressed on osteoblasts. By this it is understood that osteoclasts formation and function are regulated by osteoblasts. The mononuclear macrophage precursors join to form differentiated multinuclear osteoclasts. Concept of 'osteoclasts differentiation inhibitors' has promoted effective mode of management for

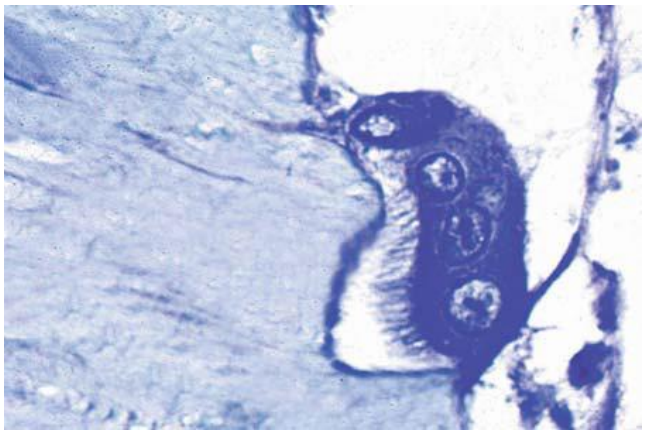
osteoporosis, rheumatoid arthritis, Paget's disease, osteosarcoma and periodontal disease.[48, 49, 52]

Picture No:08, Rabbit Osteoclast Actively Resorbing Bone[49]



They are present in close contact with surface of bone in Howship's lacunae (resorption bay). Osteoclast cytoplasm is rich in mitochondria and acid phosphatase positive lysosomal vacuoles. Sealing zone is a 'well-defined actin filament and associated proteins' zone between ruffled border of plasma membrane folds in resorption bay.[48]

Picture No:09, Active Osteoclast with Ruffled Border[48]



Most important function of osteoclasts is removing local bone during the process of bone growth and remodeling. They release proton and create an acidic environment to dissolve bone minerals and secrete lysosomal enzymes (cathepsin K) and non-lysosomal enzymes (collagenases) to remove organic matrix. [49]

Bone resorption by osteoclasts will be,[48, 49]

- Stimulated by - Local factors such as signals from osteoblasts, cytokines from macrophages and lymphocytes.
  - Parathyroid Hormone
  - 1,25 Dihydroxy Vitamin D_3 (Calcitriol)
- Reduced by Calcitonin which is secreted by C cells of thyroid follicle.

Factors and pathways through which osteoblasts control osteoclast differentiation and activity -[26, 52]

- RANK ligand expressed on immature osteoblasts and stromal fibroblasts, binds RANK receptor on immature osteoclasts during cell-cell interactions. Thereby they stimulate osteoclast differentiation and activation.
- Osteoprotegerin, a soluble decoy receptor of RANKL
- Many cytokines such as Interleukins 1, 6 and 11, Interferon β (IFN-β)

- Growth factors such as TNF
- Most of the hormones that influences osteoclasts acts through M-CSF and RANK L signaling of osteoblasts.
- PTH, 1,25 Dihydroxy Vitamin D3 influence (increase) osteoclast cell population and function only through osteoblasts.
- Estrogen also decreases osteoclasts number and activity via osteoblasts.
- Calcitonin acts directly on Osteoclasts where it binds receptor present on basal surface and directly inhibit its function.
- Glucocorticoid up-regulates RANKL and reduces OPG expression by osteoblasts leadings to increase in RANKL/OPG ratio which promote osteoclasts differentiation and activity. It also acts directly on osteoclasts and down-regulates IFN-β which is inhibitor of RANKL, leading to increased osteoclastogenesis.

As mentioned earlier osteoclastic bone resorption takes place in Howship's lacunae (resorption bay), where osteoclasts are attached in close contact to bone surface through a specific αvβ3 integrin to

osteopontin like components of bone matrix. After forming a tight seal like an extracellular lysosome osteoclasts secrete protons, chloride and proteinases into the confined space. This will demineralize the matrix and collagenases and other proteases that act in low pH like cathepsin K will resign the matrix.

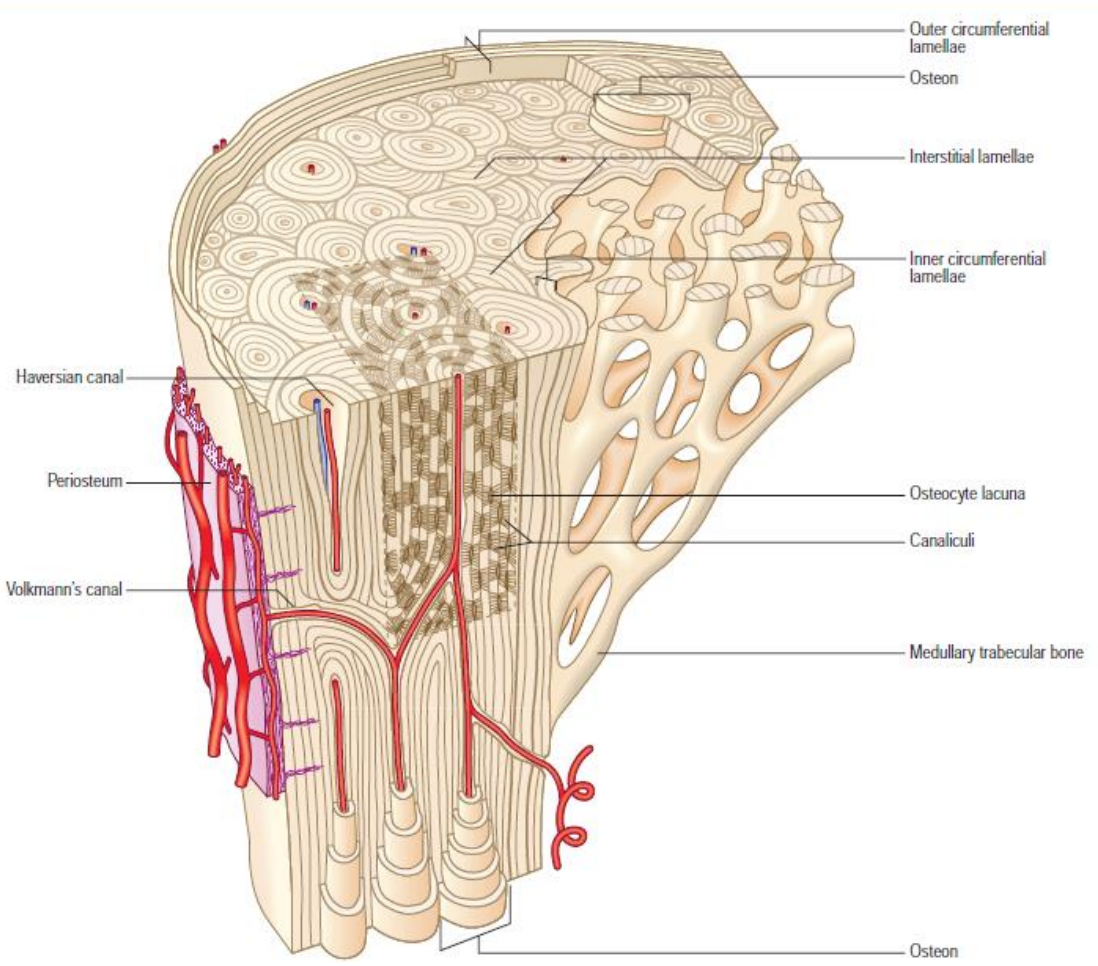
CORTICAL BONE

Cortical bones are compact bones formed of 'Haversian System' or 'Osteons' which are cylindrical structural and functional units of bone. Osteons are formed by ellipsoid osteocytes arranged in circular pattern parallel to lamellae with Haversian canal at centre. The Haversian canal contains 1 or 2 capillaries surrounded by basal lamina, they also contain few unmyelinated axons. They measure mean diameter of 50 µm and larger canals will be near marrow cavity. They communicate among each other and with marrow cavity through nutrient channels called Volkmann's canals. These channels run perpendicular to Osteons and join large vessels in periosteum and medullary cavity.[49, 77]

Osteons are estimated to be around 21 million in number and are arranged usually parallel to each other with diameter varying from 100-400 µm and has 5-20 lamellae.[77] They are distinguished from each other by a cement line (reversal line) containing very little or no collagen. Cortical

bone is found in diaphysis of long bones, cortex of metaphysis of long bones. [49, 76]

Picture No:10, Microscopic Lamellar Arrangement Of Cortical Bone[49]



TRABECULAR BONE

Trabecular bone is metabolically very active bone, also known as cancellous or spongy bone are organized basically in lamellar pattern with branching bars and curved plates of trabeculae of varying width, length and thickness. The thick trabeculae are structurally closed to compact bone and might contain small Osteons. As central blood vessels are not seen, osteocytes depend only on canalicular diffusion from medullary arteries for nutrition. The gaps created by trabecular pattern will be filled by marrow and fat. Trabecular bone is found in bones of both axial as well as appendicular skeletons such as vertebral bodies, tarsals, ribs, iliac crest, metaphysis of long bones.[49]

The trabecular bone varies in proportions according to regions as follows,

- Lumbar vertebrae - 75%
- Tarsal bones - 70%
- Proximal femur - 50 to 75%
- Distal radius - 25%

BONE MODELLING

The process of new bone formation by osteoblasts on an existing bone surface without prior resorption (formation modelling), or resorption by osteoclasts (resorption modelling), for altering the shape of bone to adopt bone to change in mechanical loading.[47] Modelling occurs at peak rate during skeletal growth and before reaching peak bone mass but continues at a low rate throughout life. It occurs on subperiosteal, endocortical, and on trabecular bone surfaces. Hence bone modelling is crucial for proper longitudinal and radial growth, cortical and cancellous bone drifts. Skeletal formation begins during first trimester of gestation in two ways,

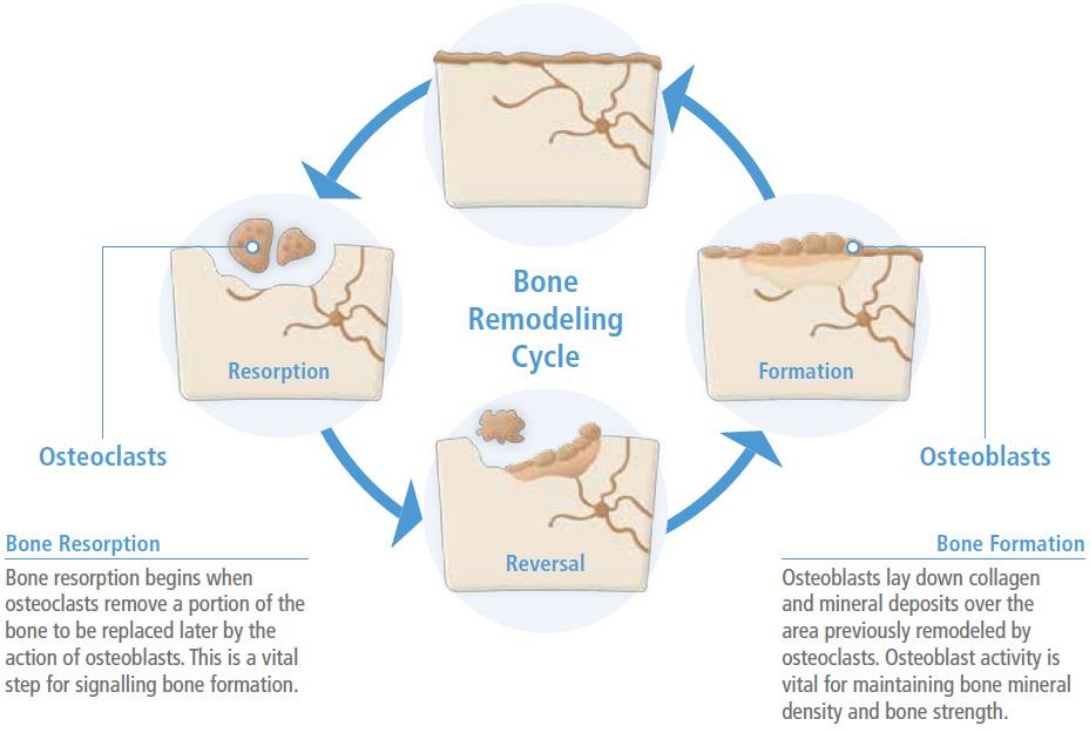
- Intramembranous ossification, which happens in skull, scapula and clavicle.
- Endochondral ossification, where bone is formed on hyaline cartilage template secreted by chondrocytes and is mineralized. Major variety of ossification seen in other bones except those mentioned above.

Normal growth and maintenance of bone needs vigorous mechanical loading, adequate dietary intake and adsorption of calcium, phosphorus, Vitamin A, C and D, a balance among Growth Hormone from pituitary, Thyroid Hormone from thyroids, Estrogen and Androgens from gonads.

BONE REMODELING

Bone is a stiff material and is vulnerable to damage during repeated stress loading like other non-biological stiff materials. Bone periodically renews itself by a process called ‘bone remodeling’ to manage damage due to these stress. Remodeling results in newly replaced matrix which might or might not be same as old in volume and orientation. It involves balanced bone resorption (osteoclastic activity) and deposition (osteoblastic activity). It is advantageous to adopt bone mass and micro architecture to prevailing mechanical demands. Its primary intention is to renew bone rather than increasing bone mass. The process of remodeling continues throughout life causing approximately 10% of bone replace each year.[21, 49]

Picture No:11, Bone Remodeling Cycle[21]



Remodeling is believed to be of two types as proposed by Harold Frost in 1960s, they are, [48]

- **Targeted Remodeling** - It occurs in an injured bone in response to local stimulus such as micro damage or osteocyte apoptosis to restore healthy viable bone.
- **Non-targeted Remodeling** - Also known as stochastic remodeling. Occurs as a random process in healthy bone likely to play role in calcium homeostasis. Acute demand for Ca^{2+} involve osteoclasts mediated resorption whereas chronic demand results in secondary hyperparathyroidism, increased remodeling and loss of bone tissue.

The remodeling process is divided into 5 stages: activation (10 days), resorption (21 days), reversal (5 days), formation (90 days - 1 year) and quiescence stages (unknown duration).

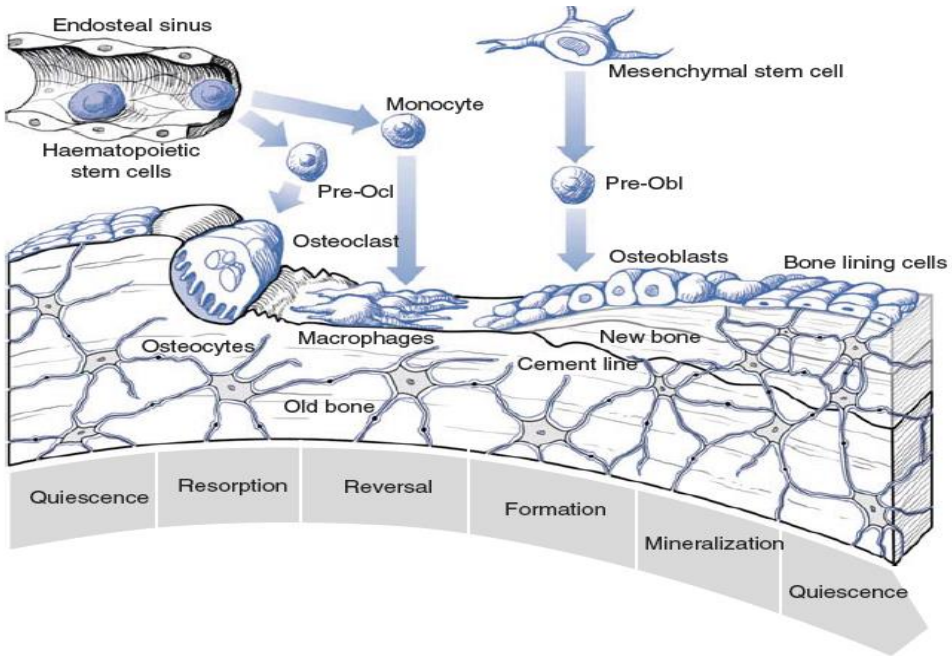
Internal remodeling of bone provides young Osteons for mineralization and it depends on resorption and formation. A remodeling unit formed of an advancing cutting cone which consists of activated osteoclasts and closing cone that consists of osteoblasts and osteocytes. Osteoclastic cutting cone creates a cylindrical tunnel of bone called ‘resorption canal’ and advances the tunnel ahead of a central growing vessel. Osteoclasts are followed by osteoblasts which secretes new osteoid

and fill the space from walls of tunnel. As the process progress layers of bone are deposited one over the other (new layer over old layer) and cohorts of osteoblasts gets embedded as osteocytes in the secreted matrix till it is most central layer is close to vessel.

The osteoblasts will be in concentration of around 4000 per mm^2. The border between resorptive cutting cone and not remodeled bony matrix is marked by cement line (reversal line). Interstitial lamellae between new osteon will be formed by remnants of lamellae of old osteons.

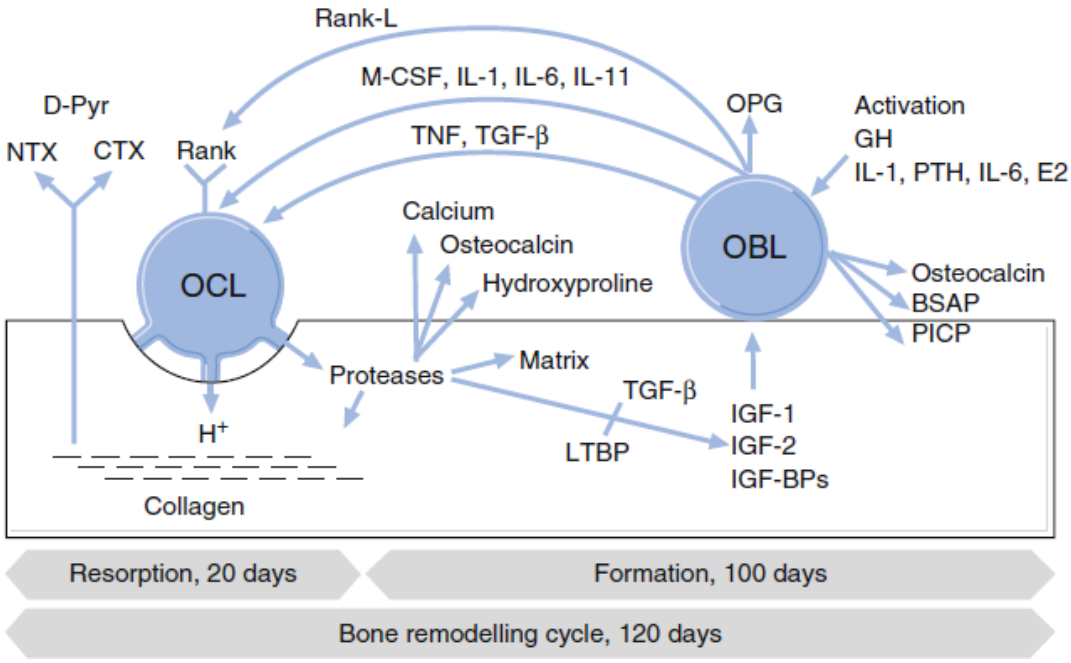
Compact bone undergoes both modelling (bone formation and resorption occurring separately independent of each other at different sites) and remodeling (sequential coupled bone resorption and formation occur at same site).

Picture No:12, Stages of bone Remodeling In Adult Trabecular Bone[48]



FACTORS AFFECTING BONE FORMATION AND RESORPTION

Picture No:13, Factors Controlling Bone Formation and Resorption[48]



Site of remodeling occurring in normal skeleton is determined based on mechanical stimuli and areas of micro damage. Increased remodeling may be in response to local or systemic inflammatory cytokines release like Interleukin-1(IL-1), and TNF in inflammatory diseases.

Many cytokines have dual effect in remodeling, i.e. stimulation of bone resorption coupled with an inhibition of formation. Calciotropic hormones such as PTH and 1,25 $(OH)_2$ Vitamin D_3 have dual activation and acts together to mobilize calcium for plasma calcium homeostasis and also to stimulate bone remodeling.[53]

Bone remodeling is also up-regulated by thyroid hormone and growth hormone and down-regulated by estrogen, androgens and calcitonin. Bone remodeling and bone mass are regulated by numerous systemic factors in response to variations in pubertal maturation and growth, dietary intake, body mass and composition including fat and also for regulating serum calcium and phosphate homeostasis.[49, 53]

The central nervous system regulates remodeling by releasing growth hormone which triggers liver to produce insulin like growth factor-1 which stimulate bone formation, and it also exerts direct effects on remodeling specifically at periosteal surfaces. It also mediates trabecular bone formation via Adipocytic hormone leptin, which lower trabecular bone mass by inhibiting trabecular bone formation and stimulating bone resorption via beta-2 adrenergic receptors relay. In contrast to above, leptin via beta-1 signaling may increase mass of cortical bone by stimulating cortical bone formation.

Estradiol(E2) secreted by ovaries and through aromatase mediated conversion of androgens, plays a crucial role in maintaining bone mass in males as well as females, and it also inhibits trabecular and endocortical bone remodeling and even periosteal growth but testosterone(T) stimulates bone formation at this level.

Calcium sensing receptors (CaSR) and circulating active vitamins D3 levels regulate level of PTH which intern is important stimulus for bone remodeling but it's basic physiologic role is to maintain serum Ca^{2+} homeostasis. PTH will also stimulates osteoblasts differentiation and survival. Hence it might increase or decrease bone mass depending on levels and duration of exposure. Active form of Vitamin D (Calcitriol) is essential for bone mineralization but it also stimulates bone turnover. Bone remodeling is regulated by immunoreactive growth hormone 2(IGH-2).[48]

Picture No:14, Schematic Representation Of Bone Remodeling[26]

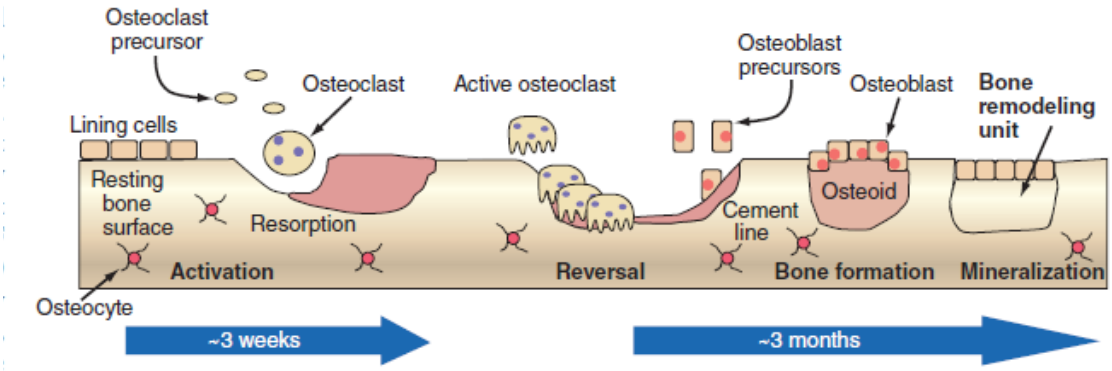


Table No: 01, Systemic & Local Factors Affecting Bone Remodeling[46]

		Stimulators	Inhibitors
Bone formation	**Systemic**	- PTH - PTH Related peptide - Sex steroids - GH: Insulin like growth factor-1 - Thyroid hormone - Leptin	- Glucocorticoids - Leptin - β_2 adrenergic - Serotonin
	Local	- Mechanical stress - TGF- β - BMPs - PDGF - Endothelial growth factor - Insulin-Like growth factors - Fibroblast growth - Prostaglandins - Want-LRPS /LRP6	- Sclerostin - Noggin - Interleukin-1β,7 - Interferon-γ - TNF-α - Dickkopfs
Bone resorption	**Systemic**	- PTH - PTH Related protein - 1,25(OH_2) D_3 - Thyroid hormone - β Adrenergic	- Calcitonin - Sex steroids
	Local	- RANKL - Macrophage-CSF - Granulocyte macrophage-CSF - Interleukin-1,6,7,11,15,17 - Interferon-γ - TNF-α - Fibroblast growth factor - Prostaglandins	- Osteoprotegerin - TGF-β - Interferon-γ - Interleukin-4,10,13,18 - Interleukin-1 receptor agonist

DEFINITION OF OSTEOPOROSIS

Osteoporosis is most common metabolic bone disease characterized by decreased bone strength which is prevalent among postmenopausal women but can also occur in any women and men with major risk factors and conditions associated with demineralization of bone.[54] Bone quality and bone density together forms concept of bone strength.[29] Decreased strength predisposes risk of fractures which in turn causes significant socioeconomic burden with disability, morbidity and mortality.[29]

In these many years many definitions have been given to osteoporosis for explaining the process that results in porous bone, the process of bone mass depletion and various outcome event (fragility fracture).[55]

Standard commonly used definition of osteoporosis is "a chronic progressive systemic skeletal disease characterized by reduced bone mass, reduced bone strength and micro architectural deterioration of bone tissue[1] with consequent fragile bones predisposing to increased risk of sustaining 'osteoporotic fractures' or 'fragility fractures' .[01, 02, 03, 04, 05]

Osteoporosis was also described as a disorder of diminution of bone mass without detectable changes ratio of mineralized to non-mineralized matrix. [56]

A recent definition from the NIH Consensus Development Panel on Osteoporosis is “a skeletal disorder characterized by compromised bone strength which predisposes an individual to an increased risk of fracture”.[57]

It has also been defined as decreased mineral per unit volume of bone. The osseous trabeculae become thin and space between them will increase. If disease continues further a compact bone will get transformed into more porous spongy bone, leading to decrease the total amount of bone tissue. Even with this thinning of trabeculae, histology of bone shows normal mineral content but with marked reduction of cell numbers. But these pathological changes in bone will be associated with normal levels of serum calcium, phosphorus and alkaline phosphatase.

WHO has defined osteoporosis operationally in term of bone density as ‘a condition with bone mineral density value that falls 2.5 standard deviations(SD) below the mean value for young healthy adult of same sex and of same region, this value is referred as T-score of -2.5.[59] The BMD value was evaluated by DEXA scan. WHO gave this definition for postmenopausal women only and not for other women and men.[21, 59]

Table No:02,

WHO Definition of Normal Bone Mass, Osteopenia, Osteoporosis and severe osteoporosis[23,] [60]

Diagnostic Category	Definition	T Score Value
Normal bone mass	BMD < 1 standard deviation below the young adult mean value	> -1
Osteopenia	BMD between 1-2.5 standard deviations below young adult mean value	-1 to -2.5
Osteoporosis	BMD > 2.5 standard deviations below the young adult mean value	<-2.5
Severe Osteoporosis or established Osteoporosis	BMD > 2.5 standard deviations below the young adult mean value with one or more fragility fractures	< -2.5

EPIDEMIOLOGY

Osteoporosis is an highly prevalent generalized bone condition affects a large number of population including both sexes, all ethnic and all age groups but its probability increases as population ages predisposing them to increased risk of fragile fractures.[61] Because of its insidious onset and silent nature, the disease remains undiagnosed and present late with osteoporotic fractures of spine, hip, shoulder or distal end of forearm

leading to significant economic burden, disability, dependency, morbidly as well as mortality. Considering this WHO has recognized osteoporosis as second global health problem next to cardiovascular disease.[21, 62]

There are limited number of studies published that explains worldwide incidence and prevalence of osteoporosis. With the available few small studies it is estimated that worldwide osteoporosis prevalence is more than 200 million with 9 million fragility fractures reported yearly at a risk of 1 in 3 women and 1 in 5 men developing fragility fractures in their whole life.[34, 63] Worldwide osteoporosis affects 1/10th of women aged 60 years, 1/5th of women aged 70 years, 2/5th of women aged 80 years and 2/3rd of women aged 90 years.[64, 65] National Osteoporosis Foundation (NOF) has estimated in 2016 in US as around 10.2 million populations were osteoporotic and additional 43.4 million were having osteopenia and more than 2 million osteoporotic fractures reported in US of which 70% are in females. In Europe 30% of postmenopausal females are found to have osteoporosis with prevalence among total population aged above 50 years is 14% with men : women ratio of 4:1.[66]

According to WHO published statistics one out of three women and one out of eight men in India are osteoporotic among population above 50 years of age. It is estimated in few studies that more than 61 million Indians are osteoporotic of which 80% are females.[07] Many small studies among women in India on prevalence of osteoporosis suggests that

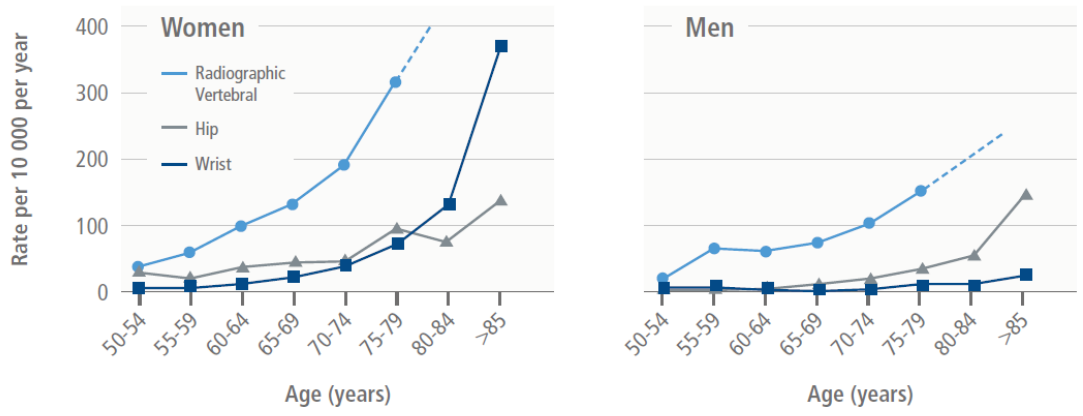
prevalence of osteoporosis is following rising trend likely because of increasing longevity leading to increased population of senior citizens. At present in India life expectancy is around 67 years and is expected to rise to ~71 years by 2025, to 77 years by 2050.[67] At present the population older than 50 years in India are about 10% and the number is likely to go up to 34% by 2050.[15, 68] At present 23.5 crore Indians are expected to be above 50 years of age, of which 20% are osteoporotic with prevalence of 8% to 62% in Indian women of different age groups making India the largest affected country in the world.[15, 69] The prevalence is raising at an alarming rate without being recognized as national and public health priority by the medical fraternity and lack of awareness among general population.[66, 70]

Chronic low back ache is the earliest and most common clinical feature of osteoporosis, but it's not being noticed and diagnosed. Hence major number of cases are presenting to health system with fragility fractures. Most common fractures seen in osteoporotic patients are vertebral compression fractures followed by hip fractures.[18] International Osteoporosis Foundation recently mentioned in age above 50 years,1 in 3 women and 1 in 5 men in their lifetime will experience osteoporotic fractures considering worldwide.[19] Each year worldwide approximately 16 lakh hip fractures are being noted and the number is expected to reach 45 to 63 lakh by 2050.[14] Hip fractures cause limitation of ambulation, chronic

pain, disability, dependency and reduced quality of life and even mortality is noted with rate up to 24% - 30% within a year of fracture. [11, 72]

Vertebral fractures are the most common osteoporotic fractures followed by hip fractures worldwide. They occur in 30-50% of all patients with osteoporosis. Total around 5,50,000 vertebral fractures are being reported per year in US. In contrast to hip fractures 2/3rd to 3/4th of total vertebral fractures are clinically silent are not being treated.[66] About 80% of patients with osteoporotic fractures are not being evaluated and treated for cause of the fracture i.e. osteoporosis.[73] The risk of fractures increases to 86% in presence of history of prior osteoporotic fractures. Hence it need a serious attention to evaluate and treat osteoporosis in cases presented with fragility fracture.[34]

Graph No:03, Worldwide Incidence of Osteoporotic Fractures.[21]



Osteoporosis in males is being recognized as major public health problem. After 50 years of age 1 in 3 fragility fractures are being noted in men. Few studies have noted morbidity and mortality in is higher (37.5%) in men with osteoporotic fractures than women.[74]

Screening for osteoporosis is recommended for males above 70 years of age. In US population total 2.8 million males are suffering from osteoporosis. In Indian population 25 million males are above 65 years of age and considering incidence rate 25000 hip fractures are expected every year.

ETIOPATHOGENESIS

Osteoporosis is a result of bone loss due to age related changes, extrinsic and intrinsic factors that affect bone remodeling process. Low peak bone mass which is caused by gender, genetic factors, nutrition and lifestyle during growth increases probability of being affected by osteoporosis.

Hereditary factors have found to de 60-80% determinant factors for bone density and size. But association studies on candidate genes for osteoporosis were inconsistent in successive generations. A genetic locus on chromosome 11 is found to be associated with high bone mass in many linkage studies. Functional mutation in LRP5 gene is found to stimulate

osteoblasts formation and activation, as well as reduce life span and activity of osteoclasts through Wnt signaling pathways. Supporting this nonfunctional mutation in LRP5 genes have resulted in osteoporosis.[26, 62]

The role of RANK ligand secreted by osteoblasts, RANK receptors on osteoclasts and Osteoprotegerin in remodeling is very important for understanding pathogenesis of osteoporosis and it has been already discussed in physiology of bone remodeling. It has been observed that estrogens, nutrition (specifically Calcium) and physical activity plays pivotal role in regulating secretion of OPG as well as RANKL.[26, 78]

The resolved bone usually will be replaced by equal quantity of newly formed bone in young adults maintaining constant peak bone mass after it is achieved. After 30-45 years of age the balance between resorption and formation of bone will be lost and resorption exceeds formation. Age at which this imbalance starts also varies between individuals and different skeletal sites. It will get exaggerated in women during and after menopause.[26, 79] Excessive bone losses could be due to either increased osteoclastic activity or reduced osteoblastic activity. Increased frequency of remodeling, which increases number of remodeling sites, also can magnify minimal imbalance occurring at each remodeling units. Increased number of bone remodeling sites will produce only reversible reduction of bone tissue but can also cause permanent loss of tissue and disruption of bone architecture. In cancellous bone when osteoclasts penetrate

trabeculae, osteoclasts won't leave template for formation of new bone consequently leading to faster bone loss and impairment in cancellous connectivity caused by high number of remodeling sites. [26]

In cortical bones high activation of remodeling causes porous bone. Biomechanical strength of long bones is reduced because of decreased deposition of newly formed bone over periosteal surface also coupled with more resorption of endocortical surface leading to cortical thinning. This process of reduced strength and disordered skeletal architecture in osteoporosis increases individual's risk of fragile fractures. [26]

The average bone loss per year after negative remodeling starts is 0.5% and is an unavoidable consequence of ageing. It happens predominantly in sites containing abundant cancellous bone like vertebral body and femoral neck. The amount of bone loss occurs in each cycle of remodeling shoots up during and after menopause. Hence women will be usually vulnerable to osteoporosis and its complications.

Pathophysiology of Postmenopausal and Senile Osteoporosis: In elderly age bone metabolism in bone cells and bone matrix will be significantly affected by ageing changes. Replicating and biosynthetic potential will be reduced in osteoblasts of elderly individuals compared to younger ones.[61] Proteins bound to ECM like growth factors, which stimulates replication of osteoprogenitor cells and osteoblastic synthetic

activities lose their biological potency over age, resulting in a bone which is populated with bone forming cells of diminished capacity to form bone. This type of osteoporosis occurring over age is called as low turnover variant, '**senile osteoporosis**'.[26]

In many animal experimental studies, it is noted that there is increased rate of bone loss in case of reduced **physical activity**. In long term bed ridden or in paralysis patients more bone loss is seen in area of absent or reduced physical activity only and is attributed to the fact that mechanical forces produced during locomotion are essential stimuli for physiological bone remodeling. Supporting this a drastic reduction in bone mass is also observed in astronauts who are subjected to zero gravity environment for long time and higher bone density and low fracture risk in athletes and rural population who are involved in high physical activity. Physical activity during active physical growth is very crucial for achieving high peak bone mass. As mentioned earlier expression of LRP5 gene stimulates osteoblasts activity is stimulated by physical activity. [26]

The **candidate genes** for osteoporosis controlling Vitamin D receptor, type 1 collagen, estrogen receptor, IL-6 and IGF-1 plays a very important role in pathogenesis of osteoporosis specifically senile osteoporosis. The inherited Vitamin D receptor molecules plays 75% role in achieving maximum peak pone mass. [98, 99]

Hormonal Deficiency: After attaining menopause yearly loss of bone mass will occur at rate of 2% in cortical bone and 9% in cancellous bone. Women lose up to 35% of cortical bone and 50% of cancellous bone in 30-40 years after menopause. As the serum estradiol and estrone levels decrease by about 15% and 35% of premenopausal level respectively and even serum testosterone level drops after menopause but to a lesser extent. Postmenopausal bone loss is mainly due to deficiency of estrogen and estrogen replacement has shown to protect from osteoporosis. The effect of estrogen on bone loss as already described, low estrogen results in increased release of IL-1, IL-6 and TNF by monocytes and marrow cells. These cytokines are highly potent in stimulating osteoclasts recruitment and activity by elevating levels of RANKL and RANK receptors. Estrogen also possesses direct effect on osteoclast lineage cells. With osteoclast stimulation compensatory osteoblast activity also occurs but at a slower pace causing high turnover osteoporosis.[26]

The causes of secondary osteoporosis are now gaining increased importance. One such important cause is prolonged glucocorticoid(GCs) therapy leading to potentially severe osteoporosis and increasing fracture risk. This adverse event of GCs long term use develops rapidly and is both duration and dose dependent. They increase bone resorption and reduce bone formation in both cortical and cancellous bone. Hence administration

of bisphosphonates has to be considered in all high risk patients while starting on long term GCs. [81]

The specific abnormalities in hormonal and genetic conditions are important in defining two subtypes of age related osteoporosis.[48]

Type 1 osteoporosis: It is seen in hypo gonadal women or men. Increased bone loss directly due to loss of gonadal function is seen in postmenopausal women, women had premature amenorrhea, men following castration and men with testosterone deficiency. Loss of estrogen causes increased osteoclastic activity through increased serum cytokines levels predominantly in trabecular bone. Hence these patients present with fractures in sites where trabecular bone is predominant, such as neck of femur, distal radius or vertebral bodies.

Type 2 osteoporosis: It is associated with normal ageing process of the individual and typically in men and women of above 60-70 years of age. In otherwise normal individual also ageing leads to reduced replicating and biosynthetic potential in osteoblasts and its supply also will decrease gradually but not with increased osteoclasts activity. There happens net loss of bone, but here by decreased formation and not by increased resorption. This group will have high risk of cortical bone fractures like femur, proximal tibia and pelvis.

The trabeculae of vertebrae in young females are typically arranged in form of dense three dimensional matrix with horizontal trabeculae are

positioned at frequent intervals between dense vertical trabeculae. With ageing generalized thinning of trabeculae occurs in both vertically and horizontally arranged trabeculae. The vertical trabeculae will be relatively conserved while horizontal trabeculae thinning will be more pronounced. As bone loss progresses the thinning of horizontal trabeculae leads to perforations, micro fractures with loss of trabecular connectivity, leading to compromised overall bone quality with reduced bone strength to resist the loading forces of gravity and physical activity. Thus the susceptibility to fracture will increase, particularly vertebral fractures.

In osteoporosis bones with low tensile strength will be significantly more susceptible to low energy trauma fractures. The quality and strength of bone present for mechanical support will fall short of withstanding threshold stress (‘fracture threshold’) and predisposes to fractures. As mentioned earlier bone loss affects both cortical and trabecular bone but trabecular variant loss will be more predominant is classical of postmenopausal osteoporosis. [82]

Other Factors Playing Role in Pathogenesis of Osteoporosis:

Calcium Nutrition: Peak Bone Mass will be affected by insufficient calcium and other nutrients intake during growth period predisposing to risk of osteoporosis in later life. In adults calcium deficiency triggers PTH causing secondary hyperparathyroidism which on long term exerts

detrimental effects on skeleton by increasing remodeling rates and imbalance between rates of resorption and formation at remodeling place leading to accelerated net bone loss. RDA of Calcium is 1000 - 1200 mg for adults. Daily total Calcium intake of <400 mg is detrimental to skeleton. [82]

Vitamin D: Deficiency of Vitamin D also leads to secondary hyperparathyroidism predisposing to risk of osteoporosis. The population living in temperate and polar regions and those using UV blocking lotions, dark skinned individuals are at higher risk. It advisable to supplement 800 - 1000 Units/day particularly in those avoiding sunlight and using UV blocking lotions.[83]

Chronic Disease: Various genetic and acquired conditions are associated with high risk of getting osteoporosis. Mechanisms causing bone loss will be unique in each condition leading to net bone loss and osteoporosis.[53, 84]

Medications: Many medications used in our regular clinical practice have potentially detrimental effects on bones, glucocorticoids are most commonly used among them. Other medications causing bone loss are Anticonvulsants, Immunosuppressant (cyclosporine and tacrolimus), aromatase inhibitors, selective serotonin reuptake inhibitors, proton pump inhibitors and thiazolidinedione.[26]

Table No:03, Causes of Secondary Osteoporosis[26]

Lifestyle Changes	Genetic Diseases	Endocrine Disorders	Others
Vitamin D insufficiency	Cystic fibrosis	Central Obesity	AIDS/HIV
High salt intake	Glycogen storage diseases	Cushing's syndrome	Amyloidosis
Smoking(Active/passive)	Menkes steely hair syndrome	Diabetes Mellitus	Chronic obstructive lung disease
Alcohol abuse	Osteogenesis imperfecta	Hyperparathyroidism	Congestive heart failure
Immobilization	Riley-Day syndrome	Thyrotoxicosis	Chronic metabolic acidosis
Excessive thinness	Ehler Danlos Syndrome		Depression
Frequent falling	Haemochromatosis	**Hypogonadal states:**	End-stage renal disease
Low calcium intake	Marfan syndrome	Androgen insensitivity	Hypercalciuria
Inadequate physical activity	Parental H/O Hip fractures	Athletic amenorrhea	Post-transplant bone disease
Excess vitamin A	Gaucher's disease	Premature menopause	Idiopathic scoliosis
	Homocystinuria	Hyperprolactinemia	Sarcoidosis
	Hypophosphatasia	Panhypopituitarism	Weight loss
	Porphyria	Anorexia nervosa	
		Turner syndrome	
		Klinefelter's syndrome	
Gastrointestinal Diseases	**Haematological Disorders**	**Neurological**	**Autoimmune**
Celiac disease	Hemophillia	Epilepsy	Ankylosing spondylitis
Gastric bypass	Leukemia & Lymphoma	Multiple sclerosis	Systemic lupus
Gastrointestinal surgery	Sickle cell disease	Muscular dystrophy	Rheumatoid arthritis
Malabsorption	Multiple myeloma	Parkinson's disease	
Inflammatory bowel disease	Monoclonal gammopathies	Spinal cord injury	
Pancreatic disease	Systemic mastocytosis	Stroke	
Primary biliary cirrhosis	Thalassemia	Proximal myopathy	
Medications			

DIAGNOSIS OF OSTEOPOROSIS

History and Clinical Examination:

Low back pain will be the earliest symptom in osteoporosis but diagnosis of osteoporosis is being neglected in patients presented with low back ache. History and clinical examination will not be sufficient for diagnosis of osteoporosis but they can be potential tool for screening the disease burden.

As mentioned earlier osteoporosis is a silent disease and most often presents to health system with Osteoporotic vertebral compression fractures. After suspecting osteoporosis radiological evaluation will be first step in investigating the patient.

Radiographic Changes of Osteoporosis:

Osteoporotic and osteopenic radiological changes appear fist in axial skeleton. Radiological features include:[85]

- Increased radiolucency of vertebrae
- 'Picture Frame Appearance' (empty box): Vertical striations of vertebrae because of reinforcement of weight bearing vertical trabeculae and resorption of non-weight bearing horizontal trabeculae giving a framed appearance.
- Ballooning of intervertebral disc leading to biconcave appearance of vertebra

- Schlorml's nodes: Due to herniation or protrusion of intervertebral disc into vertebral bodies.
- Thinning of vertebral endplates.
- Evidences of compression fractures: Genant has given a grading scheme based on reduction of vertebral height, based on which 'Spinal fracture index' (SFI) is calculated. SFI is a semi quantitative assessment of deformity and is calculated as sum of grades of all vertebra divided by number of vertebral bodies evaluated.
- Evidences of insufficiency fractures also can be seen in radiography.

Table No:04, X Ray Grading of Spinal Osteoporosis by Saville(1967) [85]

Grade	Radiographic Appearance Of Vertebra
0	Normal bone quality
1	Minimal loss of bone density; Endplates starts to stand out giving stencilled effect
2	Vertical striations are more obvious; Endplates are thinner
3	Bone density loss more severe than grade 2; Endplates becoming less visible
4	Ghost like (Box like) vertebral bodies; Density is similar to soft tissue; No trabecular pattern is visible

ASSESSMENT OF BONE MINERAL DENSITY

Many tests have been devised to assess Bone Mineral Density on the basis of the fact that osteoporosis is known to be associated with low bone mass. The WHO has produced classification and diagnostic guidelines for osteoporosis, based on BMD measurements. Although osteoporosis that is sufficiently advanced can be visualized on plain radiographs, BMD must be decreased by approximately 50% before this is possible. Therefore, an apparently normal appearing plain radiographs cannot exclude osteoporosis. BMD measurement hence remains the gold standard for the diagnosis of osteoporosis.[99]

Table No:05, WHO Definition Of Normal Bone Mass, Osteopenia, Osteoporosis and severe osteoporosis[59]

Diagnostic Category	Definition	T Score Value
Normal bone mass	BMD < 1 standard deviation below the young adult mean value	> -1
Osteopenia	BMD between 1-2.5 standard deviations below young adult mean value	-1 to -2.5
Osteoporosis	BMD > 2.5 standard deviations below the young adult mean value	<-2.5
Severe Osteoporosis or established Osteoporosis	BMD > 2.5 standard deviations below the young adult mean value with one or more fragility fractures	< -2.5

The ability to measure BMD has been one of the most significant advances in investigation and management of osteoporosis because BMD strongly correlates with bone strength. Variation in the level of BMD accounts for 60% to 80% of bone strength, but it is crucial to realize that bone strength not only depends on the amount of mineral measured by current techniques but also on the structural characteristics of the skeleton such as size, shape, and three-dimensional architecture.

Table No:06, Methods available to measure Bone Mineral Density[84]

Ionizing	Radiation	Non-Ionizing Radiation
Gamma- Radiation	X-Ray	
Single Photon Absorptiometry (SPA)	Radiogrammetry	
Dual Photon Absorptiometry (DPA)	Single X Ray Absorptiometry (SXA)	Ultrasound
Neutron Activation Analysis (NAA)	Dual X Ray Absorptiometry (DXA)	Magnetic Resonance Imaging
Compton Scattering Technique	Quantitative Computed Tomography (QCT)	

DUAL-ENERGY X-RAY ABSORPTIOMETRY

In the mid-1980s the radionuclide sources of Single-Photon Absorptiometry and Dual-Photon Absorptiometry scanners were replaced with low-dose X-ray tubes. These had a higher photon flux and so allowed faster scanning (10–15 min) and improved spatial resolution that allowed better image quality.[48]

The scanners use a constant potential X-ray source, combined with a rare earth filter with energy specific absorption characteristics due to the k-edge of the atomic structure of the element. The k-edge filter separates the X-ray distribution into two separate components of 'high-energy' and 'low-energy' photons. [13]

The original DEXA scanners used a pencil X-ray beam and a single detector, and scanned in a rectilinear fashion across the anatomical site being examined. Newer technical advancements include fan-beam X-ray sources and a bank of detectors. This allows faster scanning (approximately 1 min per site; similar times for whole body scans) with improved image quality and spatial resolution. Lateral scanning enables views to be obtained of the vertebrae in the thoracic and lumbar spine. From these, assessments for vertebral fracture can be made. DEXA can be applied to sites of the skeleton where osteoporotic fractures occur; in the central skeleton this includes the lumbar spine (L1–4) and proximal femur (total hip, femoral neck, trochanter, and Ward's area). DEXA can also be

applied to peripheral skeletal sites (forearm and calcaneus), using either full-sized or dedicated peripheral, and DEXA scanners. Central DEXA measures of lumbar spine, femoral neck and total hip are currently used as the 'gold standard' for the clinical diagnosis of osteoporosis by bone densitometry.[13, 48]

The measurements provided by DEXA are Bone Mineral Concentration (BMC) in grams and projected area of the measured site in square centimeters. With appropriate software whole-body scanning can also be performed, from which can be extracted whole-body and regional bone mineral content (BMC in grams) and whole-body and regional body composition [lean (muscle) and fat mass].

Table No:07, Artifacts that causes overestimation of BMD[48]

Degenerative changes of spine and hyperostosis (osteophytes)
Vertebral Compression Fractures
Paraspinal structure calcification (interspinous ligament, lymph nodes, aortic calcification
Sclerotic metastasis
Vertebral haemangioma
Ankylosing spondylitis
Overlying metals (surgical rods, screws, plates)
Excessive body weight
Strontium therapy
Vertebroplasty, kyphoplasty

Table NO:08, Artifacts causing underestimation of BMD[48]
Laminectomy
Osteolytic metastasis
Low body weight

Interpretation of Results:

When a BMD measurement has been made in a patient, this has to be interpreted as normal or abnormal and a report formulated that will be of assistance to the referring clinician. Age, sex and ethnically matched reference data need to be available. These databases are predominantly, but not exclusively, drawn from a white, Caucasian, American based population. A patient's results can be interpreted in terms of the standard deviations (SD) from the mean of either sex matched young individual PBM called T-score or age matched BMD called Z-score. [48, 86, 99]

The World Health Organization (WHO) has defined osteoporosis in terms of bone densitometry. A T-score of less than –2.5 defines osteoporosis. The definition applied to DEXA measurements made in the lumbar spine, the proximal femur and the distal third of the forearm. The definition is not applicable to other techniques [such as quantitative computed tomography (QCT), quantitative ultrasound (QUS)] or other anatomical sites. In calculating change over time, the absolute BMD values (g/cm2) have to be used. To be statistically significant the change in BMD has to be 2.77 multiplied by precision, in longitudinal studies in an individual patient one needs to leave an intervening period of at least 18–24 months between measures to ensure significant change.[62, 100]

TREATMENT OF OSTEOPOROSIS AND PREVENTION ITS COMPLICATIONS

Bone loss with ageing is inevitable and many will become osteoporotic in later life with increased risk of fracture. Hence measures need to be taken by all to improve bone mass and strength at all ages and to reduce risk of injuries when older. This needs to be at all stages of life. The fundamental management goals for patients who have osteoporosis are to prevent fractures, decrease pain when present, and maintain function.

Prevention of Osteoporotic Fractures

Half of all women and one third of all men are at risk of sustaining a fragility fracture during their lifetime. Increased morbidity, mortality as well as high costs associated with osteoporotic fractures make it imperative to implement prevention strategies in the community. General screening to detect low BMD is not cost effective because a modest deficit in BMD is associated with a low absolute risk of sustaining a fracture.[78]

Non-pharmacological Prevention of Osteoporotic Fractures

Lifestyle Interventions:

Maintaining a bone healthy lifestyle at all ages is an important part of mitigating the expected increase in osteoporosis and fracture.

This includes measures such as

- Adequate dietary calcium
- Adequate vitamin D through diet and sunlight
- Regular weight bearing exercises
- Avoid smoking
- Avoid excess alcohol

Physical activity and exercise

Bone tissue seems to be most adaptive to mechanical load during periods of rapid skeletal change as in the late prepubertal and early pubertal period. Mechanical loading not only increases BMD but also improves bone structure, geometry, architecture, and material properties such as strength, stiffness, and its energy absorbing capacity. Studies have shown that physical activity may increase BMD, skeletal geometry, and bone strength by up to 30 - 50% in those individuals in whom training is initiated before puberty. [61]

Bone tissue is also able to respond to exercise in adulthood although to a lesser extent than during growth. During adulthood physical activity is

more of bone preserving rather than bone building. The exercise-induced bone-preserving effect in adulthood may be of great importance in maintaining bone strength and preventing age related fractures because only a small increase in BMD is associated with a significant reduction in the risk of fracture. Exercise may also cause a reduction in the incidence of fracture through nonskeletal effects.[06]

Brisk walking, climbing up and down stairs and dancing are the most preferred activities for older people since they are easily available and are inexpensive and safe. Exercise should be lifelong if bone strength is to be maintained because cessation of exercise is followed by a rapid decline of the exercise-achieved BMD. Regular impact loading activities that create high magnitude strains and versatile strain distributions throughout the bone structure best improve bone strength. Squash, soccer, gymnastics, tennis, badminton, aerobics, step exercises, volleyball, basketball, weight and power training, and similar sports may best fulfil these demands. On the other, endurance training such as long distance running, swimming, and cycling has not proved as effective in increasing BMD.[06, 61]

Hence, activity programs for the elderly must be designed specifically for each individual and be based on the physical abilities of that person. They should be undertaken with caution and after proper training.

Nutrition:

Normal skeletal health is dependent on a balanced diet with an adequate intake of energy, minerals, vitamins, and proteins. The 1994 consensus conference discussing the optimum calcium intake recommended a daily intake of 1200 to 1500 mg for adolescents 1000 mg for adults up to 65 years of age, and 1500 mg for postmenopausal women not receiving estrogen and for elderly individuals. The positive correlation between dietary calcium and BMD has been shown in children, adolescents, and young women, indicating that higher calcium intake results in a higher BMD.[87]

Calcium absorption is also dependent on the vitamin D level and serum concentrations of 25-hydroxy vitamin D decline with age. The current recommendation is that the daily intake of vitamin D should be about 400 to 800 IU if exposure to sunlight is low, especially in the elderly, who have decreased ability to activate precursors in the skin, decreased ability to hydroxylate vitamin D in the kidney and liver, reduced dietary intake, and diminished absorption from food.

Another problem in frail elderly individuals is achieving an adequate intake of protein, total energy, and a variety of other nutritional components such as phosphorus, magnesium, zinc, copper, iron, fluoride, sodium, and vitamins D, A, C and K, all of which are required for normal bone health.

Pharmacological Prevention of Osteoporotic Fractures

Pharmacological interventions in osteoporosis principally target osteoclasts, osteoblasts, or both. The rationale for inhibition of osteoclasts stems from a number of observations where the most important was the fact that estrogen withdrawal led to increased osteoclast activation and hence blocking osteoclast differentiation and actions seemed essential. Inhibition of osteoclast action leads to a secondary gain in bone mass. Moreover, it has clearly been more difficult to stimulate osteoblasts selectively to obtain a true bone anabolic effect. The pharmacological options available are as follows:

- Calcium and Vitamin D
- Hormone Replacement Therapy
- Selective Estrogen Receptor Modulator(SERM)
- Calcitonin
- Parathyroid Hormone
- Strontium
- Fluoride
- Teriparitide
- Bisphosphonates

Calcium and Vitamin D:

Calcium supplementation of the normal diet increases bone mass in adolescents and reduces bone loss associated with advancing age. It is known to slow the rate of bone loss in the elderly and in individuals with a low calcium intake. Studies also that suggest that calcium supplements may reduce the incidence of fractures, but usually calcium supplementation is regarded as an adjunctive treatment for osteoporosis rather than as a single treatment.

Calcium supplements should be given to all patients who have low calcium intake (less than 400 mg/day), postmenopausal women, the elderly, and patients treated with glucocorticoids. Recommended total calcium intakes for white women (diet and supplementation) is 1000 mg/day for adults, 1500 mg/day for postmenopausal women and women with known osteoporosis, and 1200 mg/day for adolescents.

Vitamin D is also useful in the treatment of osteoporosis. Many studies, including a Cochrane Systematic Database Review, suggests that calcium and vitamin D should be used routinely in elderly individuals living in old people's homes because of a high prevalence of vitamin D deficiency as a result of low intake, low exposure to sunlight, and impaired vitamin D synthesis in the skin.[83, 87]

Some studies have shown that vitamin D3 plus calcium seems to reduce the risk of hip and other non-vertebral fractures by as much as 43%

in elderly institutionalized women. Calcitriol therapy requires careful monitoring of serum and urine calcium levels to avoid hypercalcemia and significant hypercalciuria.

Hormone replacement therapy:

Estrogen is important both for skeletal development and structural maintenance of bone. The balance between bone resorption and bone formation in adulthood is in part dependent on intact estrogen levels, and estrogen withdrawal has been linked to bone loss in the initial years of menopause. Estrogen exhibits its effect on both osteoblasts and osteoclasts through several mechanisms, but action via the estrogen receptors (ER) is probably most important.

The rapidly decreasing estrogen levels at menopause may lead to increased activation frequency that is the number of active resorption sites increase while the capacity to refill the site with new bone diminishes, causing bone loss. By substituting for estrogen loss or manipulating the ER activity, the rate of bone turnover should remain in balance.

A large body of clinical trial data indicates that various types of estrogens (conjugated equine estrogens, estradiol, estrone, esterified estrogens, ethinyl estradiol, and mestranol) reduce bone turnover, prevent bone loss, and induce slight increase in bone mass of the spine, hip, and total body. The effects of estrogen are seen in women with natural or

surgical menopause and also in postmenopausal women with or without established osteoporosis. Estrogens are administered orally or trans dermally.

The major concern for the role of ERT in prevention of osteoporosis and fracture is of increased risk of breast cancer, endometrial cancer, ovarian cancer, stroke, and venous thromboembolism.[124]

Selective Estrogen Receptor Modulators (SERMs) :

Estrogen exhibits agonistic effects only, whereas SERMs have both agonistic and antagonistic effects in tissues responsive to estrogen. These are non-steroidal ligands that produce agonistic effects in bone like estrogen, but antagonistic effects in other tissues such as breast tissue. In addition to the significant antioestrogenic effect on breast tissue from tamoxifen, a pronounced effect was also observed in uterine tissue, but a weak agonistic effect on bone. [26]

Raloxifine acts as a competitive ligand to estrogen receptor by blocking the conformational changes of the receptor, it modulates the gene activation and subsequent protein production. Raloxifine has a four-fold greater affinity for estrogen receptor.

When SERM binds in tissues where a primarily agonistic expression is expected (such as bone for Raloxifine), the receptor-ligand complex acts preferentially via a coactivator enhancing the agonistic effect. When

estrogen receptor-SERM binds in tissues where a primarily antagonistic expression is expected (such as breast for Raloxifine), the receptor-ligand complex acts preferentially via a corepressor enhancing the antagonistic effect.

Raloxifine reduces urinary calcium excretion, conferring a positive calcium balance and decreases bone turnover as assessed by bone markers. It decreases the bone turnover markers by 30 – 40% indicating it act as an anti-resorptive agent. The effect on bone turnover is that of an antiresorptive agent with decrease in levels of bone markers during the first 6–9 months. Raloxifine has been shown to prevent menopausal bone loss, decrease bone turnover to premenopausal levels, and reduce the incidence of fracture.[26]

Calcitonin

Calcitonin is produced by the thyroid C cells. It reduces bone absorption by osteoclast inhibition. The treatment can be provided by subcutaneous or intramuscular injection. The biological effects are mediated via the calcitonin receptor, which is highly expressed in osteoclasts, but also in cells of the central nervous system. Calcitonin suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor. Osteoclasts exposed to Calcitonin cannot maintain their active ruffled border, which normally maintains close contact with underlying

bone. Injectable calcitonin produces small increments in bone mass of the lumbar spine. [26]

Parathyroid Hormone:

The physiological function of parathyroid hormone is to maintain extracellular calcium levels. The effects are either direct on target cells or indirectly mediated through synthesis of 1,25 dihydroxyvitamin D. Serum calcium is closely regulated, with PTH secretion increasing in response to decreasing serum calcium, an effect mediated through the calcium-sensing receptor. PTH induces an activation of the lining cells, increasing the activated bone surface and the recruitment of osteoblasts without prior bone resorption. Furthermore, osteoblast apoptosis decreases, adding to the enhancement of bone formation. However, bone resorption is increased with delay, indicating that normal bone remodeling is increased. [26]

Strontium:

Strontium atoms are adsorbed onto the surface of hydroxyapatite crystals without affecting mineral structure. Later it’s exchanged with calcium in bone mineral and remains in the skeleton for a long time. Deposition in newly formed bone will increase apparent values of bone density, as strontium has a higher atomic number than calcium. Strontium

appears to result in uncoupling of bone remodeling and increases bone formation with inhibiting bone resorption.

It stimulates preosteoblast replication and there is increased matrix synthesis. There is inhibition of osteoclast differentiation and resorbing activity. An increase in trabecular bone mass, trabeculae numbers and thickness with improvement in bone strength is observed. [26]

Fluoride

Fluoride is a mineral that is incorporated into the hydroxyapatite crystal of bone. It stimulates osteoblast recruitment and activity, increases BMD in the spine but less so in the hip. However, controlled trials have failed to show that fluoride reduces fractures. [26]

Bisphosphonates:

Bisphosphonates(BP) are stable synthetic analogue of naturally occurring inorganic pyrophosphate which is simplest form of polyphosphate.[88, 89, 90] This was being used in industries from a century as antiscaling and anticorrosive agents as they inhibit calcium carbonate precipitation. In around 1960s, it was found to be biologically useful as it inhibits effects of osteoclasts and also inhibit calcification of soft tissues after which it revolutionized management of osteoporosis and became most common drug used to manage osteoporosis and prevent osteoporotic

fractures. Initially only challenge was they pyrophosphate was found to be hydrolyzed by gastrointestinal tract phosphatases and ineffective the orally but bisphosphonates like pyrophosphate had high affinity for bone mineral but were effective orally as found in an animal study on rats. Later they were found to inhibit dissolution of hydroxyapatite crystals.[91]

Chemically BPs of clinical interest have two phosphate groups and share a common carbon atom (P-C-P) and both chemical and enzymatic hydrolysis resistant. [93]

Their mechanism in reducing bone turnover is complex and multifactorial with side chains R1(-OH) influencing binding affinity and R2(-NH_2) influencing antiresorptive potency. They have specific affinity for bone and will be deposited in newly formed bone and near to osteoclasts. After absorption they stay in blood for only 30-180 minutes, but once deposited will stay for up to 10 years. The bisphosphonates in the order of their affinity from greatest to least is Zoledronate> alendronate> ibandronate> risedronate> etidronate and clodronate. After depositing on bone they directly affect macrophages, parent cells for osteoclasts and inhibit osteoclast mediated bone resorption and increase osteoclasts apoptosis. They also reduce bone formation by osteoblasts. Thus bone resorption and turnover both are reduced.[92]

They increase bone strength in following ways,[94]

- Reduce remodeling space and repair the cavities created by osteoclasts during resorption.
- Improve trabecular architecture, specifically horizontal trabeculae.
- Decrease cortical porosity.
- Increase mineralization density.
- Maintain osteocytes viability.

The treatment with bisphosphonates increases BMD by acting on osteoclasts in two mechanisms,

- Non-Nitrogen containing BPs - Produces toxic analogs of ATP, it cases cell death of osteoclasts.
- Nitrogen containing BPs - They act by inhibiting an enzyme of 3-hydroxy-3-methylglutaryl coenzyme A reductase pathway called Farnesyl Pyrophosphate Synthase which is key enzyme for Prenylation, leading to failure of anchoring of GTP-Binding proteins to osteoclasts membrane causing reduced bone resorption and accelerated osteoclasts apoptosis. Zoledronate> Risedronate> Ibandronate> alendronate is the order of potency to inhibit farnesyl pyrophosphate.

Recent studies have shown BPs increase serum OPG levels that inhibit osteoclastic activity. Each bisphosphonate has its own unique profile of binding affinity and antiresorptive potency, on which speed of onset, offset of effect, level of reduction of bone turnover, uptake by cortical vs trabecular, type of anti-fracture effect depends and varies.

Oral BPs have very poor bioavailability with less than 1% of oral dose getting absorbed by gut even under ideal circumstances.[89, 93] The reason for poor bioavailability could be its heavy negative molecular charge due to which transport across lipophilic cell membrane is difficult.[93] Hence it is recommended to take it after overnight fast with glass of water followed by post intake fast 30 minutes for alendronate and risedronate or 60 minutes for ibandronate. This is to minimize contact of drug with esophagus and avoid risk of GI side effects. The 50% of absorbed drug binds to bone avidly at active remodeling sites and the remaining is excreted rapidly in kidneys.[91, 94]

Classification: BPs are classified in three ways,

- Based on presence or absence of Nitrogen:
    - Non-Nitrogen containing BPs - Etidronate, Clodronate and Tiludronate

- They will be metabolized to components that replaces terminal pyrophosphate moiety of ATP which is nonfunctional and it competes with cellular ATP Ana hampers cellular energy metabolism leading to osteoclasts apoptosis.

- Nitrogen Containing BPs - Alendronate, Risedronate, Ibandronate and Zoledronate.
  - Acts by inhibiting farnesyl pyrophosphate synthase enzyme.

- Based on route of administration:
  - Oral BPs - Risedronate, alendronate, tiludronate and etidronate
    - Usually taken as weekly dose.
  - Intravenous BPs - Pamidronate and Zoledronate
    - Pamidronate is given as monthly dose, Zoledronate as yearly done.
  - Both Oral and Intravenous - Ibandronate and Clodronate
- Based on potency classified into 3 generations
  - First generation BPs - Etidronate and Tiludronate

    - These have simpler side chains and are least potent, rarely used.
- Second generation BPs - Pamidronate, Alendronate and Ibandronate
    - They have moderate to high potency.
- Third generation BPs - Risedronate and Zoledronate
    - They are highly potent drugs.

Toxicity and Adverse Events: Oral BPs are not well tolerated unless taken as prescribed. Side effects and adverse reactions are rarely severe and are,

- **Gastrointestinal system:** When BPs are given orally, they are known to cause gastric and esophageal disturbances such as gastric acid regurgitation and esophageal damage (reflux esophagitis), gastric mucosal cells damage, nausea, vomiting, stomach ache and diarrhea. Hence specific method has to be followed when BPs are given orally as mentioned above.
- **Acute phase reaction:** These can happen within first 24 hours after first intravenous infusion of amino bisphosphonate. Manifests as febrile illness, bones and joints pain, fatigue,

myalgia and may be associated with raised IL-6 and CRP in blood with lymphocytosis.

- **Hypocalcemia:** It is more common with IV dosing, in presence of Vitamin D deficiency, impaired PTH function, impaired renal function and in Paget's disease. It is seen in 0.2% of patients and usually asymptomatic. Oral Calcium supplement should be given till laboratory values return to normal.[89, 45]
- **Ocular Reactions:** Very rare, but seen in 0.1% of patients, might present with uveitis, episcleritis specifically after Pamidronate.
- **Osteonecrosis of Jaw:** Its association with BPs was first reported in 2003 and defined as a condition with exposed bone in maxillofacial region with no healing within 8 weeks of wound care by healthcare provider. Rare complication (1 in 10000) but most are reported in high done IV BPs given for cancer related bone disease.[89, 97]
- **Esophageal Cancer:** There is no clear evidence supporting association of esophageal cancer and treatment with BPs. But studies in Europe and Japan have shown high incidence of esophageal cancer in patients exposed to Alendronate and other oral BPs.

- **Atypical Sub trochanteric femur fractures:** Many studies published increase incidence of low trauma fractures particularly Sub trochanteric and shaft femur fractures noted in patients on long term BPs (>6 years of alendronate)[94] with 'severe suppression of bone turnover'[08]. Study in 2011 by Yoon et al in US also quoted high incidence of Sub trochanteric insufficiency fractures in patients on long term BPs[35]. But in 2010 FDA has clearly stated 'there is no evidence of connection between BPs and atypical sub trochanteric femur fractures'.[89, 96]
- **Atrial fibrillation:** The possibility of relationship between BPs and atrial fibrillation raised after a study on ZA in PMO was reported in 2007. Though it is very rare but a dreadful complication if occurs.
- **Nephrotoxicity:** Nephrotoxicity has been described in cancer patients receiving rapid IV Zoledronate as monthly dose. Hence renal function parameters have to be checked before giving IV BPs.
- A case report in 2009 has mentioned occurrence of **thrombotic thrombocytopenic purpura** following ZA infusion with a fatal outcome.[46]

Contraindications:

- In patients with **renal compromise** BPs should be avoided or given in modified doses.
- BPs are contraindicated during **pregnancy** and **breast-feeding**.

Clinical Uses: After the discovery of clinical uses of BPs they are in high demand for use in various clinical conditions,

- BPs are drug of choice for osteoporosis and they are very much capable of improving BMD and significantly reduce fracture risk.
- Because of their osteoclastic activity they are being used in Paget's disease of bone.
- They are found to be very much useful in metastatic and osteolytic bone lesions and also in hypercalcemia of malignancy.
- Their basic action of inhibition of calcification or dissolution of calcium is used in many conditions like
    - Fibro dysplasia ossicans progressiva (myositis ossificans) (mainly Etidronate),
    - In post-operative care after total hip replacement to avoid heterotrophic calcification,

- After spinal surgery to avoid ectopic calcification and ossification,
- To prevent dental calculus used in the form of tooth paste,
- Recently its being studied for its effectiveness in treating calcification in renal failure and vascular diseases.

- Because of BPs strong affinity for bone, specifically at sites of high bone turnover and its ability to be linked with a gamma emitting technetium isotope, it is being used in 'bone scanning' for detecting bone metastasis and many other bone lesions.
- BPs (mainly ZA) are found to enhance growth of bone into porous implants.

Zoledronic Acid (ZA): ZA is an highly potent, third generation, nitrogen containing, intravenous bisphosphonate with highest affinity to bone among all BPs. ZA is actually both manufacturers, doctors and patient's dream which has come true. It is administered as an intravenous yearly dose of 5 mg in treatment and prevention of osteoporosis.[42, 94]

It acts by reducing osteoclastic activity by inducing osteoclast apoptosis through a mechanism similar to other nitrogen containing BPs as explained above.

ZA is given as a 5mg single once yearly dose in 100ml normal saline infused slowly over 15-30 minutes. This dose according to many studies have shown to significantly reduce bone turnover and improve BMD after 12 months of infusion in postmenopausal or senile osteoporosis.[42]

It has also been proven that it significantly reduces fragility fracture risk like, [18]

- 70% reduction in vertebral fractures
- 41% reduction in hip fractures
- 25% reduction in other non-vertebral fractures
- 33% reduction in clinical fractures

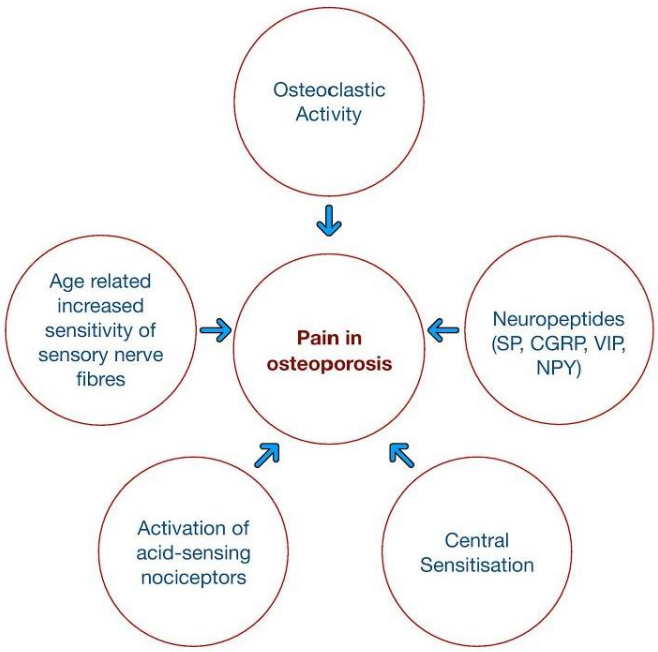
Mortality risk after hip fractures is a major challenge to handle and is about 24% of hip fracture cases and in patients of osteoporotic hip fractures treated with ZA, the risk has reduced by 28% of pre ZA era.

BACK PAIN IN OSTEOPOROSIS

Back pain is the earliest presenting symptom in osteoporosis. Chronic back pain in osteoporosis is caused by multiple factors which are depicted in below diagram. [101]

Picture No:15

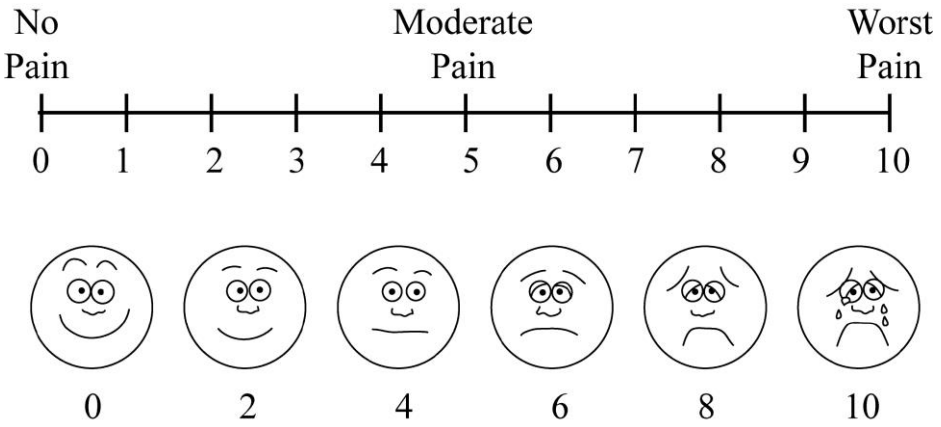
Causes of Pain in Osteoorosis



Visual Analogue Scale(VAS):

A visual analogue scale is unidimensional measure of pain intensity which is being used widely in diverse adult populations. It tries to measure an attitude of pain believed to range across a continuum of values. For example, the pain that a patient experiences ranging across continuum starting from none to an extreme amount of pain. This is a better way of assessing pain as it measures pain as continuous rather than a discrete category such as none, mild, moderate and severe which will not be existed in many conditions. Idea of VAS was designed for measuring it in a continuous scale.[56]

Picture No:16, VAS chart



Operationally VAS is usually a straight line of 100mm placed horizontally anchored by descriptors at each end. The patients are asked to mark on the line at the point corresponds to the perception of their pain at their current state. Then VAS score is determined by distance in millimeters measured from left end of the line to the point that patient has marked.

Modified Oswestry Low Back Disability Questionnaire

The Oswestry low back disability questionnaire(OSW) was originally described by CT Fairbanks in 1980. The questionnaire consists of 10 sections addressing different functional aspects. Each item is given scores from 0 to 5 with towards higher value represents greater disability. The total score is multiplied by 2 and the result is expressed in percentage. The questionnaire used widely now is a modified one by Fritz et all[01]. in 2001

where they replaced sex life item with replaced Employment or homemaking. [102]

In a study done in 2001 by Fritz et al. test-retest reliability was found to be higher and responsiveness was better with Modified Oswestry Low Back Disability Questionnaire in compared to Quebec Back Pain Disability Scale and Physical Impairment Index.[103] They have concluded that OSW is the reliable method to assess disability caused by low back pain.

Table No:09, Interpretation of MODI[102,] [103]

Scores	INTERPRETATION OF MODI
0-20% **Minimal Disability**	Patient can manage his most daily living activities. No treatment is necessary, advise on sitting, posture, lifting, physical fitness and diet modifications would be sufficient.
20-40% **Moderate Disability**	They have more pain and complaints with sitting, standing and lifting. Travel and social life affected. Management by conservative methods would improve the condition.
40-60% **Severe Disability**	Pain will become main problem in them affecting travel, personal care, social life. These patients need further detailed investigation is necessary
60-80% **Crippled**	Back pain affects all effects at this group both at home and at group. Positive management is required.
80-100%	They will be either bed bound or might be exaggerating their symptoms. This can be evaluated during clinical examination.

STUDY PERIOD: November 2016 to November 2018

STUDY TYPE: PROSPECTIVE STUDY

OBJECTVES OF STUDY:

- To measure improvement in BMD at 1 year after infusion.
- To assess improvement in pain and disability using VAS score and Modified Oswestry disability index.
- To study effect of once yearly intravenous Zoledronic Acid infusion in patients presenting with back pain associated with vertebral osteoporosis.

MATERIALS AND METHODS:

This prospective study was on patients above 60 years presented with complaint of chronic low back ache to outpatient, department of orthopaedics, RL Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College. The study period was between November 2016 and November 2018. The study includes total 70 patients who were interested to be part of study and fitting under inclusion and exclusion criteria. They were selected for study after obtaining informed consent. Demographic data, history, clinical examination and details of investigations were recorded in study pro-forma. The baseline Visual analog score and Modified Oswestry low back pain and disability assessment scores were recorded.

The assessment tool used are,

- Radiographs
- Dual Energy X Ray Absorptiometry
- Routine blood investigations
- Electrocardiogram

For the selected patients, lumbosacral spine anteroposterior and lateral view radiographs was done. The patients with osteoporotic features in radiographs were advised for DEXA of spine anteroposterior assessment. In our study, bone density was measured using GE Healthcare Prodigy encore based dual energy X Ray Absorptiometer. Those patients who turned out to be osteoporotic as per WHO definition criteria were included in study.

INCLUSION CRITERIA:

1. Patients of either sex aged above 60 years.
2. Patients with back pain more than 6 weeks of duration, not relieved by usual medications and physiotherapy.

EXCLUSION CRITERIA:

1. Patients with primary and /or secondary tumours of spine.
2. Patients on Bisphosphonates therapy.
3. Patients with traumatic fractures of spine.
4. Patients with radiculopathy.

INVESTIGATIONS:

1. Complete blood count
2. Random blood sugars
3. Blood urea and serum creatinine
4. Electrocardiogram
5. X Ray of Lumbosacral spine Anteroposterior and Lateral views
6. Bone mineral density Anteroposterior analysis.

The patients presented with chronic low back pain in compliance with inclusion and exclusion criteria and turned out to be osteoporotic on DEXA were included in study. After explaining about the study and possible adverse events of 5mg Infusion of Zoledronic Acid, the consent was taken. Blood investigations and Electrocardiography was done to find for contraindications to Zoledronic Acid infusion. The patients without contraindications were advised to take sufficient fluids orally for adequate hydration. Later 5 mg Zoledronic Acid infusion was given over minimum of 15 minutes under monitoring of vitals. The patients were observed for allergic reactions and other immediate adverse events for one day and are recorded. Prophylactic antipyretic medication Paracetamol was given to all patients. Patients were discharged with advise to practice back strengthening exercises and oral Calcium and vitamin D supplement was given to all patients for whole one year. The analgesics were avoided to assess the exact effect of Zoledronic acid.

They were followed up and assessed for improvement in pain and functional ability using VAS and MODI at 12 weeks, 24 weeks and one year follow up. In final follow up after one year all patients underwent bone density assessment by DEXA.

Visit 1/ Initial or Baseline Assessment:

1. Screening the patients clinically for factors suggestive of osteoporosis.
2. VAS chart and Modified Oswestry back pain and disability questionnaire were given and baseline scores were recorded.
3. Radiographs of lumbar spine was taken to suspect osteoporosis.
4. Patients suspected of having osteoporosis were referred for DEXA of spine AP analysis.
5. Patients turned out to be osteoporotic on DEXA were evaluated with routine blood investigations and ECG to rule out contraindications for infusion.
6. Patients who don’t have contraindications were admitted and 5mg Zoledronic Acid was infused over minimum 15min under monitoring and observed one day for adverse events and allergic reactions.
7. Calcium and Vitamin D3 supplement was advised.

Visit 2 / Week 12:

1. Clinical examination of patients.
    2. Assessment of improvement in pain and function by recording VAS and MODI.
    3. Advised to continue Calcium and Vitamin D3 supplement.

Visit 3 / Week 24:

1. Clinical examination of patients.
    2. Assessment of improvement in pain and function by recording VAS and MODI.
    3. Advised to continue Calcium and Vitamin D3 supplement.

Visit 4 / 1 year:

1. Clinical examination of the patients.
    2. Assessment of final improvement in pain and function by recording VAS and MODI.
    3. Assessment of final improvement in bone mineral density using DEXA scan.
    4. Study completed.

The duration of symptoms, bone density in initial scan, adverse effects after infusion, improvement in pain in each follow up assessed by VAS and MODI and bone density in final scan were tabulated and results were assessed.

METHOD OF ANALYSIS

Descriptive and inferential statistical analysis was carried out in our study. Results on continuous measurements were depicted on Mean ± SD (Minimum - Maximum) and results on categorical measurements were depicted in Numbers (%). Significance is assessed at 5% level of significance. Two assumptions made to arrive at results,

Assumptions: 1. Dependent variables should be normally distributed

2. Independent variables from samples (cases) drawn from population should be random.

Paired student t test (two tailed and dependent) was used to find the significance of results from study parameters on continuous scale.

Significant figures:

- Suggestive significance (P value: $0.05<P\leq0.10$)
- Moderately significant (P value: $0.01<P\leq0.05$)
- Strongly significant (P value: $P\leq0.01$)

Statistical softwares used:

The statistical softwares such as IBM SPSS Statistics Version 22, SAS 9.4, SSPS 25.0, Stata 15.1, Medcalc18.11.3 ,Systat 13.2 and R environment ver.3.5.2 were used for statistical analysis of obtained data. Microsoft word and Excel have been used to generate graphs, tables etc.

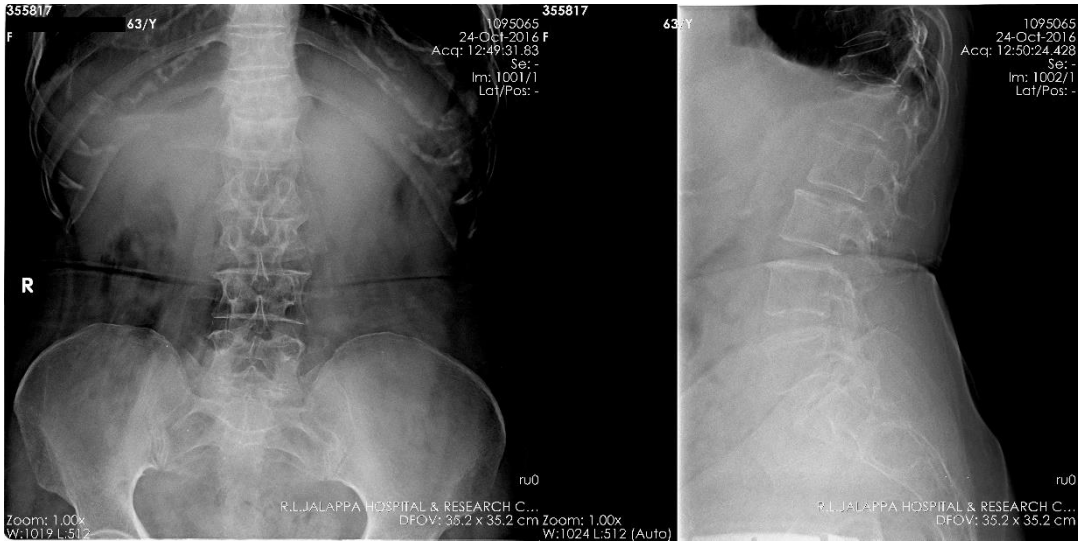
CASE EXAMPLES WITH CLINICAL

PHOTOGRAPHS

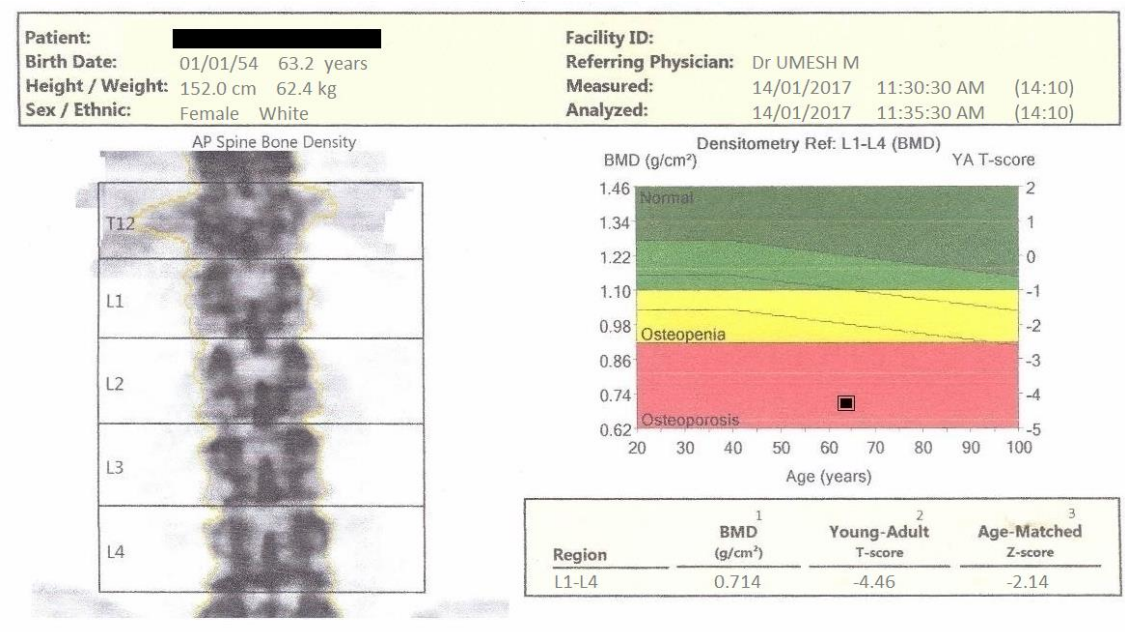
Case Example:1

A 63 year old female presented with complaint of low bach ache from

1 year with baseline VAS 7 and MODI 62.

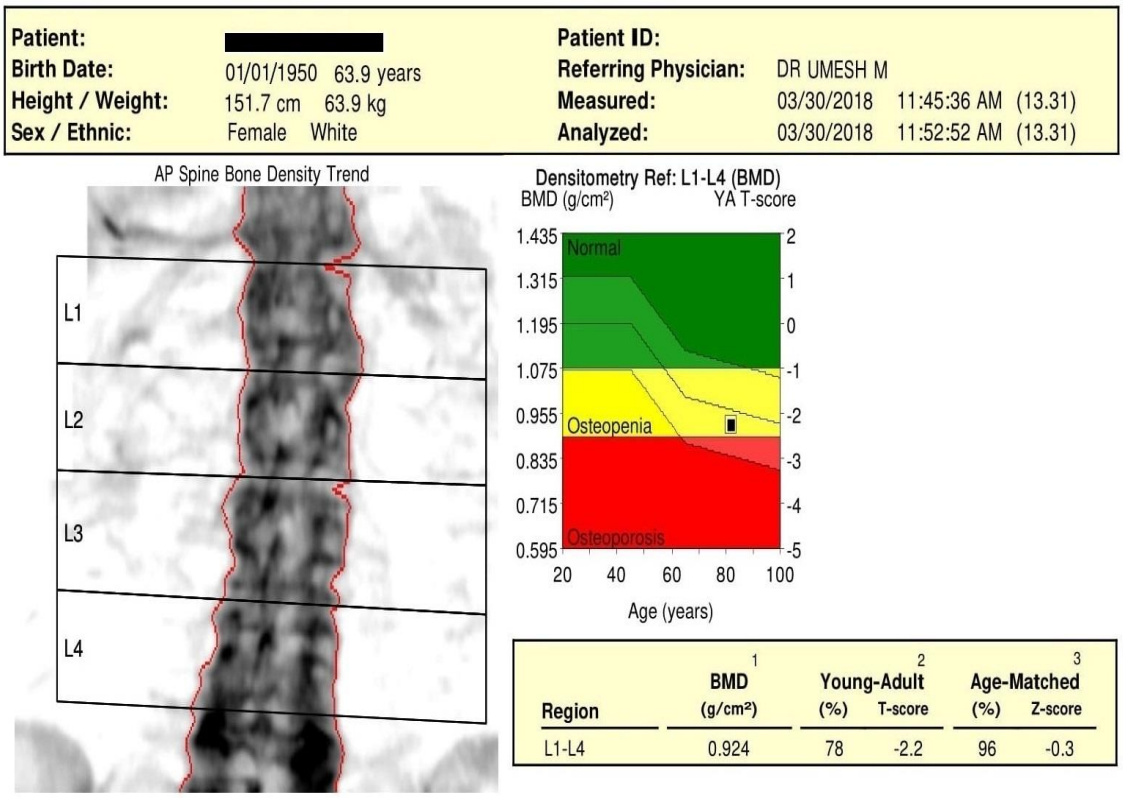


LS Spine X ray revealed osteoporotic changes, DEXA scan was advised,



- On DEXA scan BMD was 0.714 gm/cm^2, T-Score was -4.46patient was admitted and evaluated.
- 5mg ZA infusion was given.
- She got headache and fever as AEs
- During follow up she was very happy about ZA with improvement in

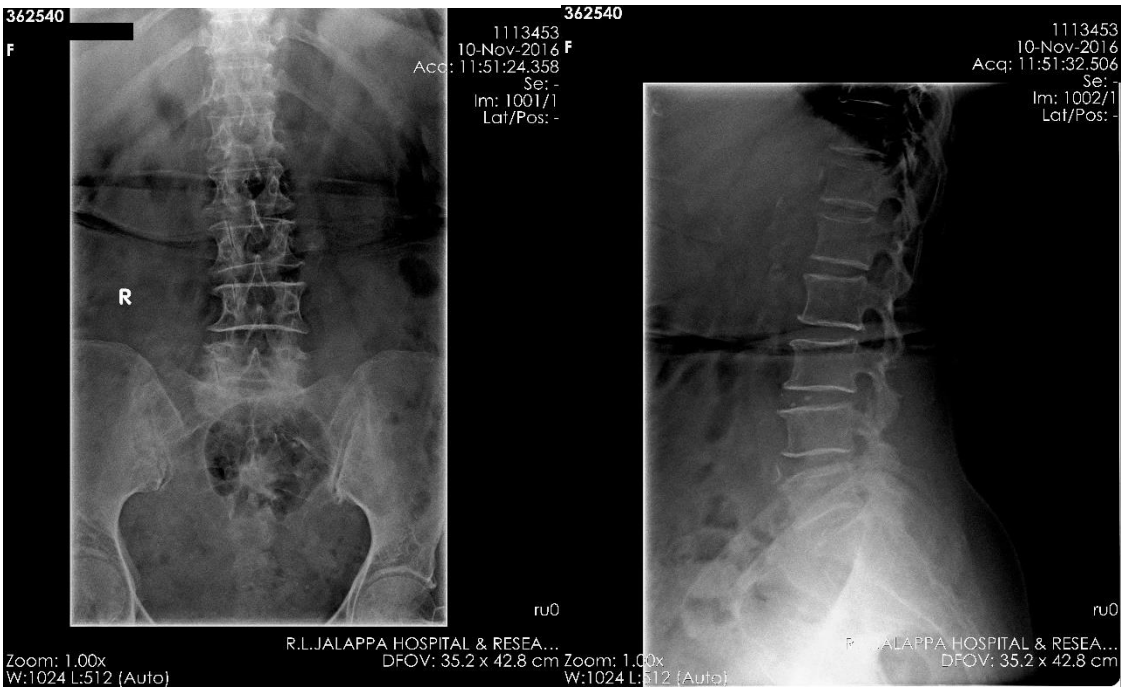
During last follow up at 1 year repeat DEXA showed,



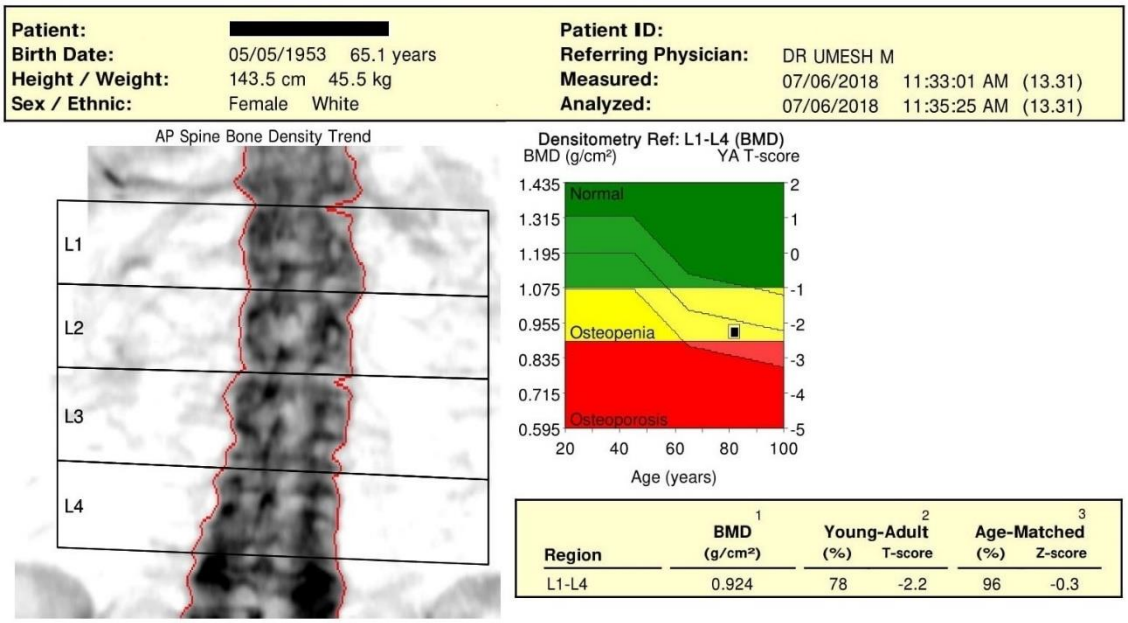
In final follow up patient's VAS was 2 and MODI was 12 compared to 7 and 62 respectively.

Case Example: 2

A 64 year old female presented with complaints of low back pain from 6 years, and baseline VAS was 5 and MODI was 36.

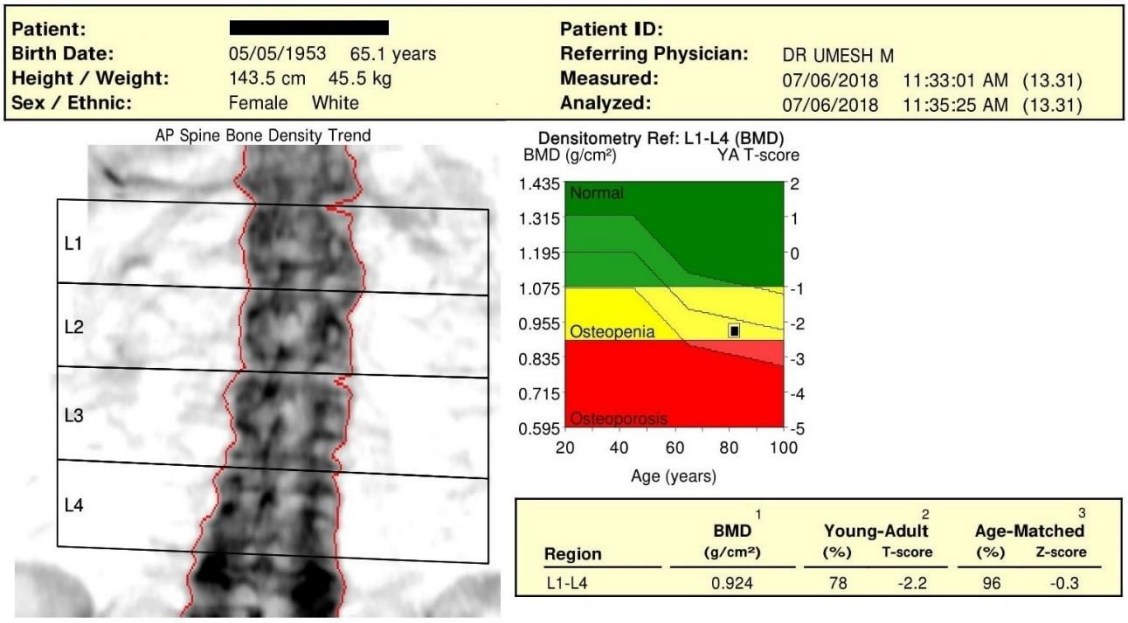


X ray showed radiolucent vertebral body with hyper dense endplates



- On DEXA scan BMD was 0.520 gm/cm^2, T-Score was -5.50 patient was admitted and evaluated.
- 5mg ZA infusion was given.
- She got headache and post transfusion palpitation as AEs
- During follow up she was very compliance with oral supplements with improvement in VAS & MODI.

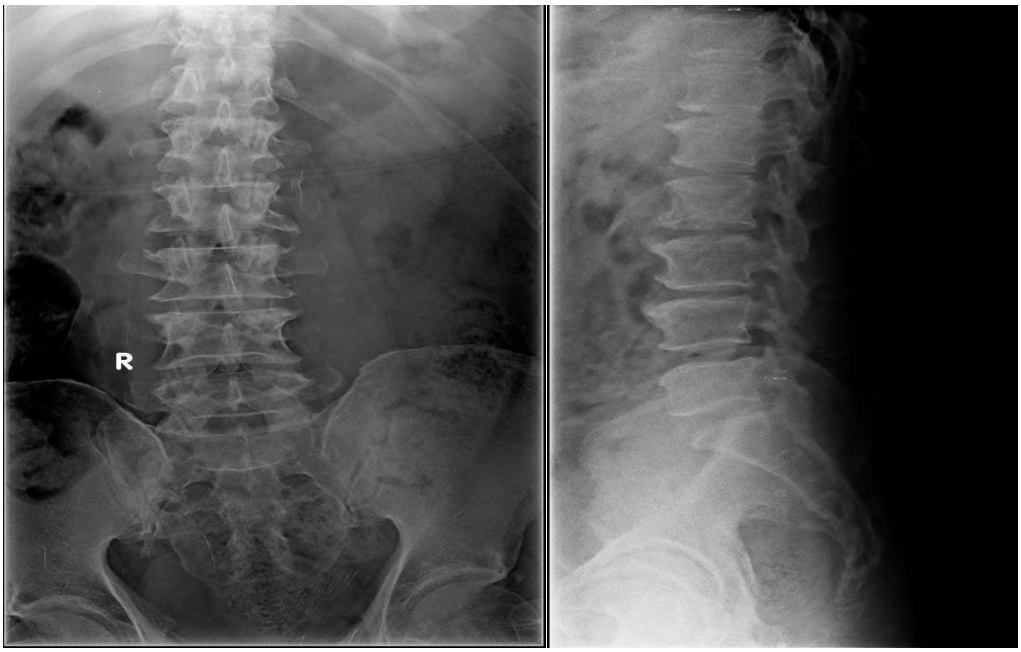
During last follow up at 1 year repeat DEXA showed,



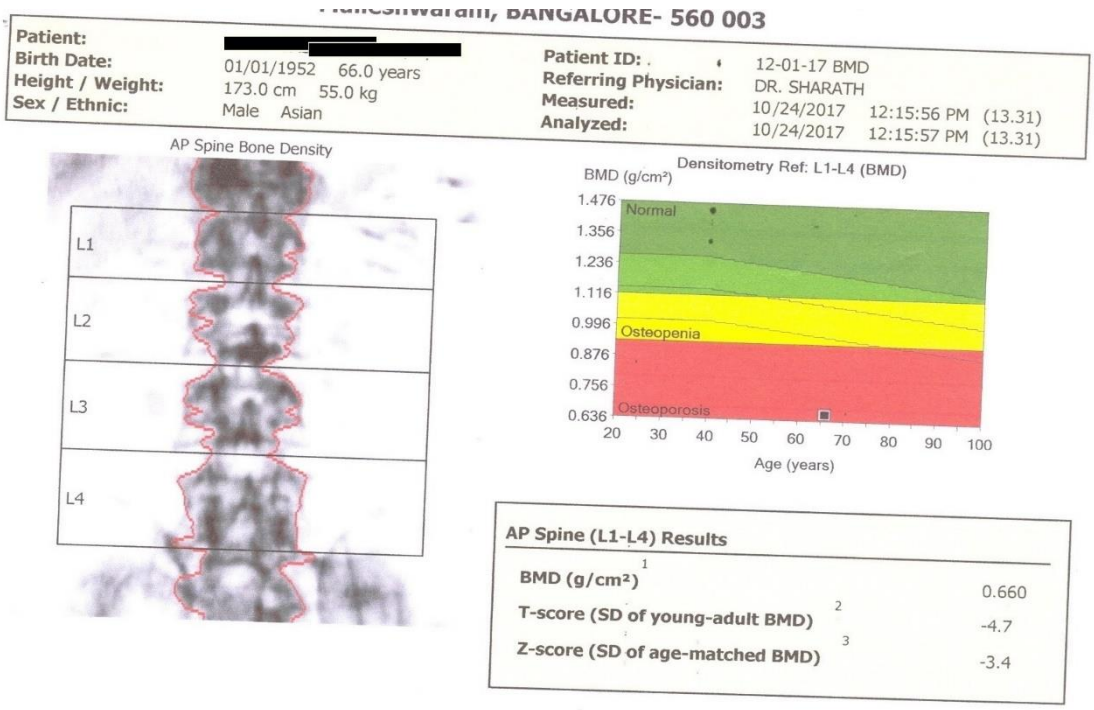
In final follow up patient's VAS was 2 and MODI was 12 compared to 5 and 36 respectively.

Case Example: 3

A 66 year old male, mechanic by occupation, presented with C/O back pain from 6 years, with baseline VAS 5 and MODI 40.

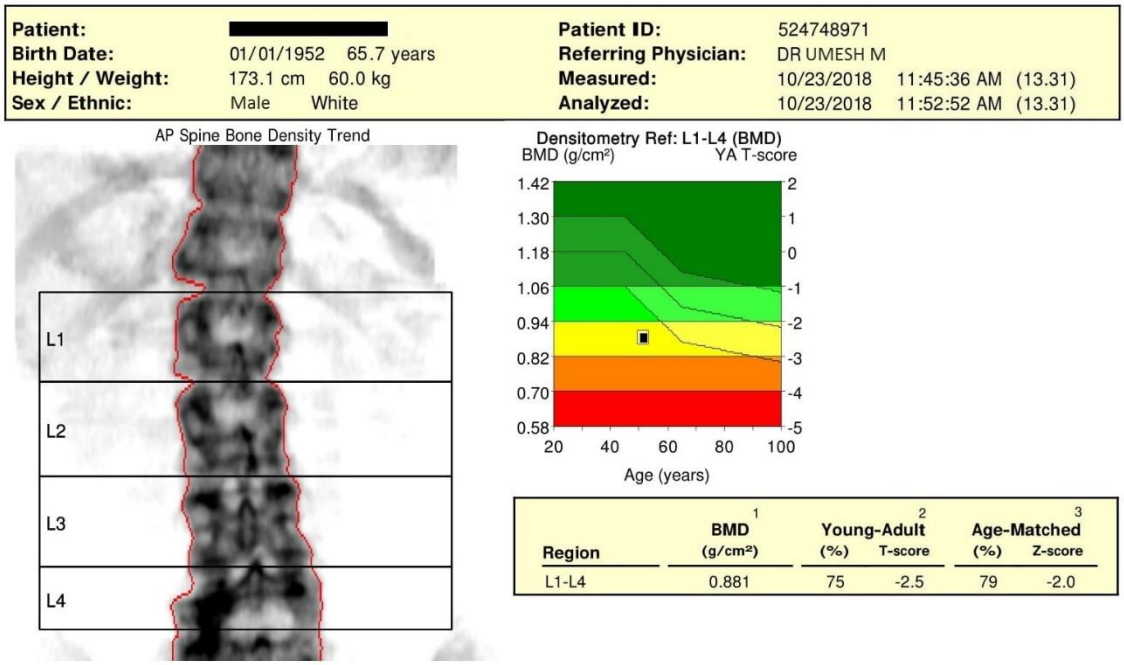


X ray prominent endplate trabeculae.



- On DEXA scan BMD was 0.660 gm/cm^2, T-Score was -4.7 patient was admitted and evaluated.
- 5mg ZA infusion was given.
- He got fever as AEs
- During discharge patient was asking for analgesics but during FU patient was comfortable without analgesics with improvement in VAS & MODI

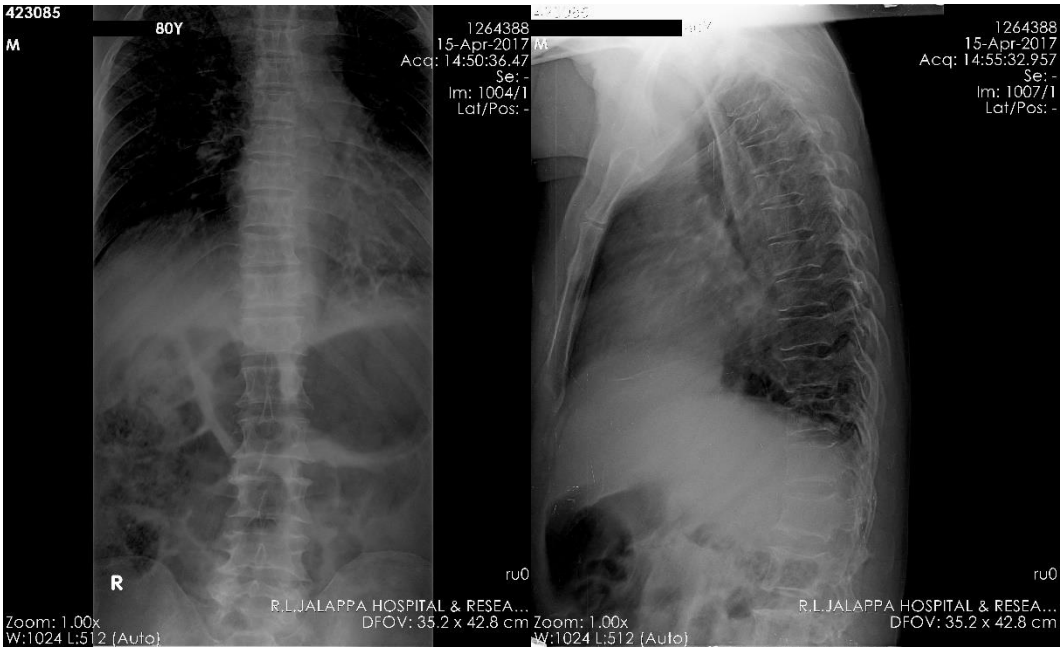
During last follow up at 1 year repeat DEXA showed,



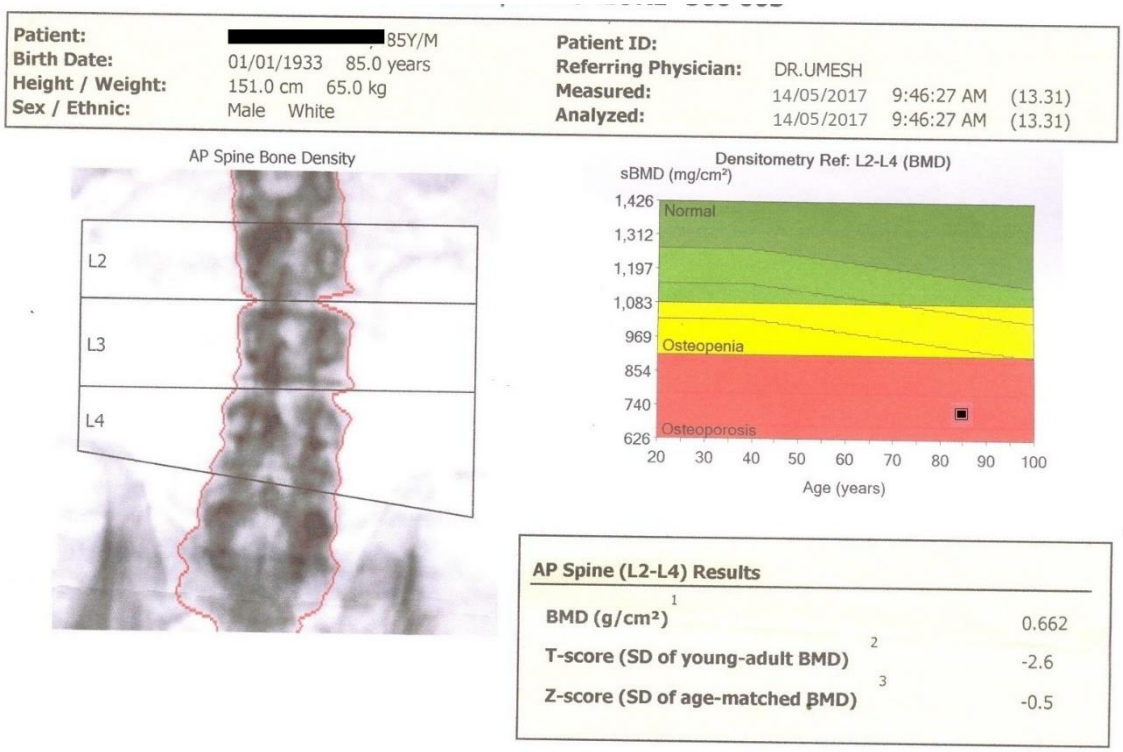
In final follow up patient's VAS was 2 and MODI was 20 compared to 5 and 40 respectively.

Case Example: 4

A 82 year old male presented with back pain from 3 years with baseline VAS 6 and MODI 36.

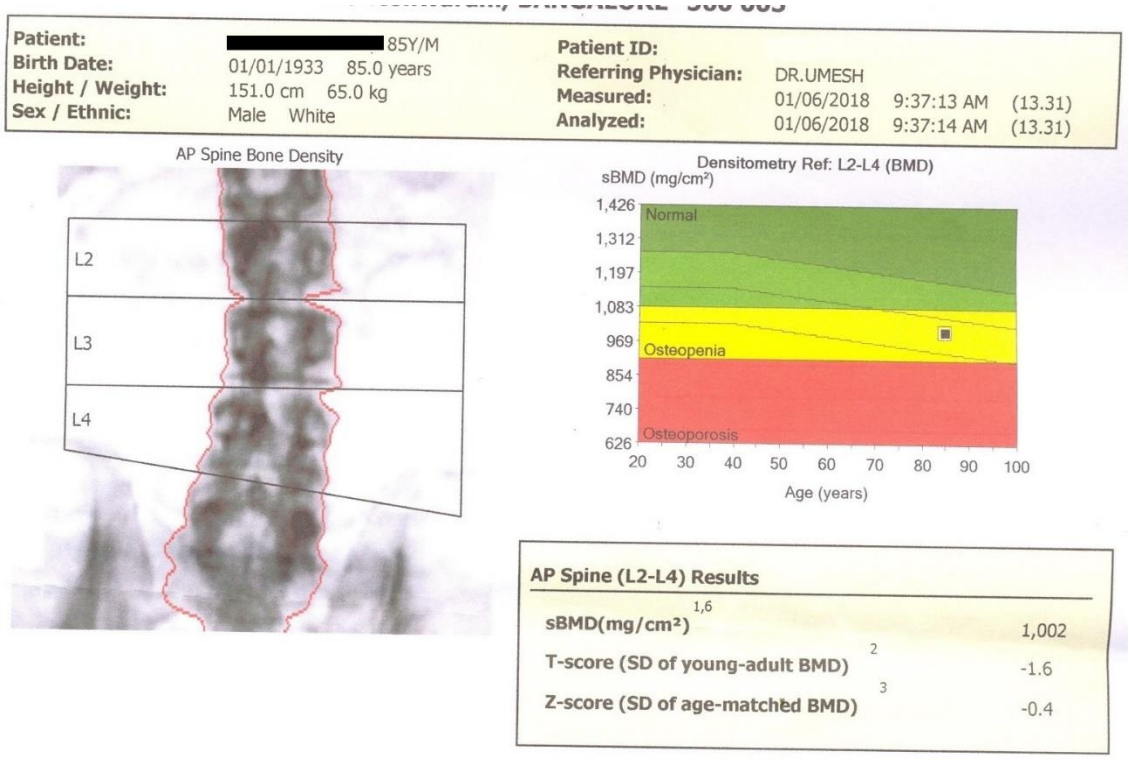


X ray of TL spine showed hyper dense end plates with mind compression of L1 vertebra.



- On DEXA scan BMD was 0.662 gm/cm^2, T-Score was -2.6 patient was admitted and evaluated.
- 5mg ZA infusion was given.
- He got head ache, fever and palpitation as AEs
- During 1st and 2nd FU patient's pain was not significantly reduced but in final FU he was comfortable with improvement in VAS & MODI

During last follow up at 1 year repeat DEXA showed,



In final follow up patient's VAS was 2 and MODI was 16 compared to 6 and 36 respectively.

RESULTS

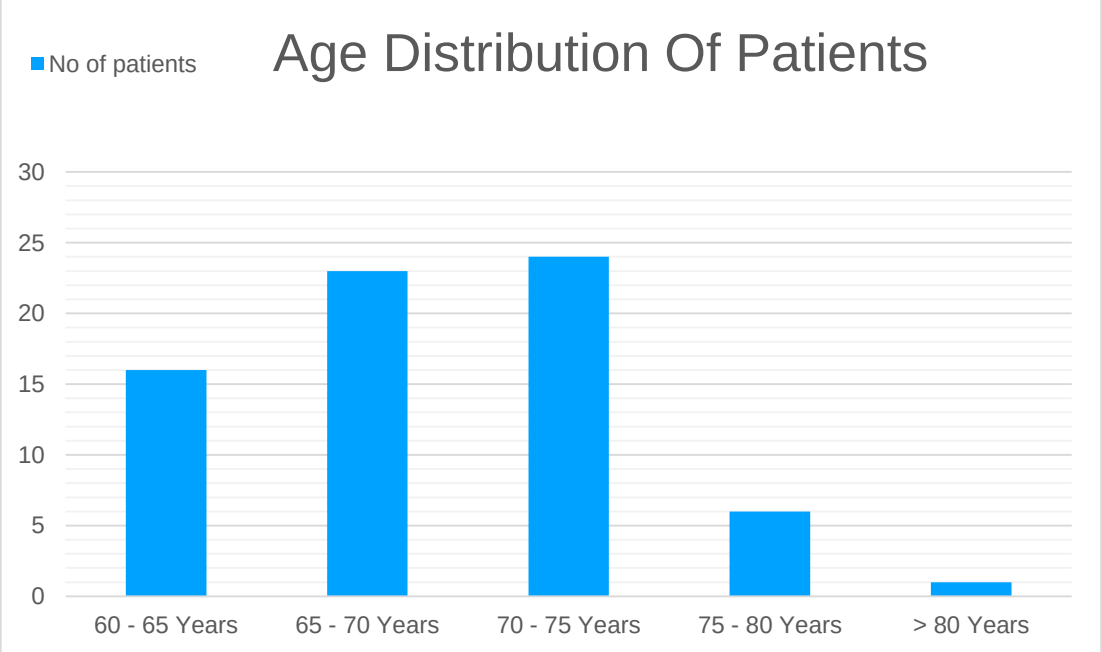
AGE DISTRIBUTION

Average age of the patients in study is 68.47 Years, ranges from 61 years to 82 years with the distribution as shown in below table No 10 and Graph no 4.

Table No:10, Age Wise Distribution Of Patients In The Study

Age in years	No of patients
60 - 65 Years	16
65 - 70 Years	23
70 - 75 Years	24
75 - 80 Years	6

Graph NO: 4, Age wise distribution of patients in study



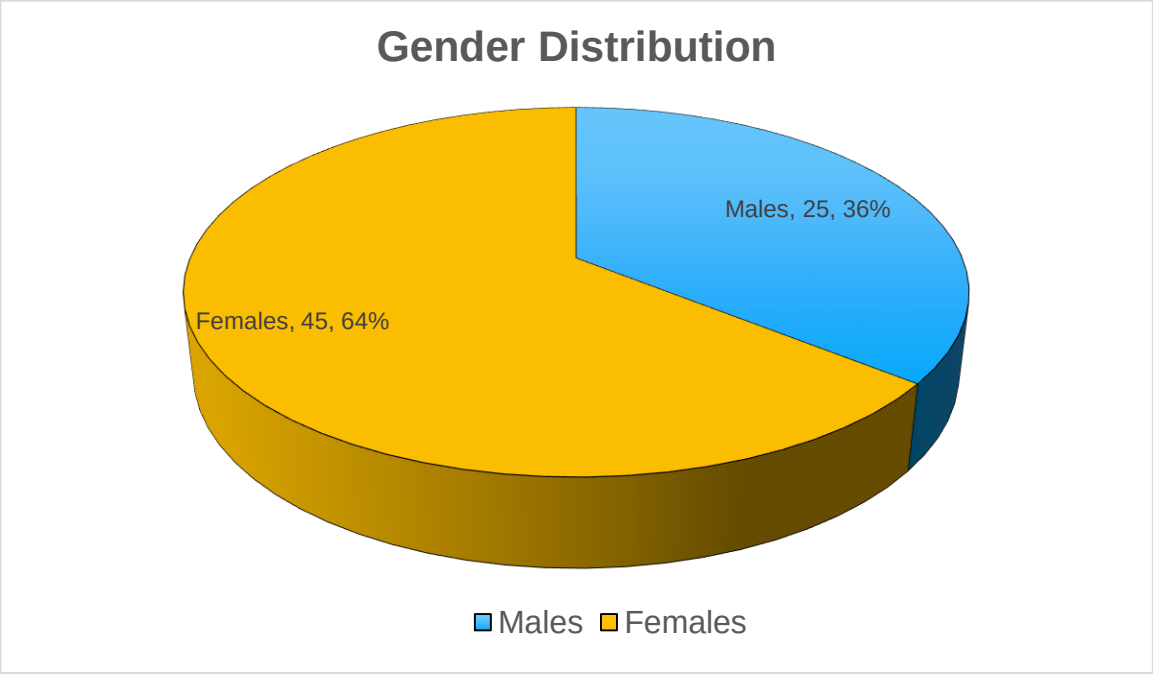
GENDER DISTRIBUTION

The study includes total of 70 patients with female predominance, has 45 female patients and 25 male patients depicted in Table No 11 and Graph No 5.

Table No:11, Gender Distribution

GENDER	No Of Patients
Males	25
Females	45

Graph No:5, Gender Distribution



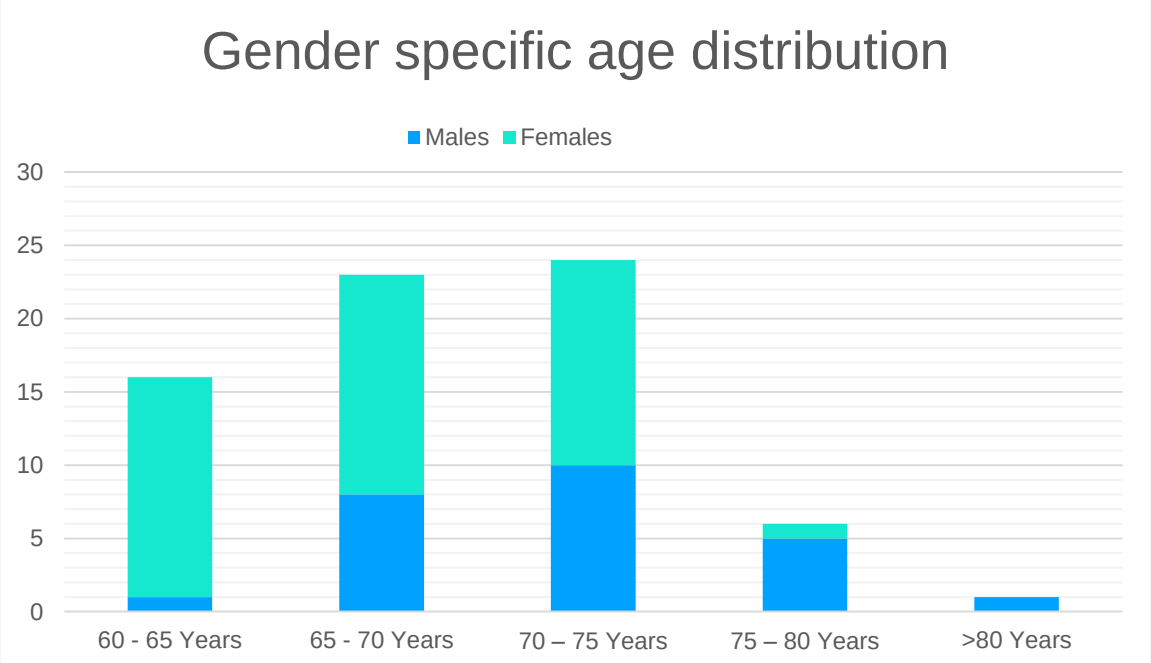
GENDER SPECIFIC AGE DISTRIBUTION

The gender specific age distribution tells us that risk of osteoporosis in females is at an early age compared to males as shown in Table No 12, and Graph No 6.

Table No:12, Gender specific age distribution

Age In Years	GENDER		Total
	Male	Female	
60 - 65 Years	1	15	16
65 - 70 Years	8	15	23
70 – 75 Years	10	14	24
75 – 80 Years	5	1	6
>80 Years	1	-	1
TOTAL	25	45	70

Graph No:6, Gender specific age distribution



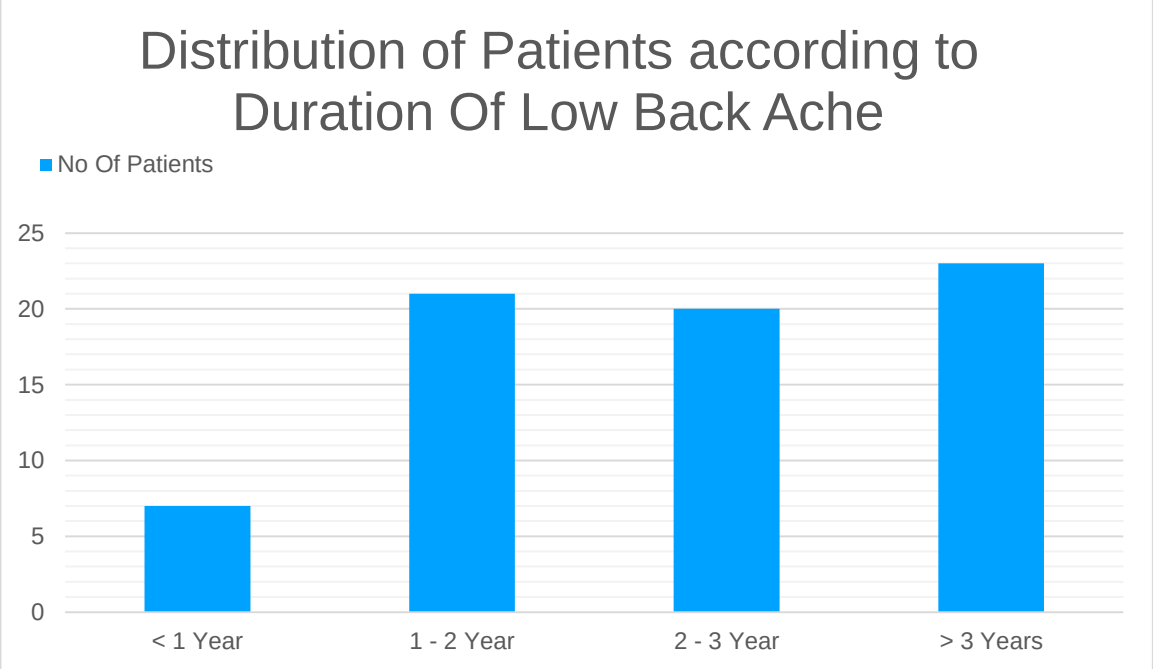
DURATION OF LOW BACK ACHE

In our study patients presented with variable duration of symptom ranges from 6 months up to 10 years depicted in Table No 13 and Graph No 7.

Table No:13, Duration Of Low Back Ache

Duration Of Back pain	No Of Patients
< 1 Year	7
1 - 2 Year	21
2 - 3 Year	20
> 3 Years	23

Graph No:7, Distribution of patients based on duration of back ache



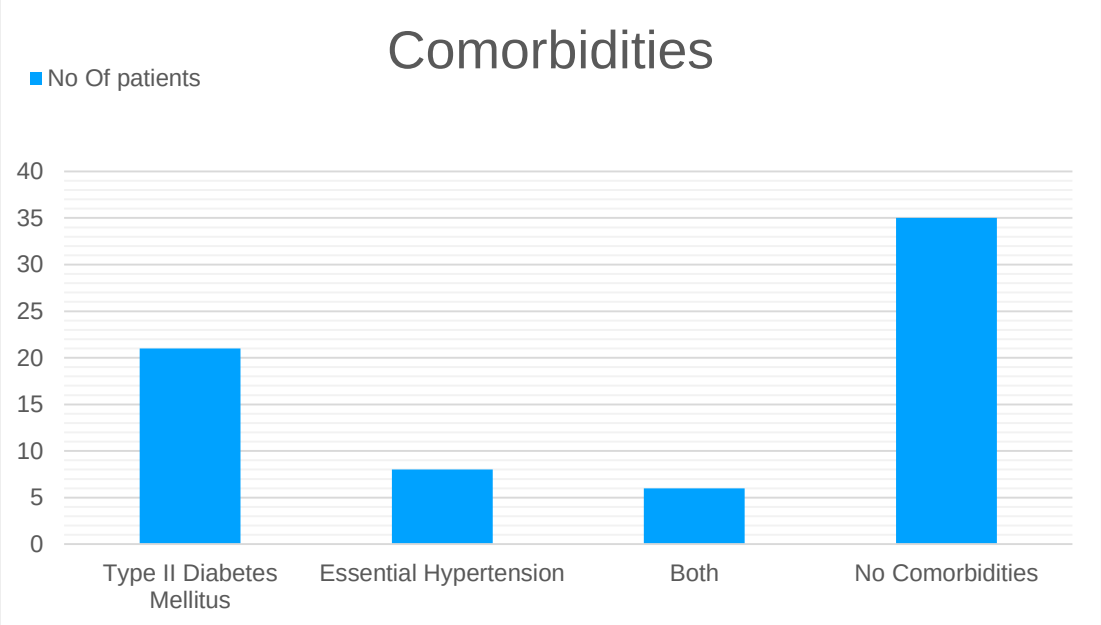
ASSOCIATED COMORBIDITIES

In our study out of 70 patients 21 had Type II diabetes, 8 had essential hypertensive and 6 had both. Remaining 35 patients did not have any comorbidities as shown in Table No 14 and Graph No 8.

Table No:14, Associated Comorbidities

Comorbidities	No Of patients
Type II Diabetes Mellitus	21
Essential Hypertension	8
Both	6
No Comorbidities	35

Graph No:8, Associated Comorbidities



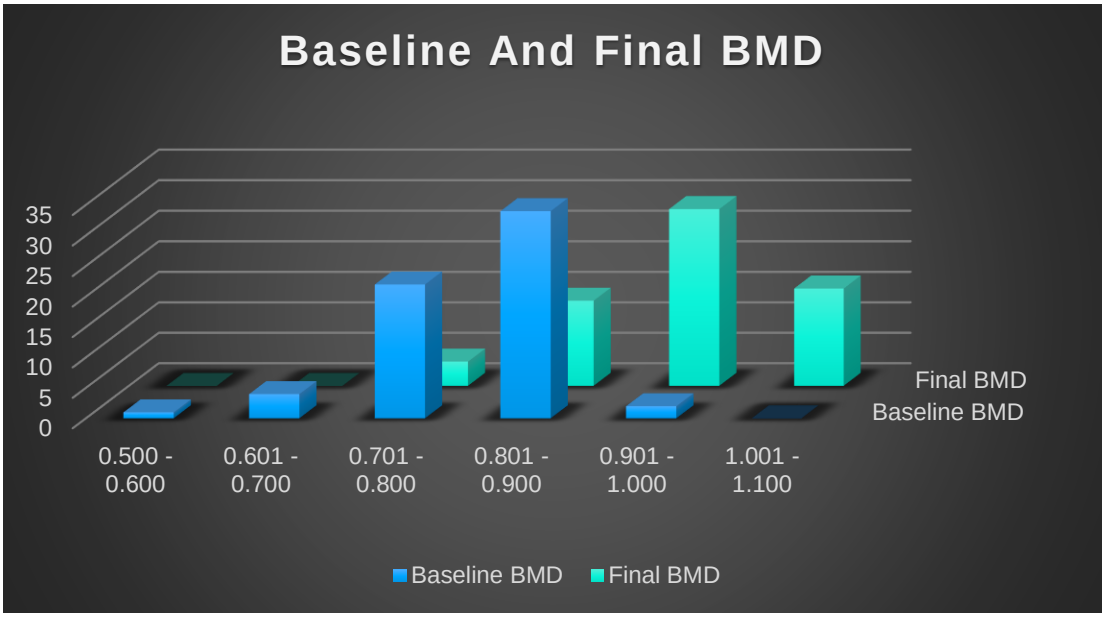
BONE MINERAL DENSITY

The average of baseline BMD done at 1st visit was 0.798 gm/cm^2 and ranges from 0.520 to 0.910 gm/cm^2. The average of final BMD done at 1 year follow up (FU) visit was 0.946 gm/cm^2 ranges from 0.701 to 1.090 gm/cm^2. The values are as shown in Table No 15 and Graph No 9.

Table No:15, Patient Distribution According to Bone Mineral Density in 1st Visit and Final FU

BMD in gm/cm^2	No of patients in first visit	No of patients at 1 year follow up
0.500 -0.600	1	0
0.601 – 0.700	4	0
0.701 – 0.800	22	4
0.801 – 0.900	34	14
0.901 – 1.000	2	29
1.001 – 1.100	0	16

Graph No: 9, Patient Distribution According to Bone Mineral Density in 1st Visit and Final FU



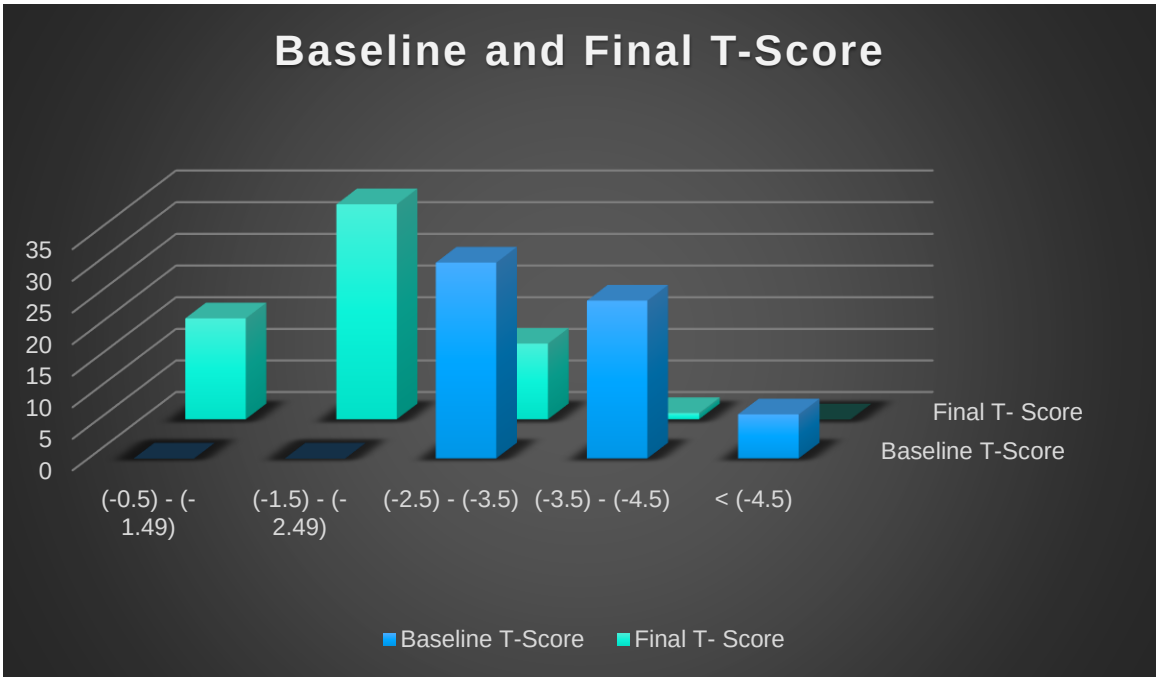
T-SCORE

Average of baseline T-Score is -3.60, ranges between -2.50 to -6.40 and the average of final T-Score is -1.90 ranges between -0.70 to -3.92. The distribution of patients according to baseline and final T- Score is as shown in Table No 16 and Graph No 10.

Table No:16, Patient Distribution According to Baseline and Final T-Score

T-Score	Baseline T-Score	Final T- Score
(-0.5) - (-1.49)	0	16
(-1.5) - (-2.49)	0	34
(-2.5) - (-3.5)	31	12
(-3.5) - (-4.5)	25	1
< (-4.5)	7	0

Graph No:10, Patient Distribution According to Baseline and Final T-Score



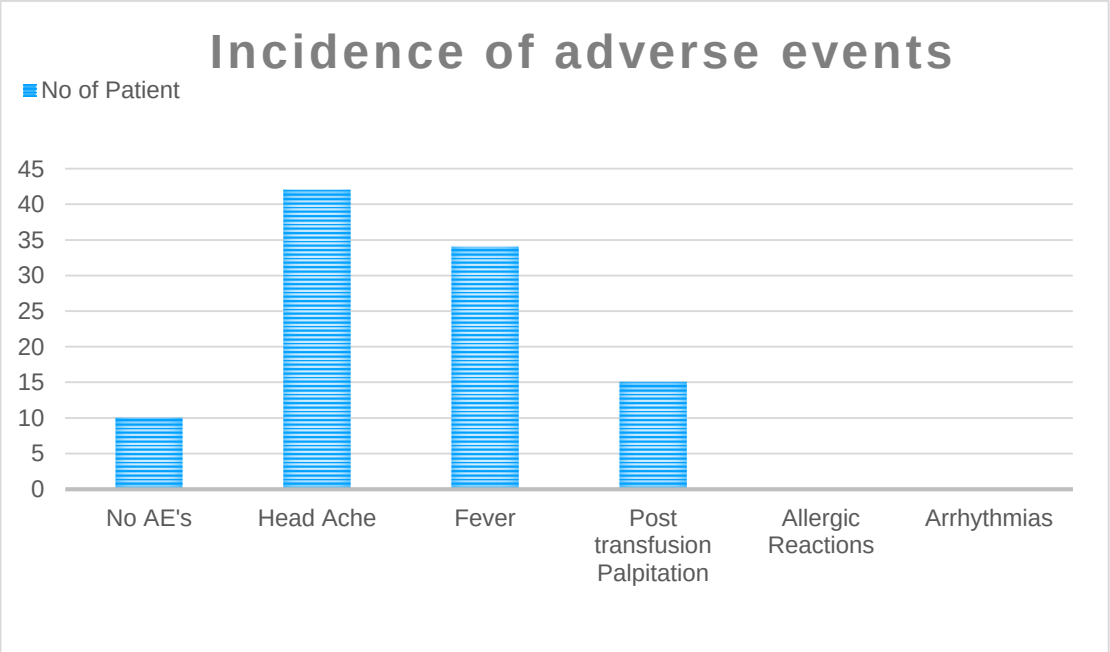
INCIDENCE OF ADVERSE EVENTS

In our study few adverse effects seen only in 1st week after infusion of Zoledronic acid. 10 patients did not have any AEs. Headache was the most frequent AE, seen in 42 patients next day after infusion. 34 patients had fever in the evening or next day after infusion. 15 patients complained of palpitation immediately after transfusion for about ½ to 1 hour. No patients had allergic reactions and arrhythmias. Same has been shown in Table No 17 and Graph No 11.

Table No:17, Incidence Of Adverse Events

Adverse Events	No Of patients
No Adverse Events	10
Head Ache	42
Fever	34
Post Transfusion Palpitation	15
Allergic Reactions	Nil
Arrhythmias	Nil

Graph No:11, Incidence of Adverse Events



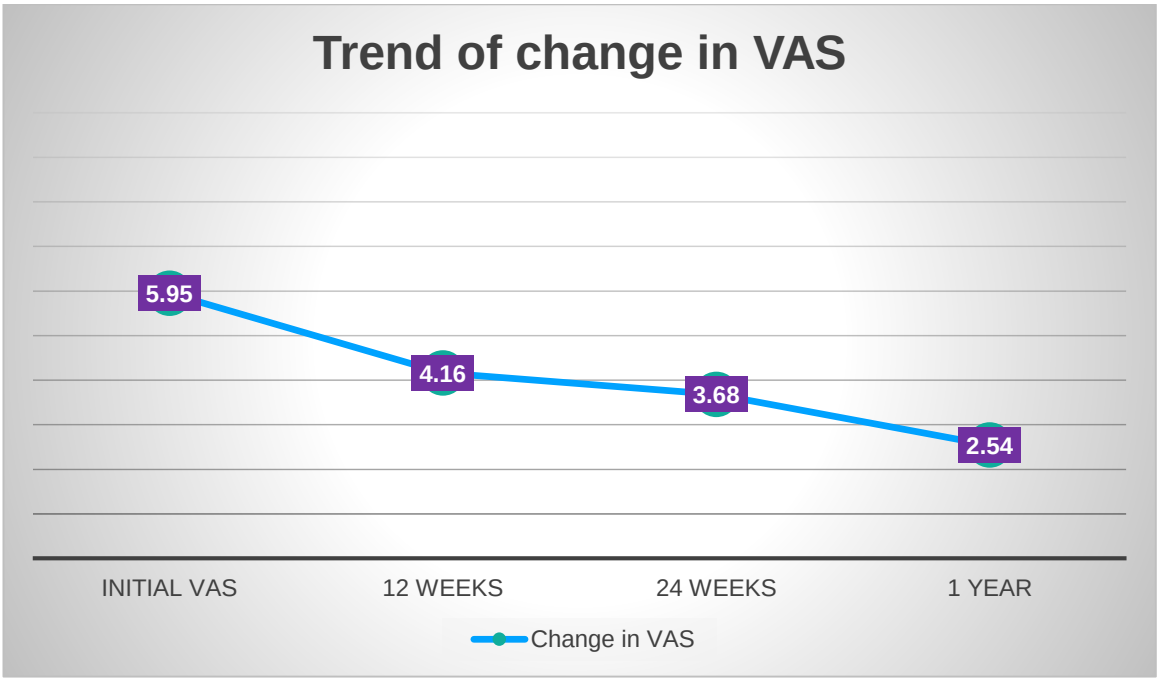
VISUAL ANALOGUE SCALE (VAS)

Average and trend of VAS score assessed at each follow up is as shown in Table No 18 and Graph No 12.

Table No:18, Change in VAS Score in Initial, 1st, 2nd, and Final Visit

Duration	Change in VAS
Initial VAS	5.95
12 weeks	4.16
24 weeks	3.68
1 Year	2.54

Graph No:12, Change in VAS Score in Initial, 1st, 2nd, and Final Visit



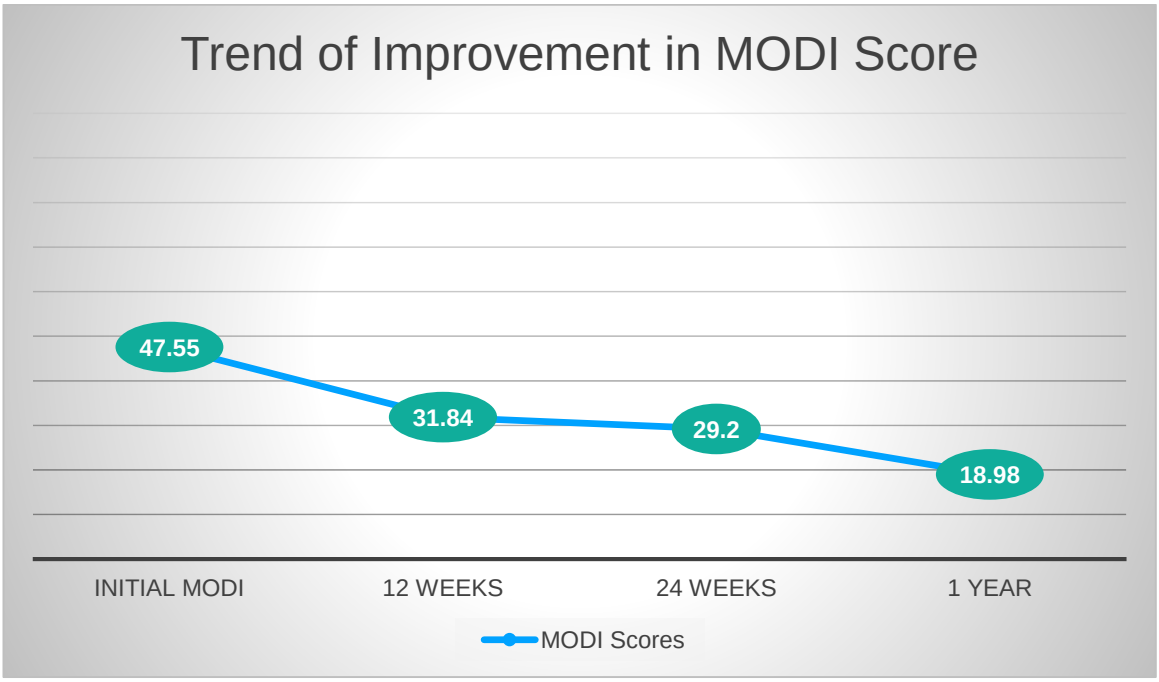
MODIFIED OSWESTRY BACK PAIN AND DISABILITY ASSESSMENT SCORE (MODI)

MODI Score average and trend in each visit is as shown in Table No 19 and Graph No 13.

Table No:19, MODI Score average in initial, 1st, 2nd and final visit

Time Of Assessment	MODI Score
Initial MODI	47.55
12 weeks	31.84
24 weeks	29.2
1 Year	18.98

Graph No: 13, MODI Score average in initial, 1st, 2nd and final visit



ASSESSMENT

The collected data were statistically assessed using IBM SPSS Statistics, Version 22.0.0.0. The calculated values are shown in following Table No,

Table No:20, Statistical calculations by Paired Student T Test.

Pairs	Paired Differences					T- Value	DF	P Value
	Mean	Std Deviation	Std Error Mean	95% Confidence Interval Of Differences				
				Lower	Upper			
Baseline BMD - BMD at 1 yr	0.14719	0.08847	0.011146	0.169471	0.12491	13.205	62	<0.0001
T-Score - T-Score at 1yr	1.37667	1.56736	0.19747	1.77140	0.98193	6.972	62	<0.0001
Z-Score - Z-Score at 1yr	1.37317	.82730	0.10423	1.58153	1.16482	13.174	62	<0.0001
Baseline VAS - VAS At 1st FU	1.7937	1.1095	0.1398	1.5142	2.0731	12.832	62	<0.0001
Baseline VAS - VAS AT 2nd FU	2.2698	1.4724	0.1855	1.8990	2.6407	12.236	62	<0.0001
Baseline VAS - VAS at 3rd FU	3.4127	1.6813	0.2118	2.9893	3.8361	16.111	62	<0.0001
Baseline OPI - OPI AT 1st FU	15.7143	11.5834	1.4594	12.7970	18.6315	10.768	62	<0.0001
Baseline OPI - OPI At 2nd FU	18.3492	12.4928	1.5739	15.2029	21.4955	11.658	62	<0.0001
Baseline OPI - OPI at 3rd FU	28.5714	15.0287	1.8934	24.7865	32.3564	15.090	62	<0.0001

DISCUSSION

The present study consists of 70 patients of either sex with Male : Female is 5 : 9 (25 : 45) presented with low back ache for more than 6 weeks duration having vertebral osteoporosis with few non-traumatic compression fractures of spine. Those patients who had radiculopathy, tumors of spine, traumatic fractures of spine and those who were already on bisphoshonates therapy were excluded.

The study had an objective to study the effect of once yearly intravenous Zoledronic Acid infusion in patients presenting with back pain associated with vertebral osteoporosis.

Zoledronic acid is a manufacturer's, doctors and patients dream came true with excellent patient tolerability. It is very effective with highest affinity to bone among all BPs. It is an approved drug for treatment and prevention of osteoporosis and shows significant reduction in fragility fractures rate.

Primary Observations of the Study:

The patients of above 60 years presented to outpatient department with complaints of low back ache, whose lumbar spine X ray showed osteoporotic features were screened for Osteoporosis using DEXA of spine. A total of 70 patients who turned out to be osteoporotic were included in study.

Out of 70 patients 7 patients were lost to follow up. Hence 63 patients who completed 1 year of follow up and underwent repeat BMD assessment at end of one year were considered for statistical calculation and assessment.

In our study effect of Zoledronic acid in reducing in pain is found to be excellent when assessed improvement using VAS scoring with P value of <0.0001 in early (3, 6 months) and long term (1 year) follow up.

The study also showed excellent results in functional improvement when assessed using modified oswestry low back pain disability questionnaire scoring with P value of <0.0001 in early (3, 6 months) and long term (1 year) follow up.

The main objective of the study was to assess efficacy of Zoledronic acid, assessed by measuring improvement in BMD, T-Score and Z-Score in one year after infusion. When assessed statistically by calculating mean, standard deviation, standard error mean, 95% confidence interval of differences, T-Value by paired student T test considering degree of

freedom as 62 (n-2). The P value was found to be less than 0.0001 which meant the study result was significant with excellent results.

The most common adverse events noted in our study is headache, followed by fever then post transfusion palpitations. No patients had allergic reactions, arrhythmic episodes or osteonecrosis of jaw.

Considering all these observations, all the patients found excellent clinical improvement following Zoledronic Acid infusion in early and long term follow up and the efficacy of Zoledronic Acid also found to be excellent with significant improvement in BMD, T-Score and Z-Score.

Secondary Observations:

The study hospital being in rural populated area serves to majority of rural population. Hence lack education and health awareness is significant challenge to handle in view of avoiding analgesics and taking advised supplements regularly. In our study all patients were founds to be in compliance with oral supplements.

All the patients being above 60 years are sedentary workers and 64 % were females.

None of the patients in the study developed new vertebral compression fractures (traumatic or atraumatic). This signifies that pain relief after ZA infusion may even be due to prevention of new compression fractures and strengthening of trabeculae of spine along with its analgesic effect.

Being once yearly intravenous dosing ZA found to have better compliance compared with oral agents with which compliance is a major issue.

Considering all the above in our study, it shows that Zoledronic Acid is an effective drug for treatment of osteoporosis and prevention of fragile fractures.

Comparison of Our Study Results with Other Standard Studies Across the World

In a study by Koivisto K et al. on efficacy of ZA for chronic back pain, 40 patients were studied with one year follow up after ZA infusion, it is found that improvement in intensity of chronic low back ache(LBA) was greater with ZA compared to placebo. They have also recommended it as an interesting treatment alternative for LBA which is difficult to treat by conservative approach. Our study also has shown an excellent pain and disability reduction following ZA.[74]

A multicentre study by Orwoll E et al, a comparison study between IV Zoledrinate and Oral Alendronate, it has been found that compliance with Zoledronic Acid is significantly better that with Alendronate with more dropout and AEs with Alendronate and out of 275 patients who responded to questionnaire 204 patients have preferred once yearly

intravenous infusion of ZA 5mg and only 42 patients preferred weekly oral Alendronate 70mg, 29 patients had no preference among the two, which is a similar finding in our study with excellent compliance for ZA. The study has also shown that Zoledronate is effective in treating osteoporosis in male.[39]

A study done in USA by Cauley J et al. A study on ZA in 7736 patients with mean age 73 years, it is shown that treatment with ZA significantly reduced number of days of hospital admission and limited activity. Women in ZA group were 10% less likely to report 7 or more days of LBP compared with placebo group. The study has also concluded that 3 year treatment with ZA significantly reduced disability and fracture compared with placebo in woman with osteoporosis. Even though without comparable placebo group, our study has also shown significant improvement with ZA. [104]

In a study done in Bengaluru by Ramalingaiah A et al, On 50 patients above 40 years, it is observed that ZA once yearly infusion has excellent compliance with minimal incidence of AEs. It has also shown to improve pain in first 6 months after infusion and modest improvement in BMD. On comparing with our study results which has shown excellent results in pain control and BMD improvement.[31]

CONCLUSION

Chronic low back ache in elderly patients without any identifiable causes will be usually due to vertebral osteoporosis. Hence evaluation for vertebral osteoporosis is must for all such patients. Early diagnosis and treatment of such condition is most important factor in preventing fragility fractures. Zoledronic Acid being an antiresorptive drug with its better compliance, is very effective in ‘controlling low back pain’, ‘improving bone mineral density’ and preventing occurrence of atraumatic fragility fractures. With all above factors Zoledronic acid is most preferable bisphosphonate for treatment and prevention of osteoporosis.

SUMMARY

This is a prospective study on the effect of Zoledronic acid in patients with chronic back pain associated with vertebral osteoporosis, analyzed in view of reduced pain, disability and improvement in BMD.

The study consists of 70 patients of which 7 lost to follow up, hence 63 considered for result analysis. Patients of age above 60 years presented with low back pain for more than 6 weeks without radiculopathy and turned out to be osteoporotic on DEXA were considered for study. Patient with tumors of spine, traumatic fractures of spine and who were already on BP therapy were excluded.

Study sample had average age of patients was 68.47 ranges from 61 to 82 years, predominantly females (Female:Male was 45:25), duration of symptom ranges from 6 months to 10 years. Baseline details noted were VAS, MODI and BMD at initial visit. The patients whose T-Score less than -2.50 were admitted and 5mg Zoledronic Acid infusion was given over minimum of 15 min and monitored for occurrence of AEs. All patients were given oral supplement of Calcium, Vitamin D3 for one year. They were called for FU at 12 weeks, 24 weeks and 1 year. VAS and MODI were noted in each FU. Repeat BMD assessed using DEXA at 1 year FU and values were noted.

None of the patients developed either traumatic, non-traumatic vertebral compression fractures or any other fragile fractures in course of the study. During the study period it was found that almost all of our study patients were in compliance with Zoledronic Acid as well as the oral supplements and they were willing for second injection.

Collected data were tabulated and statistically assessed using paired student t test. The assessed results showed significant reduction in pain, disability in both early and late FU and improvement in BMD after 1 year. At the end of the study it was observed and concluded that Zoledronic Acid having highest affinity to bone, it is an effective intravenous bisphosphonate for treatment and prevention of osteoporosis with excellent compliance with significant reduction of osteoporotic related fractures.

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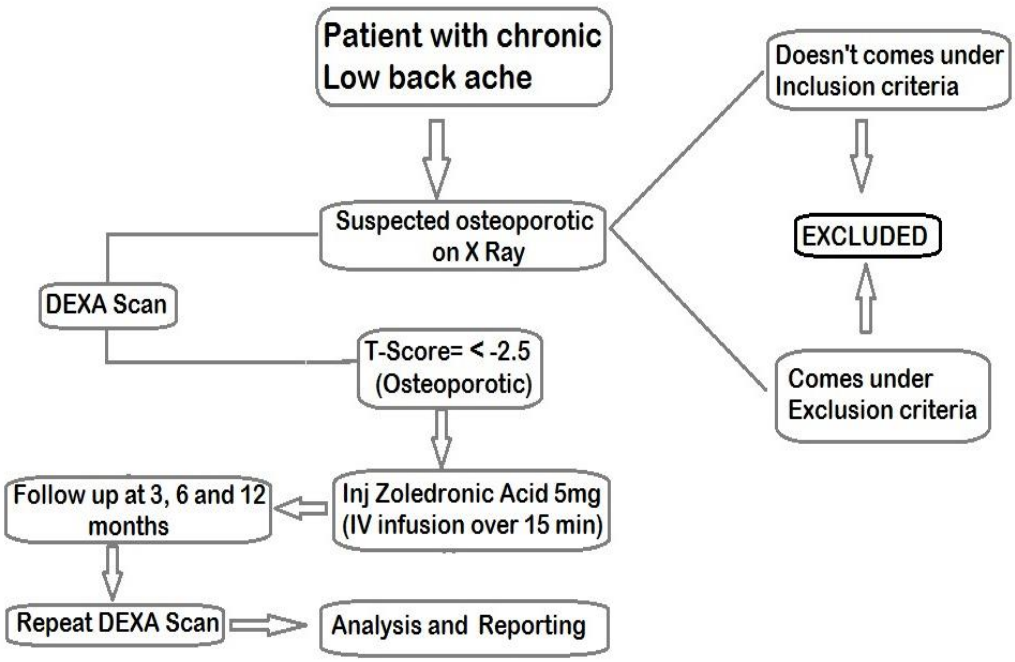
ANNEXURES

ANNEXURE: I

STUDY DESIGN:



ANNEXURE: II, INFORMED CONSENT

STUDY TITLE: THE EFFECT OF ZOLEDRONIC ACID IN PATIENTS WITH CHRONIC BACK PAIN ASSOCIATED WITH VERTEBRAL OSTEOPOROSIS: A PROSPECTIVE STUDY

CHIEF RESEARCHER/ PG GUIDE'S NAME: Dr. PRABHU E

PRINCIPAL INVESTIGATOR: Dr. UMESH M

NAME OF THE SUBJECT:

AGE :

GENDER :

a. I have been informed in my own language that this study includes x-ray of spine, routine investigations and dual energy x-ray absorptiometry scan of spine as part of procedure. I have been explained thoroughly and understand its complication and possible side effects.
b. I understand that the medical information produced by this study will become part of institutional record and will be kept confidential by the said institute.
c. I understand that my participation is voluntary and may refuse to participate or may withdraw my consent and discontinue participation at any time without prejudice to my present or future care at this institution.
d. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
e. I confirm that _____ (chief researcher/ name of PG guide) has explained to me the purpose of research and the study procedure that I will undergo and the possible risks and discomforts that i may experience, in my own language. I hereby agree to give valid consent to participate as a subject in this research project.

Participant's signature/thumb impression

Signature of the witness: Date:

1)

2)

I have explained to _____ (subject) the purpose of the research, the possible risk and benefits to the best of my ability.

Chief Researcher/ Guide signature Date:

ANNEXURE-III, CONSENT IN KANNADA

ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿ ಪತ್ರ

..... ಹೆಸರಿನ ..... ವಯಸ್ಸಿನವನಾದ .....
ಯ.ಹಚ್.ಐ.ಡಿ ಹೊಂದಿದ ನನಗೆ ಬೆನ್ನು ಮೂಳೆಯ ಎಕ್ಸ್ ರೇ, ನಿಯತಕ್ರಮದ ಪರೀಕ್ಷೆಗಳು ಹಾಗು ಡುಯಲ್ ಎನರ್ಜಿ ಕ್ಷ ಕಿರಣ ಅಬ್ಸಾರ್ಪ್ಷಿಯೋಮೆಟ್ರಿ (ಡೆಕ್ಸಾ) ಪರೀಕ್ಷೆಗಳನ್ನೊಳಗೊಂಡ "**ಬೆನ್ನು ಮೂಳೆಯ ಆಸ್ಟಿಯೊಪೊರೋಸಿಸ್ ನಿಂದ ಕಾಣಿಸಿಕೊಳ್ಳುವ ಬೆನ್ನು ನೋವನ್ನು ಗುಣಪಡಿಸುವಲ್ಲಿ ಝೂಲೆಡ್ರೋನಿಕ್ ಆಸಿಡ್ ಚುಚ್ಚುಮದ್ದಿನ ಪರಿಣಾಮಕಾರಿತ್ವ ಅರಿಯುವ ಅಧ್ಯಯನ**" ಅಧ್ಯಯನದ ಕಾರ್ಯ ವಿಧಾನಗಳು ಮತ್ತು ಅಹಿತಕರ ಪರಿಣಾಮಗಳಾದ ಮಾಂಸಖಂಡಗಳ ನೋವು, ಜ್ವರ, ತಲೆ ನೋವು, ಕೀಲು ನೋವು, ಹೃದಯದ ಬಡಿತದಲ್ಲಿ ಏರಿಳಿತ ದವಡೆಯ ಆಸ್ಟಿಯೋನೆಕ್ರೊಸಿಸ್, ಹೃದಯದ ಬಡಿತದಲ್ಲಿ ಏರಿಳಿತಗಳ ಕುರಿತು ಕನ್ನಡದಲ್ಲಿ ವಿವರಿಸಿರುತ್ತಾರೆ.

ನನಗೆ ಬೆನ್ನು ಮೂಳೆಯ ಆಸ್ಟಿಯೊಪೊರೋಸಿಸ್ ನಿಂದ ಕಾಣಿಸಿಕೊಳ್ಳುವ ಬೆನ್ನು ನೋವು ತೊಂದರೆ ಇರುವುದಾಗಿ ತಿಳಿಸಿದ್ದು, ಅದಕ್ಕೆ ಲಭ್ಯವಿರುವ ಎಲ್ಲಾ ಚಿಕಿತ್ಸಾ ವಿಧಾನಗಳ ಆಗು ಹೋಗುಗಳ ಬಗ್ಗೆ ಕನ್ನಡದಲ್ಲಿ ವಿವರಿಸಿರುತ್ತಾರೆ.

ಈ ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳ ಬಗ್ಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳುವ ಅವಕಾಶವನ್ನು ನನಗೆ ನೀಡಲಾಗಿದೆ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ತೃಪ್ತಿಕರವಾದ ಉತ್ತರಗಳು ದೊರೆತಿರುತ್ತೆವೆ

ಮೇಲೆ ತಿಳಿಸಿರುವ ಅಧ್ಯಯನದ ಕಾರ್ಯ ವಿಧಾನಗಳು ಮತ್ತು ಅಹಿತಕರ ಪರಿಣಾಮಗಳನ್ನು ಅರಿತು ಮುಚ್ಚುಮರೆ ಇಲ್ಲದೆ ನನ್ನ ಪರಿಪೂರ್ಣ ವಿವೇಚನೆಯಲ್ಲಿ ಅಧ್ಯಯನದಲ್ಲಿ ಭಗವಹಿಸಲು ಹಾಗು ನನ್ನ ಹೆಸರು ಮತ್ತು ಪರೀಕ್ಷಾ ವರದಿಗಳನ್ನು ಸಂಶೋಧನೆಯಲ್ಲಿ ಬಳಸಿಕೊಳ್ಳಲು ಒಪ್ಪಿಗೆ ನೀಡುತಿದ್ದೇನೆ.

ಈ ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಂದರ್ಭದಲ್ಲಿ ಹಿಂದೆ ಸರಿಯುವ ಸ್ವಾತಂತ್ರ್ಯ ನನಗಿದೆ ಎಂಬುದನ್ನು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದರಿಂದ ನನಗೆ ಯಾವುದೇ ಹೆಚ್ಚುವರಿ ವೆಚ್ಚ ತಗಲುವುದಿಲ್ಲವೆಂಬುದನ್ನು ತಿಳಿದಿರುತ್ತೇನೆ.

ಮೆಲೆ ತಿಳಿಸಿರುವ ಅಧ್ಯಯನದ ಯಾವುದೇ ಅಹಿತಕರ ಪರಿಣಾಮಗಳಿಗೆ ಚಿಕಿತ್ಸೆ ನೀಡುತ್ತಿರುವ ವೈದ್ಯರು,ಶುಶ್ರೂಷಾ ಸಿಬ್ಬಂದಿ ಹಾಗೂ ಆಸ್ಪತ್ರೆಯ ವ್ಯವಸ್ಥಾಪಕರನ್ನು ಹೊಣೆಗಾರರನ್ನಾಗಿ ಮಾಡುವುದಿಲ್ಲವೆಂದು ತಿಳಿಸುತ್ತಾ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿರುತ್ತೇನೆ.

ಪರೀಕ್ಷಾರ್ಥಿ: ಸಹಿ - ..... ಹೆಸರು - .....

ಸಾಕ್ಷಿ : 1) ಸಹಿ - ..... ಹೆಸರು - .....

2) ಸಹಿ - ..... ಹೆಸರು - .....

ಸಹಿ ತೆಗೆದುಕೊಂಡ ದಿನಾಂಕ: .....

ಸಂದರ್ಶಕರ ಸಹಿ
ದಿನಾಂಕ:

ಪ್ರಧಾನ ಪರೀಕ್ಷಕರ ಸಹಿ
ದಿನಾಂಕ:

ANNEXURE: IV, STUDY PROFORMA

Patient Name: **Age:** Years
Sex: Male/Female **Date of 1st Visit: / /**
UHID: **Occupation:**
Address: **Phone:**
History Of Presenting Illness:

Past History (P/H):
Diabetes:
Hypertension:
Renal Disease:
Liver Disease:
Cardiac Disease:
Other Significant P/H:
Family History:
Menstrual History (Only For Females):
Personal History:
Alcohol:
Smoking:
Other Substance Abuse:

General Physical Examination:

Days/Week	**Day-1 (Baseline)**
Pulse rate (Per Min)	
Blood Pressure (mmHg)	

Systemic Examination: At first visit

System	**Findings**
Cardiovascular System	
Respiratory System	
Per Abdomen	
Central Nervous System	

Local Examination: Spine Examination:
C- Spine:-

T- Spine:-

LS- Spine:- Tenderness-

			Right Lower Limb	Left Lower Limb
Para spinal muscle spasm				
Active Straight Leg Rising				
Power	**Extensor Digitorum Longus**			
	Extensor Halluces Longus			
Sensation				
Distal Pulse				
Other Joint Examination		**Hip**		
		Sacroiliac		
		Knee		
		Ankle		

Bone Mineral Density Assessment Using DEXA Of LS Spine AP View:

	Initial Baseline Assessment	**Assessment At 1 year after Infusion**
BMD		
T-Score		
Z-Score		

Other Investigations Conducted:

1. Complete Blood Count:

2. Random Blood Sugar:

3. Serum Urea and Creatinine:

4. ECG

5. X ray LS spine:

Comments	
Principal Investigator **Dr Umesh M**	Signature
Chief Investigator **Dr Prabhu E**	Signature

ANNEXURE: V, Kannada Version of Modified Oswestry Disability questionnaire

ಮಾಡಿಫೈಡ್ ಒಸ್ವೇಸ್ಟ್ರೀ ಬೆನ್ನು ನೋವಿನ ಅಶಕ್ತತೆ ಅಳೆಯುವ ಪ್ರಶ್ನಾವಳಿ

ಈ ಪ್ರಶ್ನೆಗಳನ್ನು ನಿಮ್ಮ ದೈನಂದಿನ ಚಟುವಟಿಕೆಗಳ ಮೇಲೆ ಬೆನ್ನು ನೋವಿನಿಂದಾಗಿರುವ ಪರಿಣಾಮವನ್ನು ಅಳೆಯಲು ಸಿದ್ಧಪಡಿಸಲಾಗಿದೆ.
ದಯವಿಟ್ಟು ಕೆಳಗಿನ ಪ್ರಶ್ನೆಗಳಲ್ಲಿ ನಿಮ್ಮ ಇಂದಿನ ನೋವಿನ ಸ್ಥಿತಿಗೆ ಸರಿ ಹೊಂದುವ ಆಯ್ಕೆಯ ಮುಂದೆ ಎಂದು ಗುರುತು ಮಾಡಿ.
ನಿಮಗೆ ಕೆಳಗಿನ ಆಯ್ಕೆಗಳಲ್ಲಿ ಸಮಾನತೆ ಕಂಡುಬಂದರೂ ಕೂಡ ನಿಮ್ಮ ಸ್ಥಿತಿಗೆ ಹೆಚ್ಚು ಹೊಂದುವ ಒಂದು ಆಯ್ಕೆಯನ್ನು ಮಾತ್ರ ಗುರುತಿಸಬೇಕು.

ವಿಭಾಗ - ೧ :- ನೋವಿನ ತೀವ್ರತೆಗೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನನ್ನ ಬೆನ್ನು ನೋವು ಸಹಿಸಿಕೊಳ್ಳುವಂತಿದ್ದು, ನನಗೆ ನೋವಿನ ಮಾತ್ರೆಯ ಅವಶ್ಯಕತೆಯಿಲ್ಲ.

..... ನನ್ನ ಬೆನ್ನು ನೋವು ತೀವ್ರವಾಗಿದ್ದು, ನೋವಿನ ಮಾತ್ರೆ ತೆಗೆದುಕೊಳ್ಳದೆ ನಿಭಾಯಿಸಬಹುದು.

..... ನನ್ನ ಬೆನ್ನು ನೋವು ತೀವ್ರವಾಗಿದ್ದು, ನೋವಿನ ಮಾತ್ರೆ ಸಂಪೂರ್ಣ ನಿವಾರಣೆ ನೀಡುತ್ತದೆ.

..... ನನ್ನ ಬೆನ್ನು ನೋವು ತೀವ್ರವಾಗಿದ್ದು, ನೋವಿನ ಮಾತ್ರೆ ಮಾಧ್ಯಮ ನಿವಾರಣೆ ನೀಡುತ್ತದೆ.

..... ನನ್ನ ಬೆನ್ನು ನೋವು ತೀವ್ರವಾಗಿದ್ದು, ನೋವಿನ ಮಾತ್ರೆ ಸ್ವಲ್ಪ ನಿವಾರಣೆ ನೀಡುತ್ತದೆ.

..... ನನ್ನ ಬೆನ್ನು ನೋವು ತೀವ್ರವಾಗಿದ್ದು, ನೋವಿನ ಮಾತ್ರೆಯಿಂದ ಯಾವುದೇ ನೋವು ಕಡಿಮೆಯಾಗುತ್ತಿಲ್ಲ.

ವಿಭಾಗ - ೨ :- ವೈಯಕ್ತಿಕ ಕಾಳಜಿ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನಾನು ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿ ವಹಿಸಬಹುದಾಗಿದ್ದು, ಅದರಿಂದ ನೋವು ಹೆಚ್ಚಾಗುವುದಿಲ್ಲ.

..... ನಾನು ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿ ವಹಿಸಬಹುದಾಗಿದ್ದು, ಆದರೆ ಅದರಿಂದ ನೋವು ಹೆಚ್ಚಾಗುತ್ತದೆ.

..... ನನಗೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿ ವಹಿಸುವುದು ಕಷ್ಟವಾಗಿದ್ದು, ಅದನ್ನು ನಿಧಾನವಾಗಿ ಹಾಗು ಎಚ್ಚರಿಕೆಯಿಂದ ನಿಭಾಯಿಸುತ್ತಿದ್ದೇನೆ.

..... ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿಯ ಬಹುತೇಕ ಕೆಲಸಗಳನ್ನು ಮಾಡಬಹುದಾಗಿದ್ದು,ಅದಕ್ಕೆ ಬೇರೆಯವರ ಸಹಾಯದ ಅಗತ್ಯವಿದೆ.

..... ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿಯ ಬಹುತೇಕ ಕೆಲಸಗಳಲ್ಲಿ ಬೇರೆಯವರ ಸಹಾಯದ ಅವಶ್ಯಕತೆಯಿದೆ.

..... ನನ್ನ ವೈಯಕ್ತಿಕ ಕಾಳಜಿಯ ಬಹುತೇಕ ಕೆಲಸಗಳನ್ನು ಮಾಡುವುದು ಅಸಾಧ್ಯವಾಗಿದ್ದು, ಎಲ್ಲವನ್ನು ಮಲಗಿದಲ್ಲಿಯೇ ಮಾಡುತ್ತಿದ್ದೇನೆ.

ವಿಭಾಗ - ೩ :- ಭಾರ ಎತ್ತುವುದು

..... ನಾನು ೧೦ ಕೆ ಜಿ ತೂಕವನ್ನು ನೋವು ಹೆಚ್ಚಾಗದಂತೆ ಎತ್ತಬಹುದು.

..... ನಾನು ೧೦ ಕೆ ಜಿ ತೂಕವನ್ನು ಎತ್ತಬಹುದು, ಆದರೆ ನೋವು ಹೆಚ್ಚಾಗುತ್ತದೆ.

..... ನೋವಿನಿಂದ ೧೦ ಕೆ ಜಿ ತೂಕವನ್ನು ಎತ್ತುವುದು ಕಷ್ಟವಾಗಿದೆ, ಆದರೆ ಅನುಕೂಲಕರವಾದ ಜಾಗದಿಂದ ಎತ್ತಬಹುದು.
(ಉದಾಹರಣೆಗೆ :- ಟೇಬಲ್ ಮೇಲಿನಿಂದ...)

..... ನೋವಿನಿಂದ ೧೦ ಕೆ ಜಿ ತೂಕವನ್ನು ನೆಲದಿಂದ ಎತ್ತುವುದು ಕಷ್ಟವಾಗಿದೆ, ಆದರೆ ಅನುಕೂಲಕರವಾದ ಜಾಗದಿಂದ ಎತ್ತಬಹುದು.

..... ನನಗೆ ಹಗುರವಾದ ವಸ್ತುಗಳನ್ನು ಮಾತ್ರ ಎತ್ತಲಾಗುತ್ತದೆ.

..... ನನ್ನಿಂದ ಯಾವುದೇ ವಸ್ತುಗಳನ್ನು ಎತ್ತಲಾಗುವುದಿಲ್ಲ.

ವಿಭಾಗ - ೪ :- ನಡೆಯುವುದಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನಾನು ಎಷ್ಟು ದೂರವಾದರೂ ನಡೆಯಬಹುದು, ಅದರಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ೨ ಕಿ ಮೀ ಗಿಂತ ಹೆಚ್ಚು ನಡೆಯಲು ಸಾಧ್ಯವಾಗುವುದಿಲ್ಲ,

..... ನೋವಿನಿಂದ ೧ ಕಿ ಮೀ ಗಿಂತ ಹೆಚ್ಚು ನಡೆಯಲು ಸಾಧ್ಯವಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ೦.೫ ಕಿ ಮೀ ಗಿಂತ ಹೆಚ್ಚು ನಡೆಯಲು ಸಾಧ್ಯವಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನಾನು ಕೋಲು ಅಥವಾ ಊರುಗೋಲಿನ ಸಹಾಯದೊಂದಿಗೆ ಮಾತ್ರ ನಡೆಯಬಹುದು.

..... ನೋವಿನಿಂದ ನನಗೆ ನಡೆಯಲು ಅಸಾಧ್ಯವಾಗಿದ್ದು, ಯಾವಾಗಲೂ ಮಲಗಿರುತ್ತೇನೆ ಹಾಗು ಪಾಯಕಾನೆಗೂ ತೆವಳಿಕೊಂಡೇ ಹೋಗಬೇಕು.

ವಿಭಾಗ - ೫ :- ಕುಳಿತುಕೊಳ್ಳುವುದಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನನಗೆ ಬೇಕಾದಷ್ಟು ಸಮಯ ನಾನು ಕುಳಿತುಕೊಳ್ಳಬಹುದು.

..... ನನಗೆ ಆರಾಮದಾಯಕವೆನ್ನಿಸುವ ಕುರ್ಚಿಯಲ್ಲಿ ನನಗೆ ಬೇಕಾದಷ್ಟು ಸಮಯ ನಾನು ಕುಳಿತುಕೊಳ್ಳಬಹುದು.

..... ನೋವಿನಿಂದ ನಾನು ೧ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚಿಗೆ ಕುಳಿತುಕೊಳ್ಳಲಾಗವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನಾನು ಅರ್ಧ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚಿಗೆ ಕುಳಿತುಕೊಳ್ಳಲಾಗವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನಾನು ೧೦ ನಿಮಿಷಕ್ಕಿಂತ ಹೆಚ್ಚಿಗೆ ಕುಳಿತುಕೊಳ್ಳಲಾಗವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಸಂಪೂರ್ಣ ಕುಳಿತುಕೊಳ್ಳಲಾಗವುದಿಲ್ಲ.

ವಿಭಾಗ - ೬ :- ನಿಲ್ಲುವುದಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನಾನು ನನಗೆ ಬೇಕಾದಷ್ಟು ಸಮಯ ನಿಂತುಕೊಳ್ಳಬಹುದು, ಅದರಿಂದ ನೋವು ಹೆಚ್ಚಾಗುವುದಿಲ್ಲ.

..... ನಾನು ನನಗೆ ಬೇಕಾದಷ್ಟು ಸಮಯ ನಿಂತುಕೊಳ್ಳಬಹುದು, ಆದರೆ ಅದರಿಂದ ನೋವು ಹೆಚ್ಚಾಗುತ್ತದೆ.

..... ನೋವಿನಿಂದ ನನಗೆ ೧ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ನಿಲ್ಲಲಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಅರ್ಧ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ನಿಲ್ಲಲಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ೧೦ ನಿಮಿಷಕ್ಕಿಂತ ಹೆಚ್ಚು ನಿಲ್ಲಲಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಂದ ನನಗೆ ನಿಲ್ಲಲು ಅಸಾಧ್ಯವಾಗಿದೆ.

ವಿಭಾಗ - ೭ :- ಮಲಗುವುದಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನೋವಿನಿಂದ ನನ್ನ ನಿದ್ದೆಯ ಮೇಲೆ ಯಾವುದೇ ಪರಿಣಾಮ ಇಲ್ಲ.

..... ನಾನು ನೋವಿನ ಮಾತ್ರೆ ತೆಗೆದುಕೊಳ್ಳುವುದರಿಂದ ಉತ್ತಮ ನಿದ್ದೆ ಮಾಡಬಹುದು.

..... ನೋವಿನ ಮಾತ್ರೆ ತೆಗೆದುಕೊಂಡರೂ ನನಗೆ ೬ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ನಿದ್ದೆ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನ ಮಾತ್ರೆ ತೆಗೆದುಕೊಂಡರೂ ನನಗೆ ೪ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ನಿದ್ದೆ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನ ಮಾತ್ರೆ ತೆಗೆದುಕೊಂಡರೂ ನನಗೆ ೨ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ನಿದ್ದೆ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಸಂಪೂರ್ಣ ನಿದ್ದೆ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

ವಿಭಾಗ - ೮ :- ಸಾಮಾಜಿಕ ಜೀವನಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನನ್ನ ಸಾಮಾಜಿಕ ಜೀವನ ಸಾಮಾನ್ಯವಾಗಿದ್ದು, ಅದರಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುವುದಿಲ್ಲ.

..... ನನ್ನ ಸಾಮಾಜಿಕ ಜೀವನ ಸಾಮಾನ್ಯವಾಗಿದ್ದು, ಆದರೆ ಅದರಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುತ್ತದೆ.

..... ನೋವಿನಿಂದ ನನಗೆ ಹೆಚ್ಚು ಸಮರ್ಥವುಳ್ಳ ಸಾಮಾಜಿಕ ಕೆಲಸಗಳಲ್ಲಿ ತೊಡಗಿಕೊಳ್ಳಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಹೆಚ್ಚು ಹೊರಹೋಗಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನ್ನ ಸಾಮಾಜಿಕ ಜೀವನ ಮನೆಯೊಳಗಷ್ಟಕ್ಕೆ ಸೀಮಿತವಾಗಿದೆ.

..... ನೋವಿನಿಂದ ನನಗೆ ಸಾಮಾಜಿಕ ಜೀವನವೇ ಇಲ್ಲವಂತಾಗಿದೆ.

ವಿಭಾಗ - ೯ :- ಪ್ರಯಾಣಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನಾನು ಎಷ್ಟು ಸಮಯವಾದರೂ ಪ್ರಯಾಣಿಸಬಹುದು, ಅದರಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುವುದಿಲ್ಲ.

..... ನಾನು ಎಷು ಸಮಯವಾದರೂ ಪ್ರಯಾಣಿಸಬಹುದು, ಆದರೆ ಅದರಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುತ್ತದೆ.

..... ನೋವಿನಿಂದ ನಾನು ೨ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ಸಮಯ ಪ್ರಯಾಣ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನಾನು ೧ ಘಂಟೆಗಿಂತ ಹೆಚ್ಚು ಸಮಯ ಪ್ರಯಾಣ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಅವಶ್ಯಕವಿರುವ ಅರ್ಧ ಘಂಟೆಗಿಂತ ಕಡಿಮೆ ಪ್ರಯಾಣವನ್ನೂ ಮಾಡಲಾಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಆಸ್ಪತ್ರೆ, ವೈದ್ಯರ ಹೊರತುಪಡಿಸಿ, ಇನ್ನಾವುದೇ ಸ್ಥಳಕ್ಕೆ ಪ್ರಯಾಣಿಸಲಾಗುವುದಿಲ್ಲ.

ವಿಭಾಗ - ೧೦ :- ಮನೆಗೆಲಸ/ ಉದ್ಯೋಗಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ

..... ನನ್ನ ಸಾಮಾನ್ಯ ಮನೆಕೆಲಸ/ ಉದ್ಯೋಗದ ಕೆಲಸಗಳಿಂದ ನೋವು ಜಾಸ್ತಿಯಾಗುವುದಿಲ್ಲ.

..... ನನ್ನ ಸಾಮಾನ್ಯ ಮನೆಕೆಲಸ/ ಉದ್ಯೋಗದ ಕೆಲಸಗಳು ನೋವನ್ನು ಜಾಸ್ತಿ ಮಾಡುತ್ತವೆ, ಆದರೂ ನನ್ನಿಂದ

ಅವಶ್ಯಕವಿರುವ ಕೆಲಸಗಳನ್ನು ಮಾಡಬಹುದು.

..... ನಾನು ಬಹುತೇಕ ಮನೆಕೆಲಸ/ ಉದ್ಯೋಗದ ಕೆಲಸಗಳನ್ನು ಮಾಡಬಹುದು, ಆದರೆ ಹೆಚ್ಚು ಸಾಮರ್ಥ್ಯದ ಅವಶ್ಯವಿರುವ ಕೆಲಸಗಳನ್ನು ನೋವಿನಿಂದ ಮಾಡಲು ಸಾಧ್ಯವಾಗುವುದಿಲ್ಲ.

..... ನೋವಿನಿಂದ ಲಘು ಸಾಮರ್ಥ್ಯದ ಕೆಲಸಗಳನ್ನು ಹೊರತುಪಡಿಸಿ ಉಳಿದ ಕೆಲಸಗಳನ್ನು ಮಾಡಲು ಆಗುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ಲಘು ಸಾಮರ್ಥ್ಯದ ಕೆಲಸಗಳನ್ನೂ ಮಾಡಲು ಆಡುತ್ತಿಲ್ಲ.

..... ನೋವಿನಿಂದ ನನಗೆ ಯಾವುದೇ ಮನೆಕೆಲಸ/ ಉದ್ಯೋಗದ ಕೆಲಸ ಮಾಡಲು ಸಾಧ್ಯವಾಗುತ್ತಿಲ್ಲ.

Sl No	Name Of The Patient	Age	Sex	UHID	Occupation	Place	Duration Of Complaints	Medical Illness	BMD	T-Score	Z-Score	BASE LINE VAS	VAS At 1st FU and Impr	VAS AT 2nd FU and Impr	VAS at 3rd FU and Impr	BASE LINE OPI	OPI AT 1st FU	OPI At 2nd FU	OPI at 3rd FU	BMD at 1 yr	T-Score at 1yr	Z-Score at 1yr
1	Patient No 01	63	F	355817	House Wife	Kolar	1	DM	0.714	-4.46	-2.14	7	4>3	4>3	2>3	62	42	42	12	0.924	-2.2	-0.3
2	Patient No 02	66	M	377838	Farmer	Bethmangala	1.5	DM	0.887	-2.73	-1.2	4	6<2	3>1	1>3	32	40	28	8	0.905	-2.3	-0.9
3	Patient No 03	68	F	374827	House Wife	KGF	1	HTN	0.881	-3.19	-1.33	5	3>2	4>1	2>3	40	26	30	16	0.898	-2.5	-1.5
4	Patient No 04	64	F	408756	House Wife	Chintamani	2	HTN	0.809	-3.91	-2.68	7	5>2	5>2	2>5	60	42	44	16	0.834	-2.97	-2.15
5	Patient No 05	66	F	392303	House Wife	Mulabagal	5	DM	0.758	-4.02	-2.22	5	5>0	4>1	2>3	40	42	20	18	0.884	-2.54	-1.46
6	Patient No 06	72	M	449663	Farmer	Kolar	1	Nil	0.87	-2.9	-1.48	4	4>0	4>0	2>2	36	40	40	28	1.052	-1.2	-0.2
7	Patient No 07	65	F	302814	House Wife	V Kota	2.5	HTN,DM	0.834	-3.66	-2.15	7	3>4	5>2	3>4	66	36	44	20	0.905	-2.3	-0.9
8	Patient No 08	75	M	430427	Farmer	Narasapura	3	DM	0.796	-3.64	-2.32	6	2>4	4>2	2>4	56	24	38	12	0.881	-2.5	-2
9	Patient No 09	62	F	405447	House Wife	Mulabagal	1.5	HTN	0.88	-2.8	-1.97	5	5>0	4>1	2>3	44	40	38	22	0.88	-2.57	-1.97
10	Patient No 10	68	M	430286	Coolie	Srinivaspura	1.5	DM	0.898	-2.62	-1.15	6	5>1	6>0	6>0	58	50	60	44	0.994	-1.12	-0.21
11	Patient No 11	71	F	376097	House Wife	Mulabagal	3.5	Nil	0.762	-3.98	-2.1	8	4>4	5>3	5>3	76	44	48	40	0.905	-2.3	-0.9
12	Patient No 12	64	F	439687	House Wife	Chintamani	6	Nil	0.714	-4.46	-2.04	6	5>1	6>0	7<1	62	52	56	60	0.886	-2.54	-1.25
13	Patient No 13	68	F	446512	House Wife	Mulabagal	1.5	DM	0.884	-2.76	-1.34	5	4>1	5>0	6<1	38	32	36	40	1.05	-1.2	0.4
14	Patient No 14	72	F	446785	House Wife	Bangarpet	3	Nil	0.824	-3.36	-1.5	6	4>2	4>2	1>5	48	32	28	16	1.014	-1.5	0.3
15	Patient No 15	65	F	396896	House Wife	Chintamani	4	DM	0.704	-4.56	-2.21	6	6>0	5>1	2>4	52	48	40	12	0.881	-2.5	-2
16	Patient No 16	71	F	474280	House Wife	Srinivaspura	2	HTN,DM	0.816	-3.44	-1.6	4	2>2	3>1	2>2	28	16	20	16	0.816	-2.91	-1.6
17	Patient No 17	65	M	475822	Farmer	Mulabagal	1	DM	0.91	-2.5	-2	8	5>3	4>4	2>6	68	36	28	16	1.063	-1.1	0.5
18	Patient No 18	69	F	362540	House Wife	Srinivaspura	6	DM	0.699	-4.91	-2.32	5	3>2	4>1	2>3	36	20	24	12	0.924	-2.2	-0.3
19	Patient No 19	70	M	435908	Farmer	Mulbagal	2	Nil	0.794	-3.66	-2.1	7	4>3	5>2	2>5	62	36	40	16	0.924	-1.84	-0.12
20	Patient No 20	68	F	452179	House Wife	Mulbagal	3	Nil	0.756	-4.04	-2.08	5	2>3	4>1	2>3	46	16	28	12	0.824	-2.6	-1.02
21	Patient No 21	72	M	413216	Farmer	Bethmangala	4	DM	0.818	-3.42	-2	4	2>2	3>1	1>3	26	12	16	12	0.924	-2.2	-0.98
22	Patient No 22	69	M	304469	Rtd Conductor	Narasapura	4.5	Nil	0.842	-3.18	-1.52	5	4>1	3>2	2>3	48	36	28	20	0.912	-2.48	-1.06
23	Patient No 23	70	F	424615	House Wife	Bangarpet	1.5	HTN	0.794	-3.66	-2	7	5>2	4>3	6>1	64	44	38	32	0.828	-2.8	-1.42
24	Patient No 24	64	M	407625	Mechanic	Kolar	5	Nil	0.734	-4.26	-2	6	5>1	4>2	3>3	64	56	40	24	1.025	-1.4	0.5
25	Patient No 25	70	F	334940	House Wife	Tamaka	6	DM	0.724	-4.36	-2.16	5	4>1	5>0	3>2	36	28	40	20	0.956	-1.82	-0.36
26	Patient No 26	62	F	442820	House Wife	KGF	1	Nil	0.715	-3.88	-2.12	6	4>2	5>1	6>0	42	26	32	40	0.997	-1.6	-0.9
27	Patient No 27	72	F	471309	House Wife	Mulabagal	5	DM,HTN	0.682	-4.78	-2.4	5	4>1	4>1	2>3	40	32	30	20	0.886	-2.08	-0.84
28	Patient No 28	65	M	510514	Farmer	Kolar	3	Nil	0.806	-3.54	-1.86	7	5>2	7>0	4>3	56	10	40	28	1.014	-1.5	0.3
29	Patient No 29	60	F	417167	Farmer	Kolar	10	Nil	0.754	-4.06	-2.04	6	4>2	4>2	2>4	48	32	32	16	0.997	-1.6	0.2
30	Patient No 30	73	M	485680	Farmer	Kolar	2.5	Nil	0.882	-2.78	-1.4	5	3>2	4>1	1>4	42	12	16	8	0.974	-1.7	-0.2
31	Patient No 31	71	M	426552	House Wife	Bangarpet	3	DM	0.896	-2.64	-1.21	8	5>3	7>1	6>2	78	62	58	44	0.994	-1.24	-0.14
32	Patient No 32	72	F	408964	House Wife	Malur	3	Nil	0.864	2.96	-1.6	5	4>1	3>2	2>3	34	22	28	14	1.09	-0.7	1.1
33	Patient No 33	65	F	351419	House Wife	Bangarpet	1.5	Nil	0.822	-3.38	-1.62	6	5>1	6>0	3>3	38	36	40	20	0.941	-1.82	-0.4
34	Patient No 34	66	F	355280	House Wife	Mulabagal	5	DM	0.718	-4.42	-2.12	8	5>3	4>4	2>6	72	44	36	16	0.924	-2.2	-0.3

35	Patient No 35	68	F	340640	House Wife	Chintamani	3	HTN	0.862	-2.98	-1.38	4	2>2	2>2	2>2	32	16	18	12	1.058	-1	0.7
36	Patient No 36	64	F	410442	House Wife	Srinivaspura	1.5	HTN	0.724	-4.36	-1.98	7	4>3	5>2	2>5	56	28	36	16	0.896	-2.42	-1.54
37	Patient No 37	73	F	154379	House Wife	Bangarpet	3	Nil	0.824	-3.36	-1.46	5	3>2	1>4	1>4	40	16	8	8	1.025	-1.4	0.5
38	Patient No 38	69	F	469481	House Wife	Bangarpet	1.5	Nil	0.882	-2.78	-1.41	5	4>1	2>3	2>3	38	30	24	18	0.997	-1.6	0.2
39	Patient No 39	70	M	330269	Mechanic	Kolar	3.5	DM	0.825	-3.35	-1.6	4	3>1	2>2	1>3	20	12	8	6	0.889	-2.26	0.96
40	Patient No 40	64	F	408756	House Wife	Bethmangala	2.5	HTN,DM	0.814	-3.46	-2.46	8	5>3	3>8	2>6	64	28	20	10	0.972	-1.7	-0.4
41	Patient No 41	66	F	469479	House Wife	Malur	10	Nil	0.701	-4.59	-2.19	8	6>2	2>4	3>5	56	28	20	12	0.701	-3.92	-2.19
42	Patient No 42	72	F	423059	House Wife	Mulabagal	2	Nil	0.779	-3.4	-1.6	6	4>2	3>3	2>4	48	32	28	12	0.924	-2.2	-0.3
43	Patient No 43	70	F	433896	House Wife	Kolar	2.5	DM	0.718	-4.42	-2.1	6	4>2	2>2	1>5	48	32	16	8	0.939	-2.1	-0.5
44	Patient No 44	70	F	375893	House Wife	KGF	2	DM	0.804	3.56	-1.86	6	5>1	2>2	3>3	50	42	20	24	0.997	-1.6	-0.9
45	Patient No 45	62	F	469754	House Wife	Kolar	3	Nil	0.824	-3.36	-1.58	6	5>1	4>2	2>4	36	28	24	12	0.978	-1.7	-0.3
46	Patient No 46	75	F	302814	House Wife	Chintamani	1.5	DM,HTN	0.838	-3.22	-1.91	7	4>3	4>3	2>5	42	22	28	12	1.062	-1.2	0.2
47	Patient No 47	76	M	375729	Farmer	Srinivaspura	5	DM,HTN	0.906	-2.54	-1.92	8	7>1	5>3	2>6	52	40	28	14	1.001	-1.6	0.1
48	Patient No 48	69	M	394258	Farmer	Srinivaspura	3	Nil	0.869	-2.91	-1.48	4	3>1	2>2	4>0	24	20	16	32	0.998	-1.12	-0.18
49	Patient No 49	75	M	469485	Coolie	Mulbagal	3	Nil	0.79	3.7	-2.39	7	4>3	3>4	5>2	58	24	20	36	0.938	-1.48	-0.31
50	Patient No 50	72	F	273507	House Wife	Mulabagal	4.5	Nil	0.682	-4.78	-2.48	8	6>2	2>6	2>6	78	48	20	10	0.978	-1.32	-0.41
51	Patient No 51	76	M	507755	Farmer	Mulbagal	3	Nil	0.881	-2.5	-2	4	3>1	2>2	3>1	32	28	20	22	0.972	-1.7	-0.4
52	Patient No 52	78	M	411422	Farmer	Malur	1.5	Nil	0.802	-3.58	-1.96	5	3>2	1>4	1>4	28	20	8	6	1.09	-0.7	1.1
53	Patient No 53	64	F	489433	House Wife	Kolar	1.5	DM	0.861	-2.99	-0.4	6	4>2	4>1	2>4	44	28	32	18	1.052	-1.2	0.2
54	Patient No 54	73	M	408498	Farmer	Mulabagal	2	DM	0.862	-2.98	-1.12	4	2>2	2>2	2>2	28	16	12	16	1.058	-1	0.7
55	Patient No 55	70	F	408105	House Wife	Mulabagal	2	HTN	0.74	-4.2	-1.98	8	5>3	4>4	2>6	74	40	32	20	1.014	-1.5	0.3
56	Patient No 56	72	M	453621	Farmer	Mulabagal	5	Nil	0.779	-3.4	-1.6	5	3>2	2>3	1>4	40	24	20	10	0.939	-2.1	-0.5
57	Patient No 57	63	F	260757	House Wife	Bethmangala	1.5	DM	0.806	-3.54	-1.26	5	3>2	3>2	1>4	28	18	16	8	0.798	-2.08	-0.94
58	Patient No 58	63	F	458053	House Wife	Srinivaspura	1	DM	0.52	-6.4	-4	8	5>3	4>4	4>4	76	40	34	24	0.946	-1.82	-0.24
59	Patient No 59	66	M	424876	Mechanic	Kolar	6	DM	0.66	-4.7	-3.4	5	4>1	2>3	2>3	40	32	20	12	0.881	-2.5	-2
60	Patient No 60	69	F	438562	House Wife	Srinivaspura	5	Nil	0.724	-4.36	-1.98	7	4>3	3>4	2>5	40	28	24	18	0.784	-2.89	-1.48
61	Patient No 61	65	F	445612	Farmer	KGF	3	Nil	0.806	-3.54	-1.23	8	6>2	4>4	3>5	52	40	26	24	0.799	-2.43	-1.09
62	Patient No 62	82	M	423085	Farmer	Bethmangala	3	Nil	0.894	-2.66	-0.5	6	6>0	4>2	2>4	36	44	36	16	1.002	-1.6	0.4
63	Patient No 63	70	M	73829	Farmer	KGF	4	Nil	0.881	-2.5	-2	6	5>1	2>4	1>5	38	36	20	10	0.978	-1.7	-0.3