"STUDY OF EFFECT OF ZOLEDRONIC ACID ON BACK PAIN IN PATIENTS WITH OSTEOPOROSIS"

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ABSTRACT

Introduction: Osteoporosis is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility, resulting in decreased bone strength and increased risk of fracture. Zoledronic acid is a bisphosphonate which can be given once in a year IV, has better patient compliance and good clinical efficacy compared to other oral bisphosphonates. The present study aimed to evaluate the effect of Zoledronic acid in patients with low back pain due to osteoporosis

Materials and Methods: This longitudinal study was conducted among the patients attending OPD / admitted with low back pain at the KLES DR. Prabhakar Kore Hospital and Medical Research Centre and Charitable Hospital, Belagavi in between 1st January 2021 to 31stDecember 2021, over a period of one year. The patients were assessed for the BMD, BMI, VAS, ODI, FRAX score at the various interval of time till one year. Outcome measures were analyzed using the SPSS (Statistical package for social sciences) program.

Results: Total of 30 patients included with mean age of 63.43±9.38 yrs and 60 percent were female patients. There was insignificant change in the BMD, T-score, and significant improvement in VAS among the patients compared to the baseline at each visit. However, the reduction in the mean score of osteoporotic fracture probability and the hip fracture probability did not show significant difference in one year follow-up. ($p>0.05$)

Conclusion: The present study is successful in demonstrating significant improvement in associated pain among the patients with osteoporosis at the end of one year of follow-up and the insignificant change in the bone mineral density at the end of one year follow-up. Long term follow-up treatment is required to assess the change in bone mineral density.

Keyword: Bone Mineral Density, Zoledronic Acid, Bisphosphates, Osteoporosis, Mineralization

ABBREVIATIONS

AP	ANTERO POSTERIOR
AVG	AVERAGE
BMD	BONE MINERAL DENSITY
COX	CYCLOOXYGENASE
DEXA	DUAL ENERGY X-RAY ABSORPTIOMETRY
DMP-1	DENTIN MATRIX PROTEIN
FRAX	THE FRACTURE RISK ASSESSMENT TOOL
GE	GENERAL ELECTRONICS
IGF-1	INSULIN-LIKE GROWTH FACTOR 1
ISCD	INTERNATIONAL SOCIETY FOR CLINICAL DENSITOMETRY
ICMR	INDIAN COUNCIL FOR MEDICAL RESEARCH
LS	LUMBOSACRAL
LVS	LATERAL VERTEBRAL STUDY
MRI	MAGNETIC RESONANCE IMAGING
MSCs	MESENCHYMAL STEM CELLS
NOF	NATIONAL OSTEOPOROSIS FOUNDATION
NSAIDs	NONSTEROIDAL ANTI-INFLAMMAT0RY DRUGS
OA	OSTEOARTHRITIS
ODI	OSWESTRY DISABILITY INDEX
OPG	OSTEOPROTEGERIN
PTH	PARATHYROID HORMONE
RA	RADIOGRAPHIC ABSORPTIOMETRY
ROS	REACTIVE OXYGEN SPECIES

SPA	SINGLE PHOTON AND X-RAY ABSORPTIOMETRY
TRAP	TARTRATE-RESISTANT ACID PHOSPHATASE
TRPV1	TRANSIENT RECEPT0R POTENTIAL VANILLOID 1
VAS	VISUAL ANALOGUE SCALE
VCF	VERTERBAL COMPRESSION FRACTURES
WHO	WORLD HEALTH ORGANIZATION
ZA	ZOLEDRONIC ACID
PBM	PEAK BONE MASS
PKP	PROHYLACTIC KYPHOPLASTY
aBMD	AREAL BONE MINERAL DENSITY
RANK-L	RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA – LIGAND
FGF	FIBROBLASTIC GROWTH FACTOR
BRC	BONE RESORPTION-COMPARTMENT
CSF	CEREBROSPINAL FLUID
IGF	INSULIN-LIKE GROWTH FACTOR
CM	C-MECHANOSENSITIVE FIBRES
CMi	C-MECHANO-INSENSITIVE FIBRES
NGF	NERVE GROWTH FACTOR
IV	INTRAVENOUS
PGE2	PROSTAGLANDIN E2
LIFS	LUMBAR INTERBODY FUSION SURGERY
CTX	C-TERMINAL TELOPEPTIDE COLLAGEN
P1NP	PROCOLLAGEN TYPE 1N PROPEPTIDE
MC	MODIC CHANGES

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INTRODUCTION

Osteoporosis, a disease with decreasing bone-mass, mostly in post-menopausal women, but it can also affect people who have any hidden illnesses/significant risk factors for bone-mineral loss.[1] Peak bone mass(PBM), which refers to the bone mass and strength attained at the completion of the development phase, is crucial in determining the likelihood that an adult would have an osteoporotic fracture. A one standard deviation increase in peak-bone mass is thought to lead to a drop of half in the risk of fracture. The comparative benefaction of peak-bone mass to fracture risk been determined by analyzing the changeness of areal bone mineral density (aBMD) individual values in response to age. If peak-bone mass were almost always irrelevant in defining aBMD and fracture-risk in old life, one could foresee extension in the range of aBMD values with age.

Clinicians frequently struggle with managing bone pain, which is mostly seen in older patients. The potential to function and quality of life of a someone can be irreparably harmed by back pain. In Europe, 19% of persons have serious chronic pain. in Italy, this number rises to 26 percent.[3,4]

However, every musculoskeletal location is liable to fractures, vertebral and hip fractures are its main clinical manifestations. In a study by Thulkar J et al., osteoporosis was estimated to affect 24.6 percent of men and 42.5 percent of women over the age of 50.[5] More than 10-million Americans have osteoporosis, but only a small percentage receive diagnosis and treatment.

INTRODUCTION

Seventy patients with symptomatic vertebral fractures report difficulty standing, sixty-five percent report difficulty bending, and forty-one percent report constant pain.[6] According to Klotzbuecher et al., having one vertebral compression fracture raises the risk of developing another.[6]The antiresorptive zoledronic-acid slows the rate of bone dissolution.

Numerous investigations are mentioning that zoledronic-acid, with a handful of the other bis-phosphonates, also has analgesic effects/results, however the mechanism is still being researched.[7–13]

In comparison to other oral bis-phosphonates, zoledronic-acid, can be administered intravenously just one time a year, has higher patient compliance plus effective clinical use. Another noteworthy feature is the paucity of studies on osteoporosis prevalence in the Indian-population.

This study evaluates the functional efficacy of yearly infusion of Zoledronic-acid in vertebral osteoporosis.

AIMS AND OBJECTIVES

AIM:

1. To evaluate the effect of Zoledronic acid on patients with back pain due to osteoporosis.

OBJECTIVE:

1. To measure the bone mineral density among all the included patients
2. To follow-up and assess the effect of Zoledronic acid on the bone mineral density at each follow-up for one year.

REVIEW OF LITERATURE

Osteoporosis is an extensive reduction in bone-density that happens when bone resorption outpaces bone-formation. Osteoporosis, as WHO mentions when bone-mineral-density that is 2.5 S-D falling-below the mean for young-people of the same sex (Tscore).

An osteoporotic fracture occurs every three seconds due to micro-bone mineral loss, which results in more than 8.9 million fractures each year.[14] 200 million women are thought to be afflicted by osteoporosis globally, with one in ten in their 60s, one out of five women in their 70s, two out of five women in their 80s, and out of five, two in their 90s are inflicted.[15]The lifetime risk of cracking one hip, spine, or forearm is 40% due to osteoporosis, which affects 45% of women over the age of 50. Men over the age of 60 have a higher risk of developing osteoporosis later in life due to secondary causes. Alcohol-abuse, glucocorticoid excess (endogenous Cushing's syndrome or more commonly chronic glucocorticoid use) and hypogonadism are the three main causes of osteoporosis in men.[16,17]

Bone Morphology[18]

Certain-cells in the bone make 10 per cent of bone volume. They are four in numbers:

Osteoprogenitor Cells (stem-cells): Osteoprogenitor type of cells can develop intoosteoblasts.[19]

Bone-making Cells(osteoblasts): They cover the outer layer of the skeletal unit closely. They generate and secrete bone matrix (osteoid).Vit-D and parathyroid signaling molecule (PTH) induce osteoblasts to releasemacrophage-CSF and express RANK-L, both of which areso important.

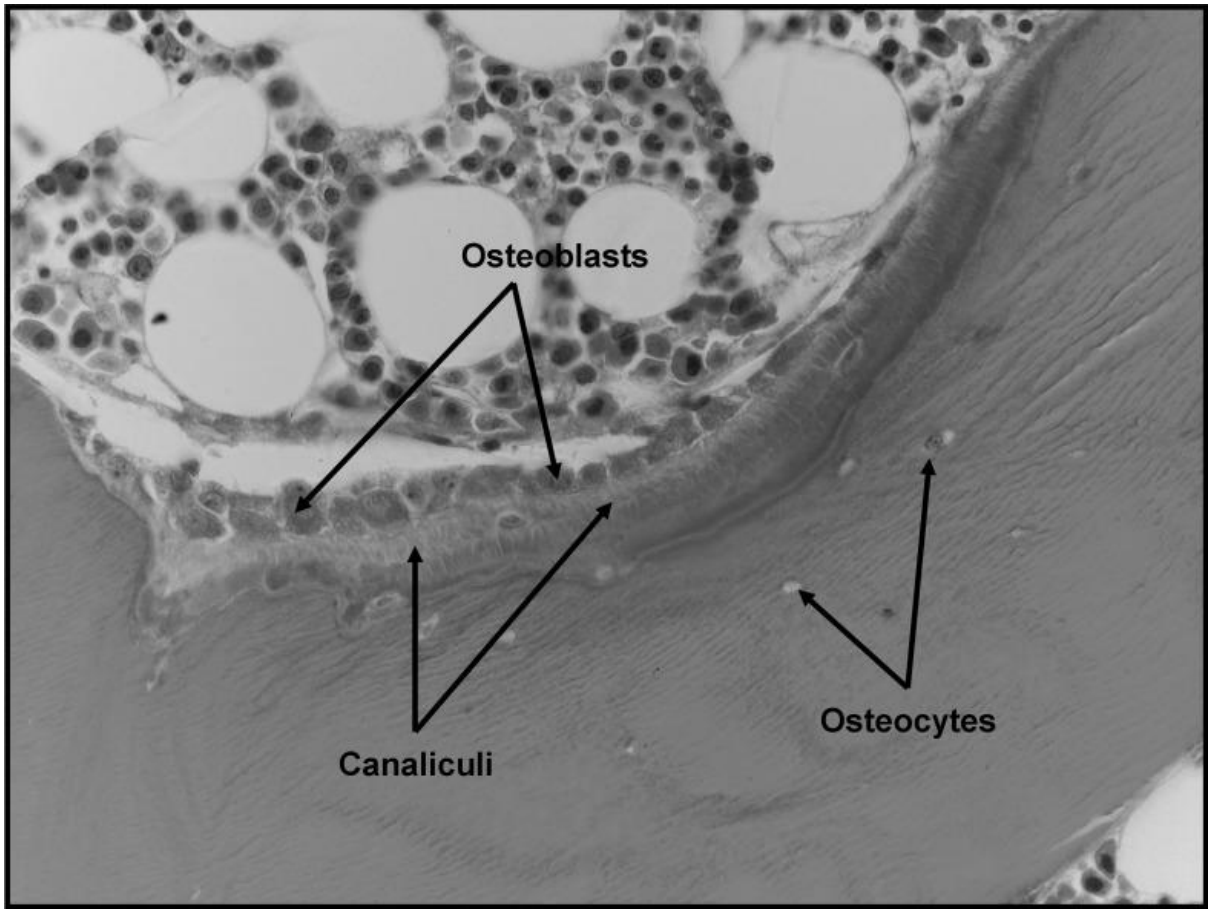

Figure 1: Osteoblasts synthesize proteinaceous matrix[20]

Osteocytes (Mechano-sensing Cells) make about 90percentof all bone-cells. They are made up of osteoblastic cell. Osteocytes are endocrine cells because they direct the remodeling of the bone. They release FGF23 to alter serum phosphate levels. Increased renal phosphate excretion by both kidneys is the result of FGF23 decreasing the expression of sodium and phosphate co-transporters in the kidneys and intestine.[21]

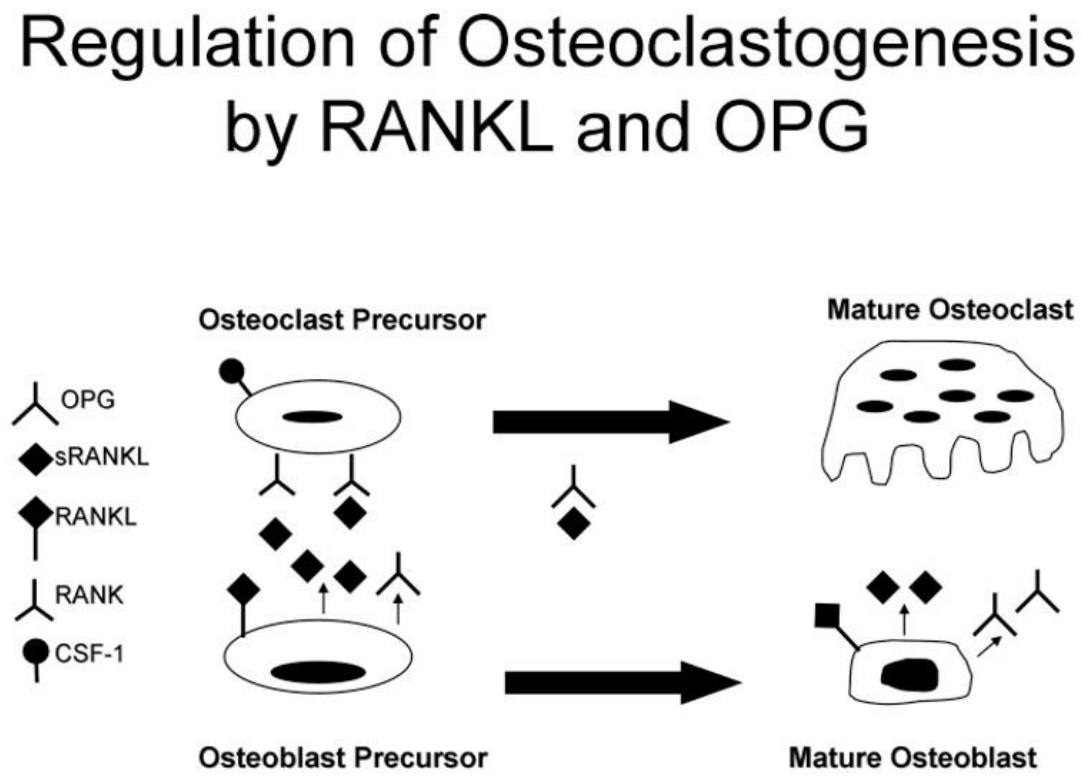

Figure 2: Schematic illustration of osteoclastogenesis[20]

Osteoclasts-bone resorbing cells: the production of hydrogen ions by osteoclasts, tartrate resistant acid phosphatase (TRAP) and cathepsin-K enzymes are required for bone resorption. The mineral component of bone matrix is dissolved by hydrogen ions in the resorption compartment underneath osteoclasts, whereas cathepsin K and tartrate-resistant acid phosphatase (TRAP) decompose the proteinaceous matrix, which is largely made of type I collagen. PTH increases osteoclast activity while calcitonin decreases it.[22]

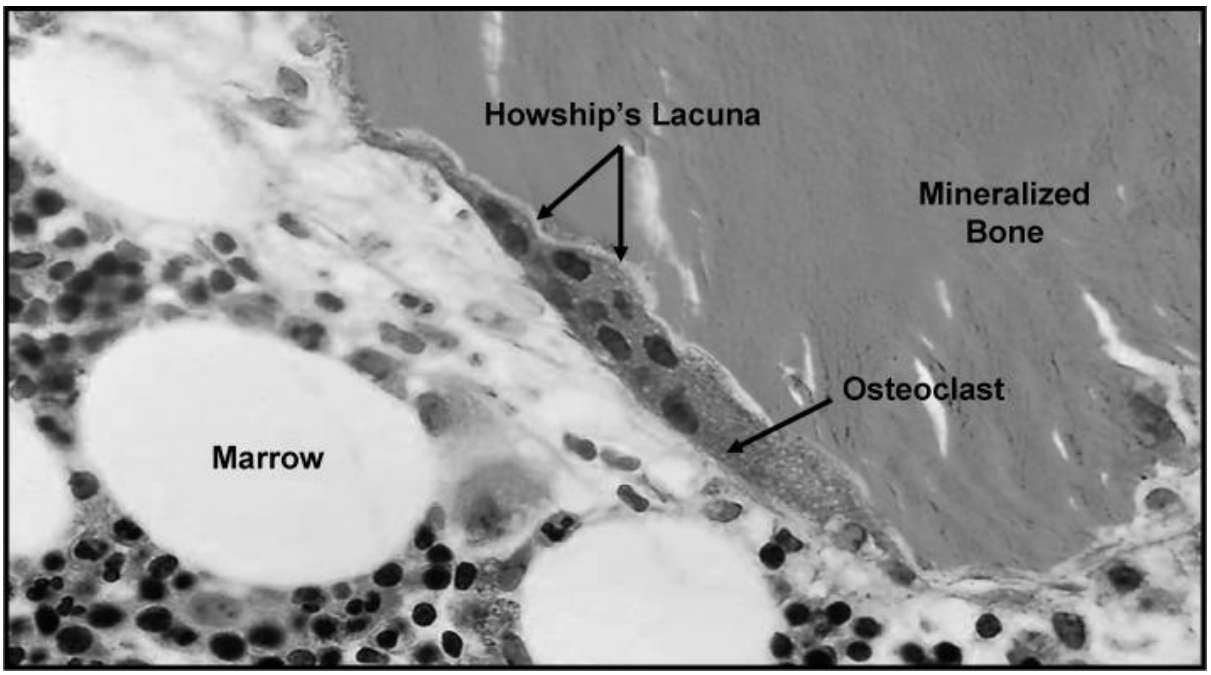

Figure 3: Multinucleated osteoclasts resorb bone to form resorption pits known as Howship's lacunae.[20]

Bone extracellular matrix[18]

This accounts for 90percent of total bone volume. It is made up of both inorganic (mineral) and organic matrices.[23]

Inorganic Bone Matrix: responsible for 99percent of calcium storage in the body, 85percent of phosphorus storage, and 40 to 60percent of magnesium and salt storage. It mostly takes the form of hydroxyapatite [Ca10(PO4)6(OH)2] and is responsible for the bone's strength, rigidity, and resistance to compressive stresses. Organic Bone Matrix: is mostly type I collagen and is released by osteoblasts. Glycoproteins, growth factors, and proteoglycans are also present. Growth factors (such as osteocalcin, osteonectin, and bone sialoprotein) are vital in the creation, mineralization, and remodeling of osteoid. The organic matrix gives bone its shape and offers tensile resistance.

Bone remodelling:[18]

It is a physiologic action where the osteoclastic-cells eat away old worn out/damaged skeleton and then osteoblasts come to add new units of the bone over there. A remarkable link is there between skeletal unit formation and its dissolution in order to ensure that there is ultimately no net difference in the amount/quality after every cycle of remodeling. This action does require a synchronous function of all the 4 different kinds of cells of the bone. It is figured out into 4 types but do exist in a co-existing stage:

I: Inception of the bone remodeling where the bone remodeling-compartment attracts the osteo-clasts.

II: Osteoprogenitor recruitment and the subsequent resorption of bone. The initial-process here is bone-resorption, however mesenchymal stem-cells and/or osteoprogenitors are also recruited into the BRC i.e., bone resorption-compartment.

III: Creation and role of osteoblasts (osteoid synthesis). Osteoid, which is created by osteoblasts, replaces removed bone.

IV: Consummation of bone remodeling and mineralization of osteoid. The mineralization of the osteoid completes the bone remodeling cycle.[24]

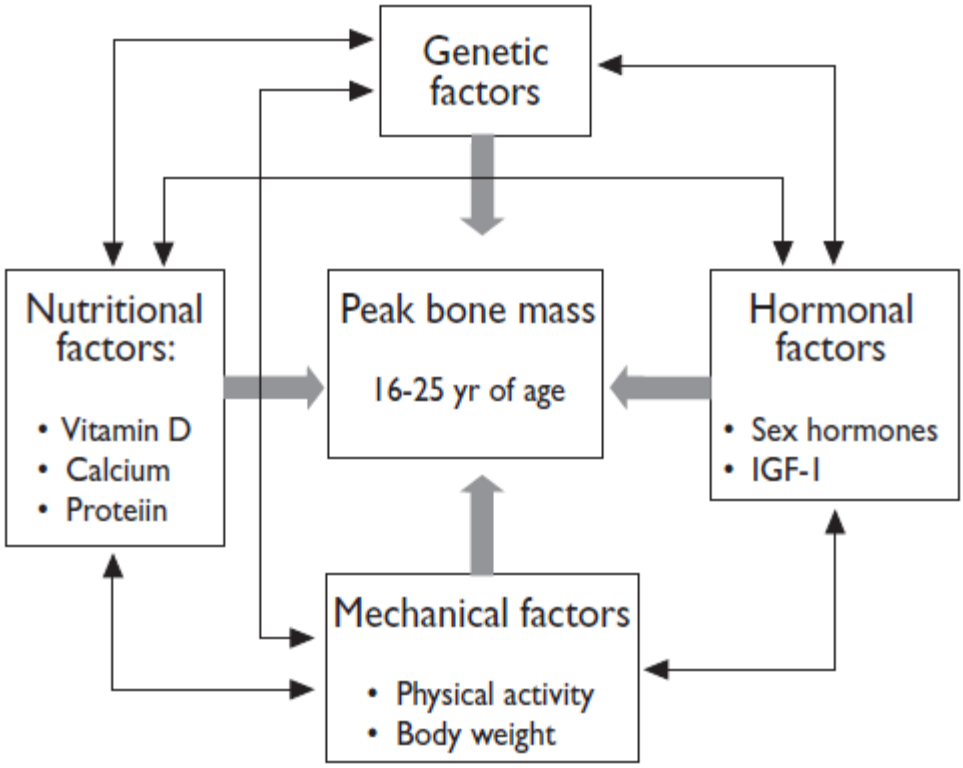

Figure 4 : Peak bone mass determining factors.[2]

Pain process

Pain is a dynamic sensation that is frequently useful in that it warns of imminent or current injury, avoiding or limiting tissue damage. Aside from this, pain has solely negative impacts in terms of the metabolic and behavioral reactions it causes. The immediate effects of pain include irritability, anxiety, disruption of sleep and waking state, increased oxygen demand, ventilator-perfusion mismatch, reduced nutrient intake, and increased stomach acidity. Increased catabolism, decreased immune function, postponed recovery, and poor emotional bonding are short-term impacts of pain.[25]

Long-term effects of pain might include alterations in reaction to future painful experiences, pain memory, and developmental retardation. Painful memories have long-term effects on

pain perception and reaction.[26]

It is thought that learning about pain begins with the first unpleasant experience and may have an impact on how further painful experiences are perceived and responded to.

Pathway: Transduction, transmission, modulation, and perception are the four major processes.

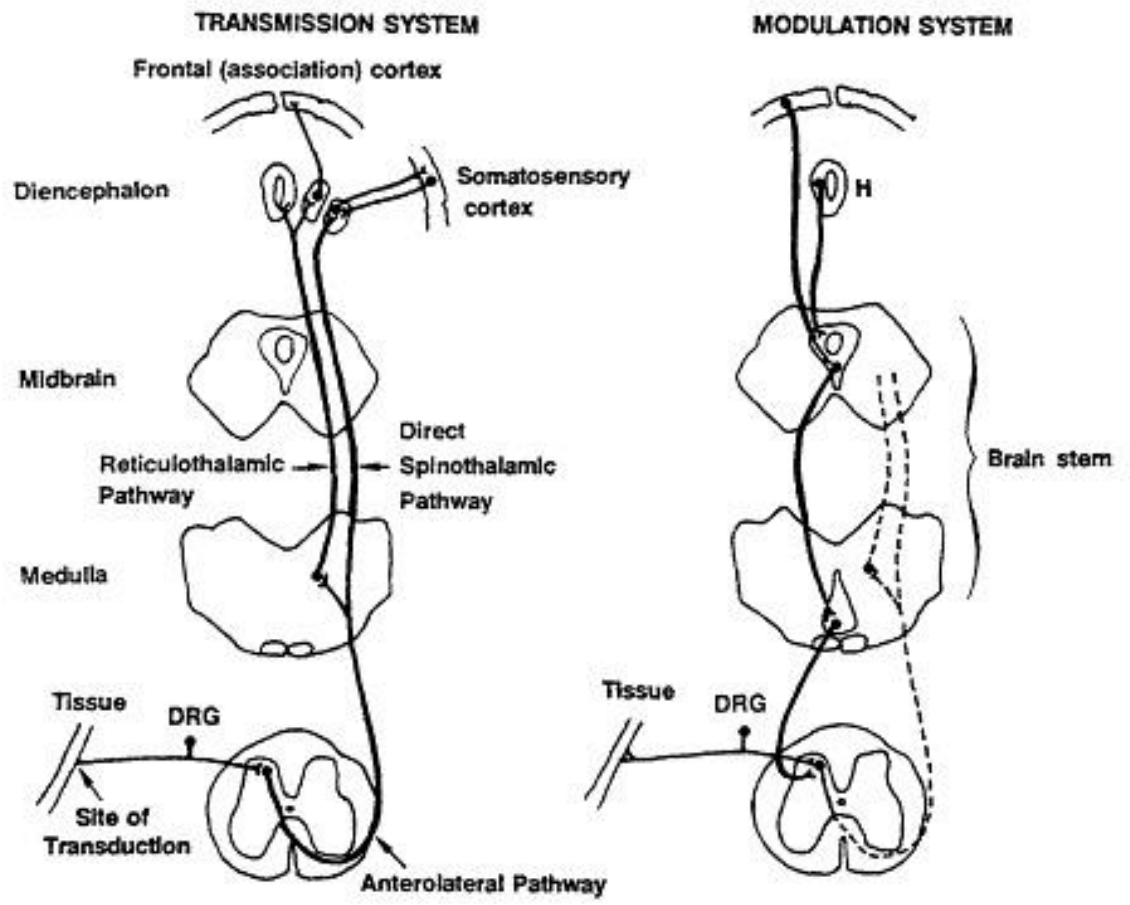

Figure 5 : Pain reflex

A diagrammatic representation of the primary brain structures involved in pain. The chain of events that leads to Transduction (bottom left) is the very first step in the transmission network that leads to the production of nerve signals in the primary afferent nociceptor in response to noxious stimuli. Either way directly through the spinothalamic tract or indirectly through the reticular formation and reticulothalamic route, central pain-transmitting cells

send their message to the thalamus.

The thalamus transmits the message to the cerebral cortex. The pain-modulating system receives signals from the hypothalamus and frontal associative cortex (H). The midbrain and medulla are traversed by the outflow on its way to the dorsal horn of the spinal cord. There, it prevents cells from transmitting pain, lessening how uncomfortable you feel.

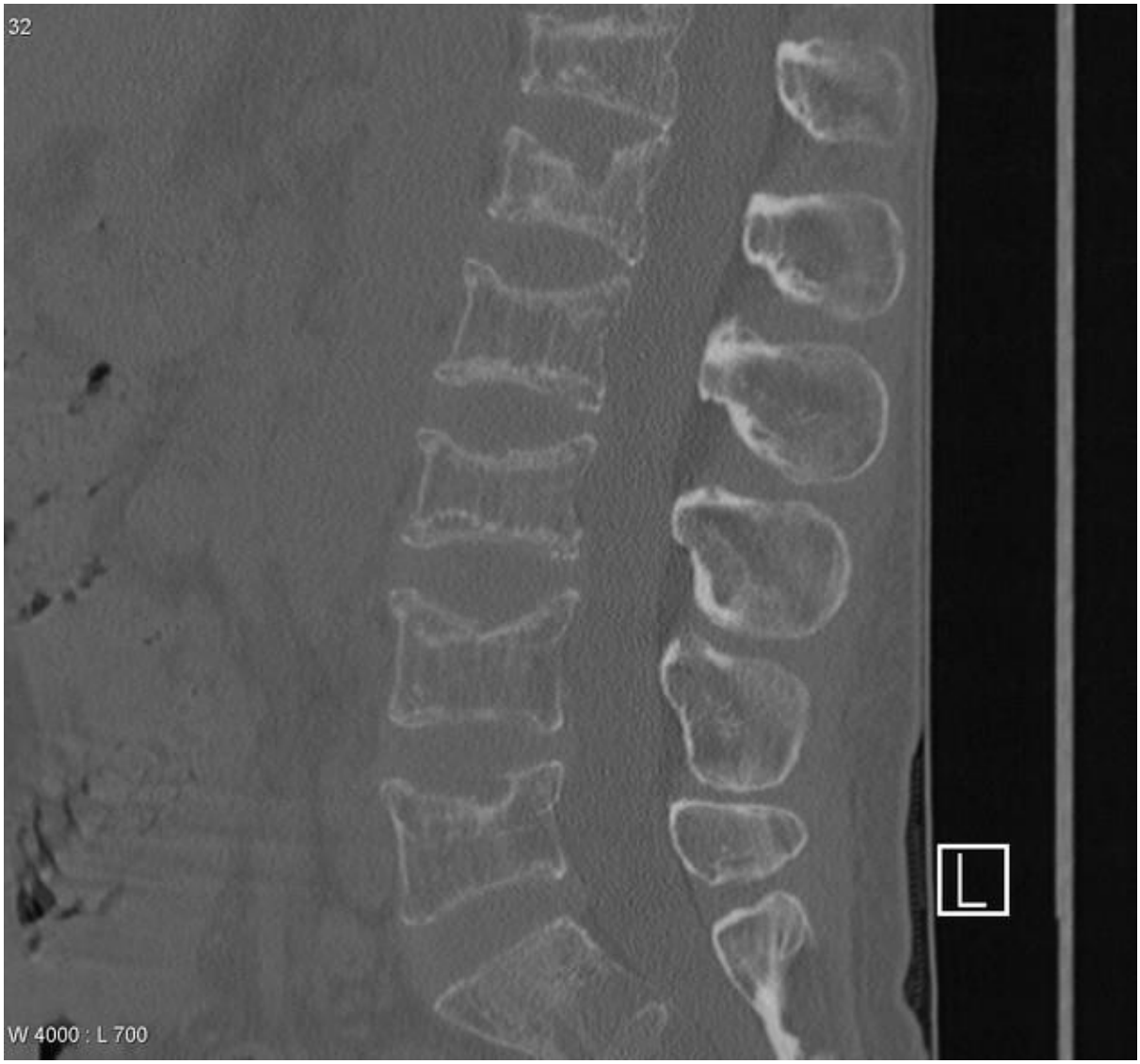

Figure 6 : Osteoporotic spine

Osteoporosis[18]

This is a common disorder of bone remodeling which is characterized by low bone mass and structural deterioration of bone. It causes bone fragility and increased vulnerability to fractures.[24, 27-29] There are two types of osteoporosis:

Primary osteoporosis: Type I and Type II

Secondary/Glucocorticoid-induced osteoporosis

Type I: (postmenopausal osteoporosis),outcomes following the menopause-related reduction in estrogen levels. According to the pathophysiology behind it, estrogen insufficiency increases the production of RANKL and M-CSF, which in turn induces an increase in osteoclast activity. It also inhibits osteoclast apoptosis by decreasing the expression of FasL by preosteoclasts.

Type II: In addition to bone resorption in postmenopausal women, it is mostly age-related and focused on osteoblasts (bone production). According to the pathophysiology described, aging-related alterations in reactive oxygen species (ROS), insulin-like growth factor 1 (IGF-1), and PTH levels lead to reduced bone production in both men and women.

Secondary/Glucocorticoid-induced osteoporosis: Multiple sclerosis and rheumatoid arthritis are two inflammatory diseases that are treated using glucocorticoids, which are immunomodulatory medications. One of the common negative effects of glucocorticoid therapy is bone loss and an increased risk of fractures. Glucocorticoids encourage the development of osteoprogenitors into adipocytes while inhibiting the differentiation of osteoprogenitors into osteoblasts (fat cells). Additionally, they worsen osteoblast function and raise apoptosis rates. Furthermore, glucocorticoids work to extend the lifespan of mature osteoclasts, which worsens the already existing imbalance between bone production and bone resorption in favor of bone resorption.

Risk factor assessment[30]

All people are susceptible to fractures, but those who have just gone through menopause, men over 50, and those who have had a fragility or low-trauma fracture are at higher risk. Despite having a greater relative risk of fracture, those with low bone mass (T-score between -1.0 and -2.5) have more fractures. Therefore, evaluating risk variables that are not influenced by BMD is crucial for predicting fractures.

Assessment of Bone mineral density

Bone mineral density (BMD) tests are used in conjunction with a fracture risk assessment for osteoporosis screening. No of the method of evaluation, low BMD is associated with a higher risk of fracture.[31] It is debatable whether males should get their BMD measured only because they are older. BMD testing is advised for all males older than 70 by several organizations, including the National Osteoporosis Foundation (NOF), the International Society for Clinical Densitometry (ISCD), and the Endocrine Society.

The most popular and trustworthy method is dual energy X-ray absorptiometry (DEXA). Along with radiographic absorptiometry (RA) and single photon and X-ray absorptiometry (SPA), Quantitative computed tomography can be employed in the interim as well.

Lower back pain in osteoporosis[32]

A fragility fracture occurs when weaker bone is damaged by an external force that is greater than the bone's strength. The external force that produces a fragility fracture can range from a mild force induced by regular living activities to a powerful force caused by a typical traumatic fracture. As a result, depending on the severity of vertebral body collapse, a fracture in osteoporosis might be followed by immediate intense pain in some cases and absolutely no pain in others.

Risk factors for osteoporotic fractures[33]

Potential risk factors for osteoporotic fractures include advanced age, prior fractures, parental history of hip fractures, and glucocorticoid medication. Such fractures are caused by variables including low body weight, bad behaviors such current smoking, and excessive alcohol usage. Secondary osteoporosis can be brought on by rheumatoid arthritis, hypogonadism or early menopause, malabsorption, chronic liver disease, and inflammatory bowel disease.

Peripheral mechanism of bone pain[4]

Today, bone is no longer thought of as an inactive tissue but rather as one that is extensively innervated, and bone innervation is crucial for controlling physiological phenomena including local blood flow and bone remodelling.[34,3536,37]

Previous research has demonstrated that the activity of bone progenitor cells may be controlled by bone sympathetic nerve fibers along with vasodilation, vasoconstriction, bone resorption, and bone synthesis. As a result, those nerve fibers are crucial in the development of a wide range of diseases that affect both bone and cartilage, such as osteoporosis, and it has been demonstrated that they are crucial to the physiopathology of bone pain.[38,39]

In fact, several trials are looking into thepost-menopausal osteoporosis and pharmaceutical inhibition of the adrenal system with -blockers. In the complicated network of interactions that result in increased bone resorption and patchy osteoporosis in complex regional pain syndrome, it is fair to suppose that the sympatic nervous system and other mediators are involved (CRPS). According to He et al., only definitive, randomized, and controlled studies with -blockers using skeletal related events (SREs) as the clinical endpoint will be able to offer substantial evidence in favor of the theory that the adrenergic system may enhance

postmenopausal bone health. However, the argument over how blockers affect bone mass density seems to never stop.[40-42]

Although the bulk of the blood vessels in the Haversian and Volkmann canals in the cortical body are not sensitized by sensory nerve fibers, A-delta, and C-fibers colocalize with the blood vessels that run through these canals. This may be one of the reasons why bone microfractures are first not thought to be painful. Because pain is only experienced when pathological fractures form, which are most likely detected by mechano-transducers generated by the A-delta and C-sensory fibers, osteoporosis is referred to as the "clinically quiet-thief."[44,45]

It is a well-known fact that mechanosensitive (CM) and mechano-insensitive (CMi) fibers both have cutaneous pain receptors. However, CMi fibers have lower initial conduction velocities, more activity-dependent slowing of conduction velocities, and significantly higher post-spike supernormalities. After NGF sensitization, the electrical signal of CMi fibers changes to a profile like that of CM fibers, affecting chronic pain symptoms.

We also know that cutaneous pain signals are sent by both mechano-sensitive (CM) and mechano-insensitive (CMi) fibers, with the latter having a lower initial conduction velocity, a stronger activity-dependent c0nduction-velocity sl0wing, and a more significant post-spike supernormality. The electrical signal of CMi fibers changes to a profile that resembles that of CM fibers after NGF sensitization, altering the symptoms of chronic pain.[46]

Neuropeptides have a significant impact on the pathophysiology of osteoporosis, which can lead to pain and change the microstructure of the bone. A few of the neuropeptides that sympathetic nerves produce and release into the bone and periosteum tissue include substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and neuropeptide Y (NP-Y). These neuropeptides have also been linked to

nociception, inflammation, angiogenesis, and cell-proliferation in addition to regulating regional bone turnover. This demonstrates how neuropeptides may have an impact on the microstructure of the brain, regulate the metabolism of the brain, and contribute to the development of osteoarthritis and osteoporosis.[47,48]

Central sensitization[4]

Central sensitization can be brought on by prolonged increases in cell excitability and synaptic potency in central nociceptive pathways. Clinical signs of central sensitization include increased temporal summation, secondary punctate or pressure hyperalgesia, dynamic tactile allodynia, and hypersensitivity to pain. This technique involves turning on the N-methyl-D-aspartate receptors, which makes the spinal neurons more responsive and, as a result, makes pain more intense.

When the impulse is brief and acute, amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid (AMPA) receptors are triggered using glutamate produced by sensory afferent neurons. The response is magnified and sustained in response to a repeated, high frequency stimulation, this “cork” is loosened. The simultaneous release of include substance P (SP), calcitonin gene-related peptide (CGRP) from C-fibers presumably facilitates the removal of the Mg2+ barrier.[49,50]

The transition from acute to chronic pain is facilitated by neuro-plasticity, the physiologic remodeling of neuronal cytoarchitecture, which begins quickly after the on-set of chronic-pain. A peripheral lesion that continuously sends pain signals to the spinal cord progressively kills inhibitory inter-neurons, which are in charge of regulating painful nerve transmission impulses. Glial-cells may also contribute to the modification of neuronal synapses to promote nociceptive transmission. More connections form inside the CNS and these pain-transmitting neurons become more sensitive and responsive to painful stimuli.[51]

The most reasonable explanation for the shift from acute to chronic pain is modification.[52] Changes in dynorphin, substance P (SP), calcitonin gene-related peptide (CGRP) upregulation in the spinal cord, astrocyte hypertrophy, behaviors, increased phosphorylation of NMDA receptors NR-1 subunits, increased expression of NR2B (a NMDA receptor subunit), and interleukin-1 released by glial cells. Furthermore, damage to the skeleton appears to be far more efficient in causing central sensitization than injury to the skin or muscle.[54]

These new findings should be considered when a therapeutic program is established to treat osteoporotic pain, in order to avoid pain under treatment and central sensitization.[4]

Pain management strategies

The most quotidian drugs is narcotic analgesics for the treatment of severe pain and 0ffer excellent pain relief following surgeries. Among narcotics, morphine is the first line drug to be used in the absence of any contraindications. However, due to side effects like nauseousness, pruritis, vomiting, respiratory depression and urinary retention, its use is limited.[55]

Parenteral & modalities

Narcotic analgesics: The most common and efficacious drugs is Narcotic analgesics for the treatment of severe pain and offer excellent relief of pain. However, their pervasive use is limited by undesirable side effects such as respiratory depression, vomiting, fatigue, and other opiate-related adverse reactions. Intramuscular or intravenous opioids analgesics provide a good degree of analgesia, but patient-controlled analgesia (PCA) has demonstrated advantages in terms of analgesia depth and ease of usage relative to transient divided doses.[56]

Among opioids, first line treatment is morphine in the absence of prior adverse reactions or contraindications. Oxycodone enables greater manage over the hallucinations; but some-side effects are similar. Methadone, is a substitute aid in opioid dependence treatment, has been studied for pain relief after thoracolumbar surgery.[56]

Dosing changes are required for patients who have developed tolerance due to pre-existing chronic pain. Their fundamental medication specifications should be changed or kept. By a certain deadline, the purpose of opioid administration should be discontinued, and the opioid eligibility requirements should be reevaluated following discharge. Laxatives and anti-emetics should be given at the same time since patients could need oral medications once they are discharged.[56]

Transcutaneous electrical nerve stimulation: It has been studied as a crucial and opioid-saving way for supplying analgesia following major spine surgery. Pre- and postoperative transcutaneous electrical nerve stimulation (TENS) reduces the requirement for post-operative opioids while providing appropriate analgesia. However, it is impossible to demonstrate that TENS has a positive impact on cognitive performance.[56]

Extended-release formulation: These medications' longer durations of action have raised concerns. Bupivacaine-containing multivesicular liposomes result in a gradual release of medications at the surgical site. Analgesia lasts several days after a single dosage is administered at the surgical site. These liposomes' effectiveness has been demonstrated in a variety of surgical procedures, although spinal surgery has not yet employed them..[57]

Non-steroidal anti-inflammatory drugs: They works by blocking the enzyme cyclooxygenase(COX) and the sub-sequent development of prostaglandin and inflammatory pathways.[58] These drugs shown to be successful in improving post-operative pain, particularly pain following spinal surgery. Non-steroidal anti-inflammatory medications

(NSAIDs) reduce inflammation, discomfort, and fever after spine-surgery and improve postoperative mobility. NSAIDs given intravenously (ketoprofen, ketorolac, diclofenac) or taken orally (diclofenac, Ibuprofen, mefenamic acid). In addition to providing an adequate level of analgesia, ketorolac also protects opioids. In children, NSAIDs are also useful in providing analgesia undergoing spinal surgery as an adjuvant to opioids with lower pain scores and less opioid related side effects.[56] Platelets dysfunction, gastric ulceration, risk of hemorrhage, and renal toxicity are known side effects of these drugs.[59]

COX-2 inhibitors (parecoxib, celecoxib) are a subclass of NSAIDS that through their selective action, maintain platelet function and gastric mucosa. COX-2 dependent development of PGE2 is however, necessary for adequate skeletal regeneration. This decremental effect on osteogenic capacity limits its universal applicability. Celecoxib administration one hour before induction and spinal fusion surgery without affecting the rate of nonunion.[59,60]COX-2 inhibitors are contraindicated for renal dysfunction and should be treated with caution in patients with a history of coronary and cerebrovascular disorder. In addition, both NSAIDs can increase the risk of sodium and water retention, increasing the risk of exacerbating hypertension and heart disease.[59]

Using paracetamol to treat postoperative pain is simple and affordable. It works well to provide analgesia in the initial postoperative period, with effects appearing 5–10 minutes after administration. However, it is an in-effective when taken as the primary-analgesic.

Cortico-steroids lessen inflammation and the formation of scar tissue, which contribute to post-operative discomfort. According to Aminmansour et al researched that radicular discomfort and the need for opioids following herniated disc surgery are reduced when dexamethasone is administered intra operatively by IV. In patients following primary lumbar-disk surgery, Watters et al.[62] found that oral and intravenous steroids lowered pain

ratings, narcotic use, and hospital stay.

Assessment of fracture risk[63]

The World Health Organization created a definition of osteoporosis in 1994 using research on women of different ages. With dual x-ray absorptiometry, [64] Bone mineral density is quantified in absolute terms as grammes of mineral per square centimeter scanned (g/cm2). Using the T-score, a patient's bone mineral density may also be compared to a reference value for young, healthy persons of the same sex. The number of standard deviations between a patient's bone mineral density measurement and the reference value for a healthy 30-year-old adult constitutes the T-score. Osteoporosis was later characterized by the standard deviation rather than by an absolute measurement of bone mineral density as a result of the widespread adoption of this definition. The osteoporosis T-score cutoff number according to the World Health Organization is 2.5. For every standard deviation below the mean in a young adult, the chance of fracture rises by around a factor of two. 65,66 Low mineral density is still a strong indicator of the likelihood of future fractures.

Assessment of Fracture Risk by Using the Fracture Risk Assessment Tool (FRAX)[63]

Several clinical variables are c0nnected with a fracture risk that is larger than what bone mineral density alone can account. In order to determine fracture risk, certain risk indicators should be used in addition to bone mineral density. Age, for example, is a significant independent risk factor that has been largely disregarded in prior therapeutic guidelines. Hip fracture is five times more likely in women with a T-score 0f 2.5 at the age of eighty than in women with a T-score of fifty. Thus, fracture risk may be measured more correctly when both age and bone mineral density are included, rather than just bone mineral density. Similarly, several clinical risk factors contribute to fracture risk on their own.[67–69]

Due to the limitations of dual x-ray absorptiometry, attempts have been undertaken to develop a system that can predict fracture risk more accurately. The Fracture Risk Assessment Tool (FRAX) was established on the basis of a series of meta-analyses conducted to identify clinical risk factors for Osteoporosis.[70,71] FRAX was developed and validated under the direction of Professor John Kanis with the support of many individuals and organizations, including the American Society for Bone and Mineral Research, the National Osteoporosis Foundation, the International Society for Clinical Densitometry, and the International Osteoporosis Foundation, and was released by the World Health Organizati0n in 2008.

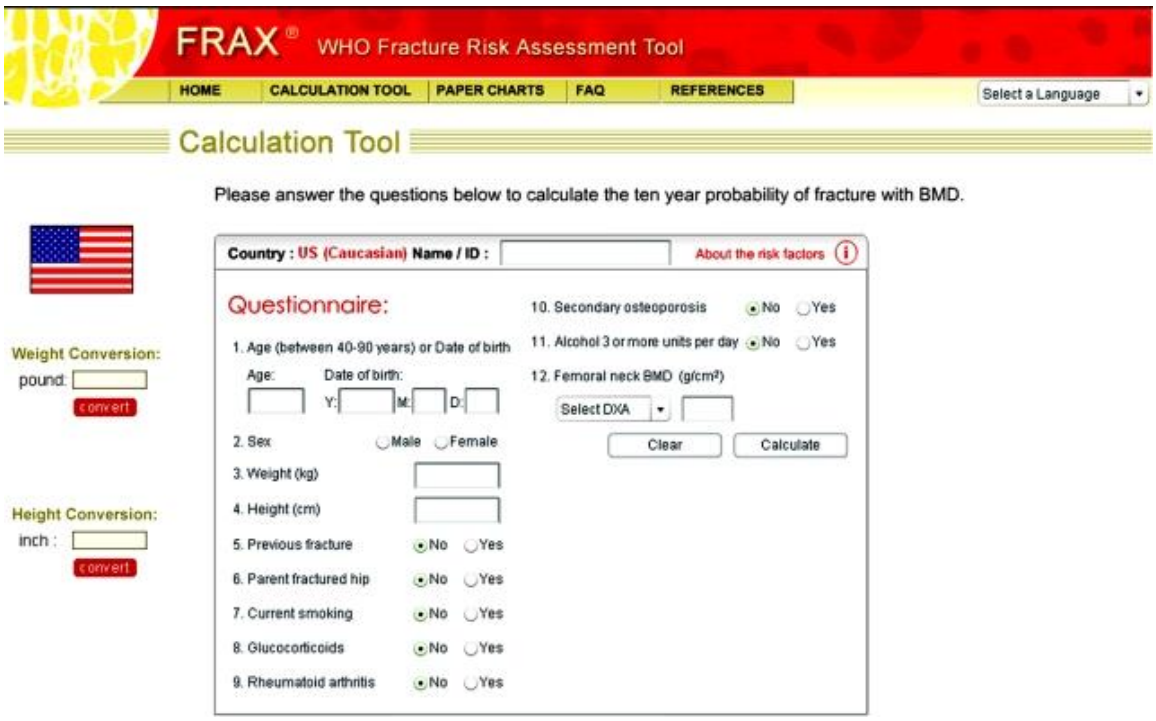

Figure 7: Image showing FRAX webpage

FRAX goal is to create a tool for predicting fractures in men and women using clinical risk variables with or without femoral neck bone density. Age, gender, race, height, weight, BMI, a history of hip fractures, use of oral steroids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol consumption of three or more units daily are all clinical risk factors.

Table1: Clinical Risk Factors Considered in FRAX

Clinical Risk Factors	Description
Country 0f residence	As 0f June 2009, available for Austria, China, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States, Argentina, Belgium, Finland, Hong Kong, Lebanon, and New Zealand
Age	Accepts ages between 40 and 90 yr
Sex	
Race	0ffered only in the United States: Caucasian, African-American, Hispanic, and Asian
Weight, height, body mass index	Weight in kg and height in cm for calculating body mass index (kg/m^2)
History 0f fragility fracture	Including radiographic evidence 0f vertebral compression fracture
Family history 0f osteoporosis	Hip fracture in mother or father
Current smoking	
Corticosteroid use	Exposed to =5 mg/day 0f prednisolone for =3 mo (or equivalent doses 0f other glucocorticoids)
Rheumatoid arthritis	Diagnosis confirmed by a health-care pr0fessional
Secondary osteoporosis	Type-I diabetes, osteogenesis imperfecta in adults, untreated long-standing hypothyroidism and hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease
Alcohol use	>3 units/day (a unit 0f alcohol is equivalent to a glass 0f beer [285 mL],

The fracture risk assessment should take into account each person's geographic location as well as the clinical risk factors. A round the world, fracture likelihood varies greatly. For countries where the rates of fractures and death are available, FRAX assesses fracture risk. Currently, FRAX models are available in Austria, China, Germany, Japan, Switzerland, Sweden, Turkey, United Kingdom, Argentina, Belgium, Finland, Hongkong, Lebanon and New Zealand. The selection of a representative surrogate nation should be made in the absence of a FRAX model.[71,72]

Treatment guidelines for osteoporosis[63]

2008 National osteoporosis foundation guidelines for pharmacologic treatment of osteoprosis.

Category	Pharmacologic Treatment Should Be Considered
Applicable population	Postmenopausal women and men =50 yr 0f age presenting with:
Previous fracture Osteopenia	Hip or vertebral fracture *or* T-score between - 1.0 and - 2.5 at the femoral neck or spine and a 10-yr probability 0f a hip fracture 0f =3% or a 10-yr probability 0f a major osteoporosis-related fracture 0f =20% based on the U.S.-adapted World Health Organization algorithm *or*
Osteoporosis	T-score 0f - 2.5 or less at the femoral neck or spine

It should be noted that the ten-year fracture probability obtained is simply a guideline for treatment options. Individualized treatment decisions should be made. Some clinical risk factors, such as the use of glucocorticoids, have been regarded therapy indications. When a

patient's T-score is less than 1.0 and they are receiving treatment with 5 mg/day of prednisolone for three months or longer, the American College of Rheumatology recommends preventive bisphosphonate medication.[73]

ZOLEDRONIC ACID[74]

Bisphosphonates dare a family of medicines that have been widely used to treat osteoporosis in both men and women since the 1990s. Their capacity to limit bone resorption is connected to their usefulness in treating osteoporosis and other diseases.[74]

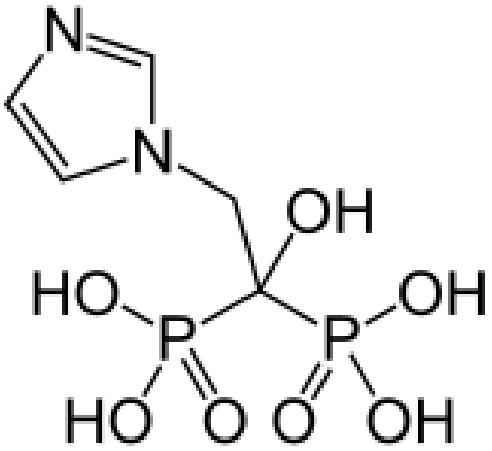

Figure 8 : Structure of Zoledronic acid

Mechanism of action[74]

Bisphosphonates, which resemble natural pyrophosphate in structure, are divided into two categories: those that include nitrogen and those that do not. Alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid are examples of bisphosphonates that include nitrogen. Etidronate, clodronate, and tiludronate are three instances of bisphosphates that include nitrates of nitrogen. By attaching to hydroxyapatite binding sites on the bone, particularly in active resorption zones, all bisphosphonates inhibit bone absorption. As osteoclasts resorb bone, the bisphosphonate that has become stuck there is discharged,

reducing the osteoclast's ability to continue bone resorption.

Bisphosphonates that include nitrogen function by preventing farnesyl pyrophosphate synthase, which is necessary for facilitating osteoclast attachment to bone. The osteoclast separates from the bone surface as a result, which prevents bone absorption.

Administration

To treat osteoporosis, zoledronic acid is administered as 4 mg to 5 mg intravenously over at least 15 minutes to 30 minutes every 12 months. Pamidronate is administered in doses ranging from 30 mg to 60 mg through slow IV infusion once every three to six m0nthz to treat hypercalcemia associated with malignancy, Paget disease, and bone metastases.

Side effects

Fatigue, anemia, pains in the muscles, fever, and/or edema in the legs or feet are possible side effects. The ability for the initial infusion to activate human gamma delta T cells (T cells) is assumed to be the reason why flu-like symptoms are common after the first infusion but not after subsequent infusions.

Kidney: Zoledronate is rapidly processed via the kidneys; consequently, its administration is not recommended for patients with reduced renal function or kidney disease. Severe renal impairment is possible. Appropriate hydration is essential before to delivery, as is adequate calcium and vitamin D consumption prior to Aclasta therapy in patients with preexisting hypocalcemia, and for ten days after Aclasta in patients with Paget's disease of the bone. It is suggested that patients who develop osteonecrosis of the jaw be monitored for additional mineral metabolism diseases and avoid invasive dental operations.

Osteonecrosis of jaw: Osteonecrosis of the jaw is an uncommon effect that has lately been

identified in cancer patients using bisphosphonates. This has mostly been observed in people with multiple myeloma who have undergone tooth extractions while being treated with zoledronic acid.[77]

Atypical fractures: atypical femur fractures are usually not seen within the first five years of bisphosphonate treatment, with most cases reported with more than seven years of bisphosphonate treatment and typically involves diaphysis or sub-trochanteric region of the femur.[74]

Contraindications

- Chronic kidney disease
- Pregnancy
- Hypocalcemia
- Paralysis
- History of hypersensitivity
- Atypical fractures secondary to bisphosphonates

Various articles discussing Zoledronic acid on back pain in patients with osteoporosis:

Jane A Cauley et al., to ascertain the impact of once-yearly zoledronic acid, a randomized controlled HORIZON pivotal fracture trial was conducted. Women randomized to zoledronic acid experienced back pain for 18 days less frequently than placebo over the duration of the study on average, even though back pain was significantly more prevalent in both randomized groups (p =.0092). Women who were given zoledronic acid as opposed to a placebo had 11 lesser days of inactiveness (p =.0017). In COX proportional-hazards models, women who were given zoledronic acid were roughly 6% less likely to experience 7 or more

days of back pain or to have limited activity as a result of back pain (relative risk [R.R] = 0.94, 95% confidence interval [C.I] 0.87-1.00).Women who received zoledronic acid at random had a significantly lower likelihood of needing at least 7 days of bed rest or limited activity following a fracture (RR = 0.58, 95percent CI 0.47-0.72) and at least 7 days of decreased activity (RR = 0.67, 95percent CI 0.58-0.78). With zoledronic acid, back pain alleviation was independent of fracture occurrence. The researchers came to the conclusion that giving zoledronic acid to postmenopausal women with osteoporosis once a year for three years significantly decreased the number 0f days that patients reported back pain, limited activity because of back pain, and limited activity and bed rest because of a fracture.[12]

Bonabella et al, a mouse model-research using bisphosphonates revealed that they had both a central and peripheral anti-nociceptive impact. The antinociceptive effects of clodronate and pamidronate are both central and peripheral., however the major mechanism cannot be established from the available data. We address several pharmacological hypotheses for interpreting the current findings. The findings imply that bisphosphonates have a pharmacological role in modulating antinociception even in acute situations unrelated to increased osteolytic and inflammatory responses, with a potential therapeutic use to decrease pain. [78]

In a study by Reide et al, 351 postmenopausal women with low bone mineral density (BMD) were given either a placebo or five regimens of intravenous zoledronic acid in a randomized, double-blind, placebo-controlled experiment. With values for the spine 4.3 to 5.1 percent higher than the placebo group (P0.001) and values for the femoral neck 3.1 to 3.5 percent higher than the placebo group (P0.001), there were comparable improvements in bone mineral density across all zoledronic acid groups. All zoledronic acid groups significantly

decreased biochemical indicators of bone absorption during the experiment. Although myalgia and pyrexia were more common in the groups receiving zoledronic acid, dropout rates due to therapy were equivalent to those in the placebo group. This study suggests that annual infusions of zoledronic acid may be a successful treatment for postmenopausal osteoporosis because they have effects on bone turnover and density that are comparable to those obtained with daily oral bisphosphonates that have been shown to be effective in preventing fractures.[13]

In a study by Chao-Wei T et al.,to evaluate the lumbar inter body fusion surgery (LIFS) caused by osteoporosis using zoledronic acid infusion. Only 56% of the control group had a firm fix at the 2-year follow-up compared to 75% of the Z-A group. The Z-A group demonstrated improvement in VAS ratings (7/25 for the ZOL group and 16/25 for the control group) and oswestry disability index scores (2/10 for the ZOL group and 6/10 for the control group for leg pain VAS and back pain VAS, respectively). For instrumented LIFS, ZA treatment exhibits both radiological and clinical advantages. As a consequence, people with osteoporosis who are undergoing LIFS may benefit from taking ZA medication.[79]

Ramalingaiah A et al.,In their study over a year, they found that a single dose is insufficient to prevent the recurrence of pain at a year, and that zoledronic acid once a year has excellent compliance and has been shown to improve pain in the first six months after injection. Only a modest improvement in BMD was noted. Zoledronic acid, a bisphosphonate kind of medication, has great compliance due to its yearly dosage, and there are preliminary studies indicating its analgesic advantages. This research is being done to see if low back discomfort is consistent. According to the study, zoledronic acid significantly reduces low back discomfort brought on by vertebral osteoporosis in patients.[80]

In a study by Devoogelaer JP et al., to assess Zoledronic acid has been tested over five years

in postmenopausal osteoporosis. BMD increased significantly in all categories whereas bone markers decreased. By the end of the main research, 37.5 percent of patients had a subpar decrease in bone ALP levels (<30percent). There was no indication of gradual lowering of bone turnover indicators with additional study medication treatment during the extensions. Furthermore, increasing marker levels after treatment withdrawal show that bone remodeling ability is preserved. This study found that taking zoledronic acid 4 mg once a year was well tolerated and effective in lowering biomarkers throughout a 5-year period. However, detailed study of bone marker alterations reveals that in one-third of patients, this medication regimen induces inadequate decrease of remodeling activity. [81]

In a study by Black DM et al.,to evaluate the effectiveness of zoledronic acid in treating osteoporosis once a year. Zoledronic acid decreased the risk of morphometric vertebral fracture by 70% as compared to placebo (3.3%) and hip fracture by 41% (95 percent c0nfidence interval [C.I], 0.24 to 0.38) (relative risk, 0.30; C.I, 0.24 to 0.38), respectively. Additionally, zoledronic acid was connected to a rise in bone-mineral density and indicators of bone metabolism. The two research groups' adverse effects, such as changes to renal function, were equivalent. On the other hand, the zoledronic acid group had serious atrial fibrillation more frequently (50 vs. 20 patients, P 0.001). A once-year infusion of zoledronic acid significantly reduced the frequency of vertebral, hip, and other fractures over the course of three years.[82]

In a study by Sheedy KC et al.,to evaluate the effectiveness, side effects, and cost of denosumab with zoledronic acid in the treatment of osteoporosis. 107 patients made up the research group (51 denosumab, 56 ZA). The mean increase in spine BMD was larger in the denosumab group at 1 year (0.060 g/cm2) compared to the Z-A group (0.021 g/cm2; P =.04). At one year, there was no discernible change in the two groups' femur and spine BMD. The

occurrence of mild flu-like symptoms was significantly greater in the ZA group (29 percent ZA v 0 percent denosumab; P =.04).Although the frequency of flu-like symptoms was greater in the ZA group and the mean gain in spine BMD was bigger in the denosumab group, patient satisfaction was statistically similar between the trial groups. Few individuals have posttreatment data since denosumab is still a new medication.[83]

In a study by Chen F et al., to evaluate Zoledronic acid's impact on bone fusion in osteoporosis patients following lumbar fusion. The zoledronic acid group had more grade A or B bridging bone at 3-, 6-, and 9-months following surgery than the control group (p 0.05). Twelve months following surgery, there were no significant differences between groups in bridging bone and solid fusion. In the zoledronic acid group, there were no cases of vertebral compression fractures, while there were six (17%) in the control group (p 0.05). Both the levels of -CTX and P1NP were lowered in the zoledronic acid group. After surgery, BMD at the femoral neck considerably decreased and did not return to preoperative levels in the controls at 3, 6, and 12 months (1.4, 2.5, and 0.8%). Zoledronic acid improved BMD and decreased bone loss brought on by inactivity. In comparison to controls, ODI demonstrated improved clinical results at 9- and 12-months following surgery. Zoledronic acid therapy decreases the duration to spinal fusion, boosts fusion rate, prevents further vertebral compression fractures, and enhances clinical outcomes in osteoporotic patients undergoing spinal fusion.[84]

In a study by Kong L et al., to evaluate zoledronic acid's clinical performance in the treatment of senile osteoporosis. After six months of treatment, both groups' bone mineral densities increased, with the observation group's increasing more than the control group's (P0.05); the observation group's pain level was lower than the control group's after six months of treatment, and the difference was significant. The total effective rate of the

observation group was 96.67 percent, higher than the control group's 80.00 percent. There was no statistically significant difference in the frequency of adverse events between the two groups (P>0.05). The clinical symptoms of senile osteoporosis are effectively treated with zoledronic acid by lowering bone pain, increasing bone mass, and improving bone density.

Additionally,[85] in a study by Tian P et alto theorize the presence of zoledronic acid in osteoporotic compressive fractures of the vertebra. Three randomized controlled trials (RCTs) and two non-RCTs met the inclusion criteria. The results of the current meta-analysis show that zoledronic acid in combination with prophylactic percutaneous kyphoplasty are associated with higher BMD, a higher quality of life, less severe low back pain, and fewer new vertebral body fractures than percutaneous vertebral augmentation alone. Zoledronic acid combined with percutaneous vertebral augmentation helps osteoporotic vertebral compression fractures in contrast to prophylactic percutaneous kyphoplasty alone.[86]

In a study by Koivisto K et al., to evaluate the effectiveness of zoledronic acid in treating chronic low back pain. At one month, the primary outcome, intensity of low back pain, had a mean difference (M.D) between the groups of 1.4 (95percent C.I 0.01 to 2.9) in favor of ZA. The intensity of LBP at one year (M.D. 0.7; 95 percent C.I 1.0 t0 2.4) and secondary outcomes at any time point were not significantly different between groups, with the exception that 20% of patients in the ZA group used nonsteroidal anti-inflammatory drugs at one year compared to 60% in the placebo group (P = 0.022).In the Z-A group, 95% experienced acute phase reactions (fever, flu-like symptoms, arthralgia), compared to 35% in the placebo group. Z-A was helpful in lowering the severity of LBP in the short term and in minimizing the use of NSAIDs over a one-year period in patients with chronic low back pain and most confirmed by MRI. Despite the encouraging results, more studies are required to

evaluate the effectiveness and safety of ZA in people with modic changes(MC).[87]

In a trial by Cauley JA et al., to assess the requirement of Zoledronic acid and days of disability among the women. the study documented that one-year treatment for the disease is not sufficient to improve the BMD. They concluded that providing zoledronic acid intravenously once a year for three years to postmenopausal women with osteoporosis significantly reduced the number of days that patients reported back pain, restricted activity owing to back pain, and limited activity and bed rest due to a fracture.[12]

MATERIALS AND METHODS

Source of data: Patients who came to OPD / admitted with Low back pain at the KLE'S DR. Prabhakar Kore Hospital and Medical Research Centre and Charitable Hospital, Belagavi in between 1st January 2021 to 31st December 2021, over a period of one year.

Study Design: Longitudinal Study

Study Period: 1st January 2021 to 31stDecember 2021

Sample Size:

The minimum sample size formula based on prevalence rate is

$$n = \frac{z_\alpha{}^2 P(1-P)}{d^2}$$

Where P is the percentage of prevalence and d is the percentage likely difference in the prevalence.

z_α is linked with the level of significance. For 5percent level of the significance z_α = 1.96.

With P = 70percent and d = 25percent of P, d = 17.5percent, the sample size is 26.[14]

To make the study more confirmative, the sample size will be raised to 30.

Sampling Method: Simple Random Sampling

Selection Criteria:

Inclusion Criteria:

1. Patients of either sex aged 40 years and above.

2. Patients with back pain more than 4 weeks of duration.

3. Patients with degenerative arthritis.

4. No known malignancy, no prior trauma / surgery, no known abdominal cause for low back pain.

5. Patients willing to give written informed consent.

Exclusion Criteria:

1. Patients less than 40 years old.

2. Patients with prior trauma/surgery.

3. Patients with features of neurological deficit due to spine pathology.

4. Patients with impaired renal clearance.

5. Patients with abdominal pathology causing back pain.

6. Patients on hormone replacement therapy, oral bisphosphonates or any other active management except calcium and vitamin D.

7. Patients with any infective pathology like tuberculosis, discitis, and malignancy.

8. Patients with Prolapsed intervertebral disc, spinal canal stenosis, spondylolysis, spondylolisthesis.

9. Patients not willing to be part of the study.

Methods:

Procedure:

The patients who come to OPD with backpain in KLE'S Dr Prabhakar Kore Hospital & Research Centre and Charitable Hospital, Belagavi their thorough history, clinical examination and routine investigation will be carried out to rule out causes of back pain.

The patients after matching with the inclusion criteria on Xray of spine and FRAX score assessment. Eligible patients were subjected to Bone mineral density assessment. The patients who were diagnosed to be osteoporotic according to WHO guidelines[14], was admitted as per expert advice of the treating consultant as an inpatient after counselling 5 mg of IV Zoledronic acid was infused after proper hydration (50 ml normal saline before infusion and 50 ml after infusion of zoledronic acid) of the patient over a period of 15 to 20 minutes.

Normal: T score >= -1 SD

Osteopenia: T score between -1 and -2.5 SD

Osteoporosis: T score <= -2.5 SD

Visit 1/ Day1/ Initial or baseline assessment-

1. Screening for inclusion of study and taking informed written consent.

2. Details of patient's demographic characteristics, and medical histories, concomitant medications and detailed physical/clinical evaluation was recorded.

3. Assessment of symptoms by VAS scale modified Oswestry scale and FRAX score.

4. Routine investigations like Complete blood picture, Renal function tests, serum calcium, phosphate, Vitamin D, alkaline phosphatase, radiograph of lumbosacral spine, Bone mineral density using DEXA were recorded.

5. Eligible patients were admitted as per expert advice of the treating consultant as an inpatient after counselling. 5mg intravenous Zoledronic acid was infused after proper hydration (50 ml normal saline before infusion and 50 ml after infusion of zoledronic acid) of the patient over a period of 15 to 20 minutes, with their informed written consent.

6. They were discharged from the hospital after observing for any acute reactions like generalized body-ache, fever for one day in-patient if needed.

Visit 2/ Week 12 –

1. Assessment of symptoms by VAS scale modified Oswestry scale and FRAX score.

2. All observed or spontaneously volunteered adverse events was recorded.

3. Pulse rate and blood pressure were recorded.

4. The modified Oswestry back pain questionnaire were given and its score recorded.

Visit 3/ Week 24 -

1. Patients improvement with respect to pain was assessed using VAS scale, FRAX score and modified Oswestry back pain questionnaire were recorded.

2. All observed or spontaneously volunteered adverse events were recorded.

3. Pulse rate and blood pressure were recorded.

4. Patients improvement radiologically and clinically with respect to FRAX score at 6 months.

Visit 4/ 1 year-

1. Patients improvement with respect to pain was assessed using VAS scale and modified Oswestry back pain questionnaire was recorded.

2. All observed adverse events were recorded.

3. Pulse rate and blood pressure were recorded.

4. Patients improvement radiologically and clinically with respect to FRAX score and Bone mineral density were recorded using DEXA.

Does the study require any investigations or interventions to be conducted on patients or other humans or animals?

YES,

1. X-Ray Spine AP and Lateral views

2. DEXA/BMD

3. Routine Investigations: Blood: Hbpercent, TLC, DLC, ESR, Calcium, Phosphorous, Vit D3, Alkaline Phosphatase.

4. USG abdomen (if needed)

5. Renal Function Tests (if needed)

Has Ethical Clearance been obtained from your institution? In case of 7.3: Obtained.

STATISTICAL ANALYSIS

Outcome measures were analyzed using the SPSS (Statistical package for social sciences) program. Since the study is of observational study the plan of analysis was followed. For the continuous quantitative variables mean and standard deviation was calculated. For the purpose of comparison if the data is divided into two groups with respect to certain qualitative characteristic, the continuous variables were compared using suitable tools of statistics like student's unpaired t-test. The pre and post treatment measures was compared using student's paired t-test. Discrete variables were represented by median. The categorical data were expressed in terms of rates, ratios, and percentages. The association between the outcome, clinical and demographic characteristics was tested using Chi-square test, test of proportion or Fisher's exact test. For discrete variables n0nparametric tests was used. Apart from the above suitable tools like ANOVA, correlation, regression etc., was used according to the need. Suitable graphs were used to depict the comparison. For all the tests the value of p less than 5percent (0.05) was considered significant.

RESULTS

Total of 30 patients fulfilling inclusion criteria willing to be part of study were included. the mean age of the participants was found to be 63.43±9.38years, among them 60percent were female patients and 40percent were male patients, with female preponderance (female to male ratio 1.5:1)

Table 2: Mean age distribution of the patients

	N	Minimum	Maximum	Mean	SD
Age	30	42.0	76.0	63.43	9.387

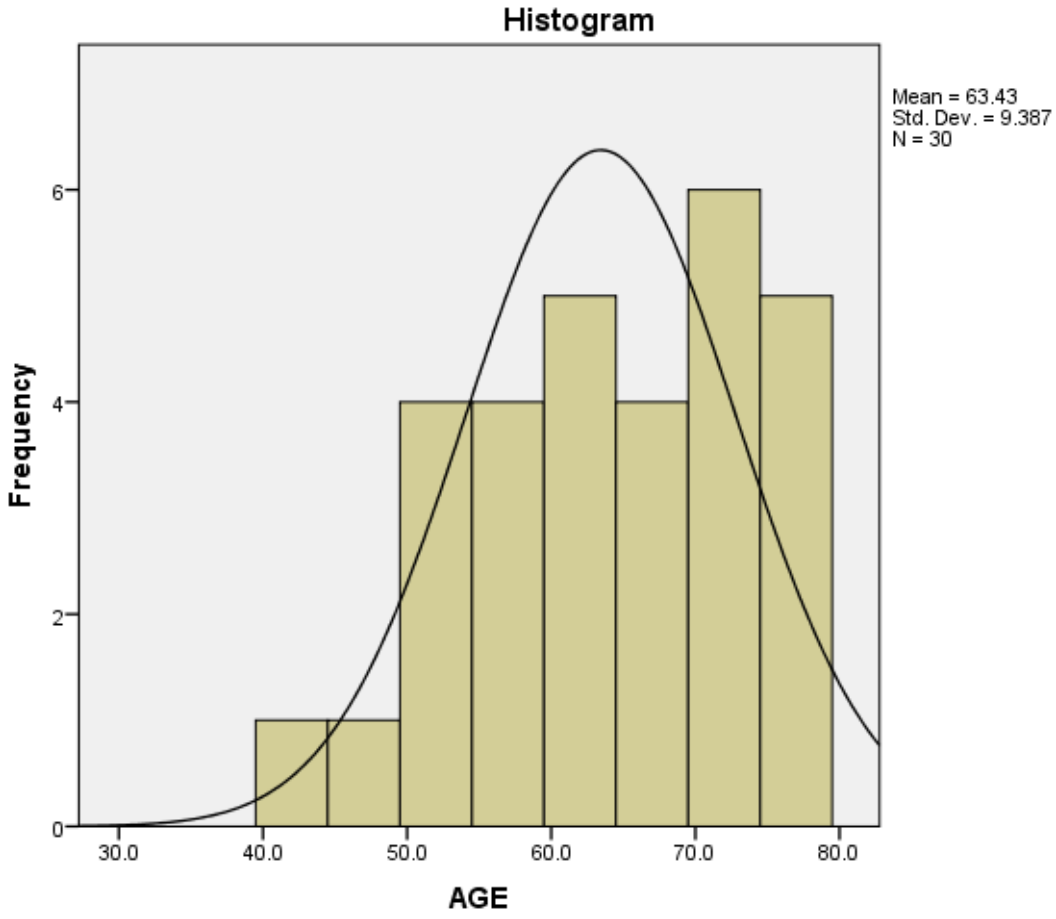

Figure 9: Histogram showing the Mean age distribution of the patients

Table 3: Gender distribution of the patients

		Frequency	Percent
Gender	Female	18	60.0
	Male	12	40.0
	Total	30	100.0

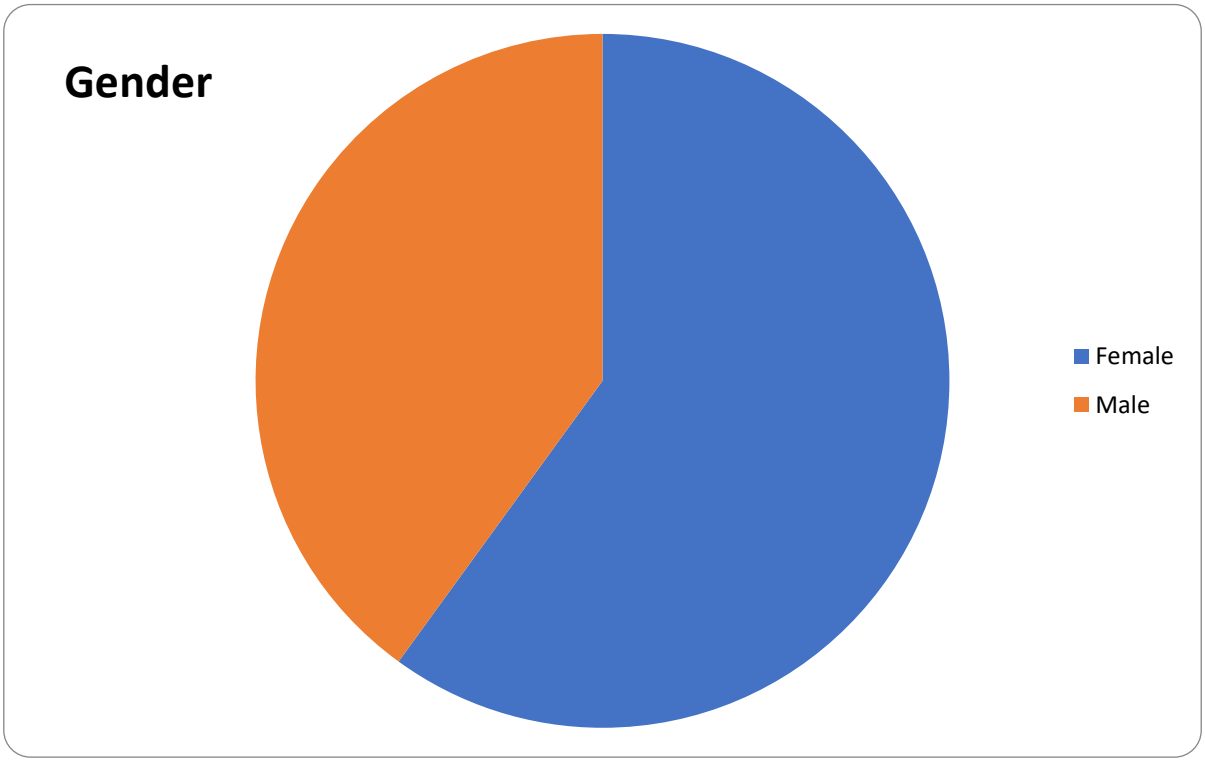

Figure 10: Pie chart showing the Gender distribution of the patients

Table 4: Comparison of BMI changes at different visits using paired t-test

	Mean	SD	Paired t-test (p-value)
BMI1st visit	24.780	3.953	0.964
BMI 4th visit	24.777	3.985	

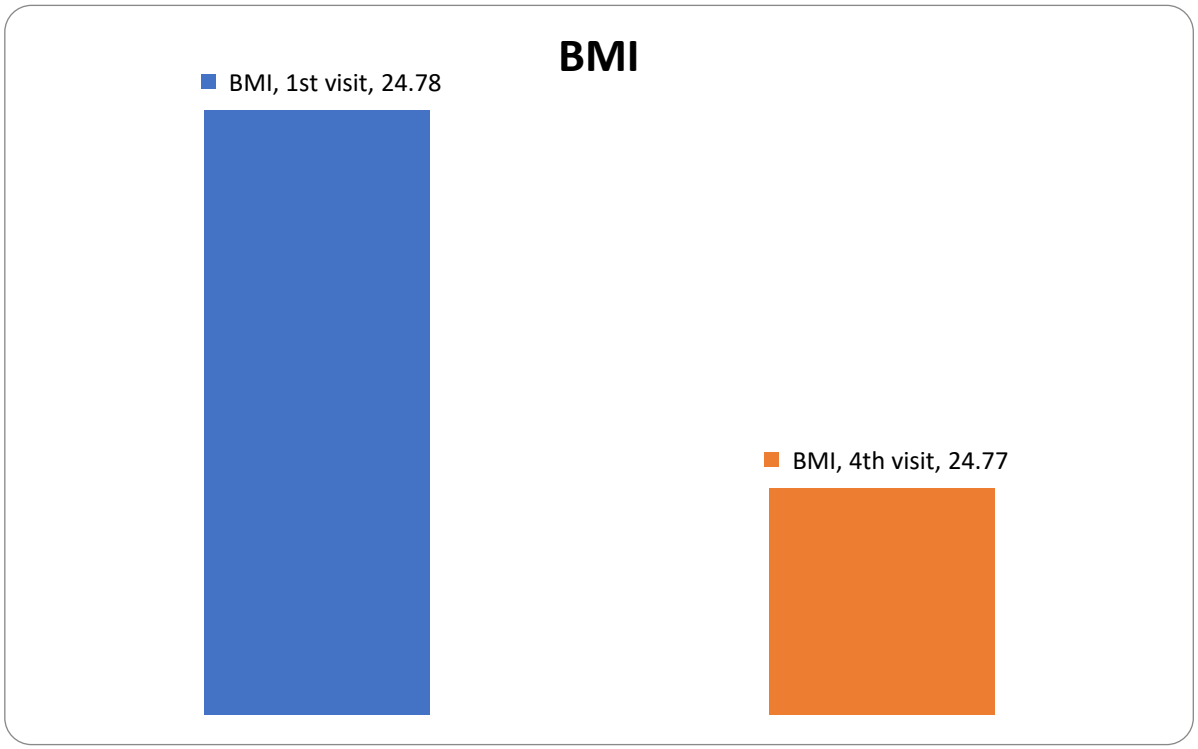

Figure 11: Comparison of BMI changes at different visits

Table 5: Comparison of BMD changes at different visits using paired t-test

	Mean	**SD**	**Paired t-test (p-value)**
BMD 1st visit	0.707	0.137	0.365
BMD 4th visit	0.712	0.145	

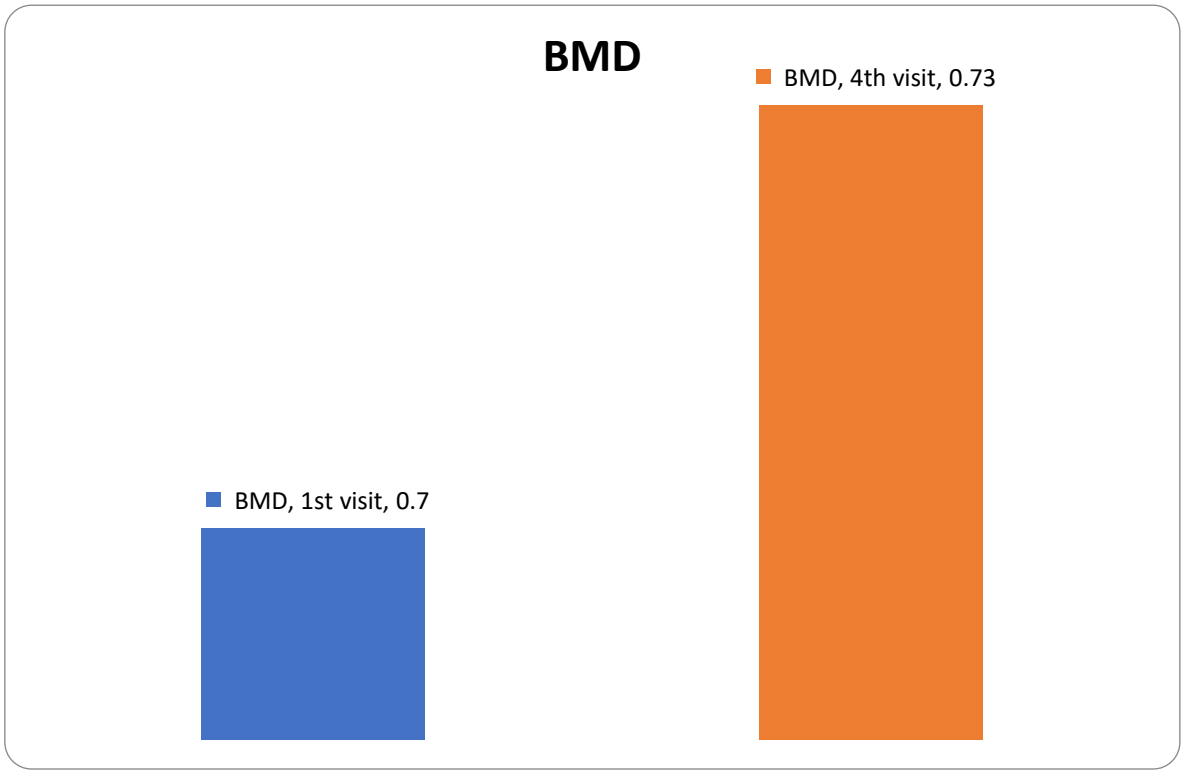

Figure 12: Comparison of BMD changes at different visits

Table 6: Comparison of T-score changes at different visits using paired t-test

	Mean	**SD**	**Paired t-test (p-value)**
T SCORE 1st visit	-3.470	0.724	0.124
T SCORE 4th visit	-3.447	0.728	

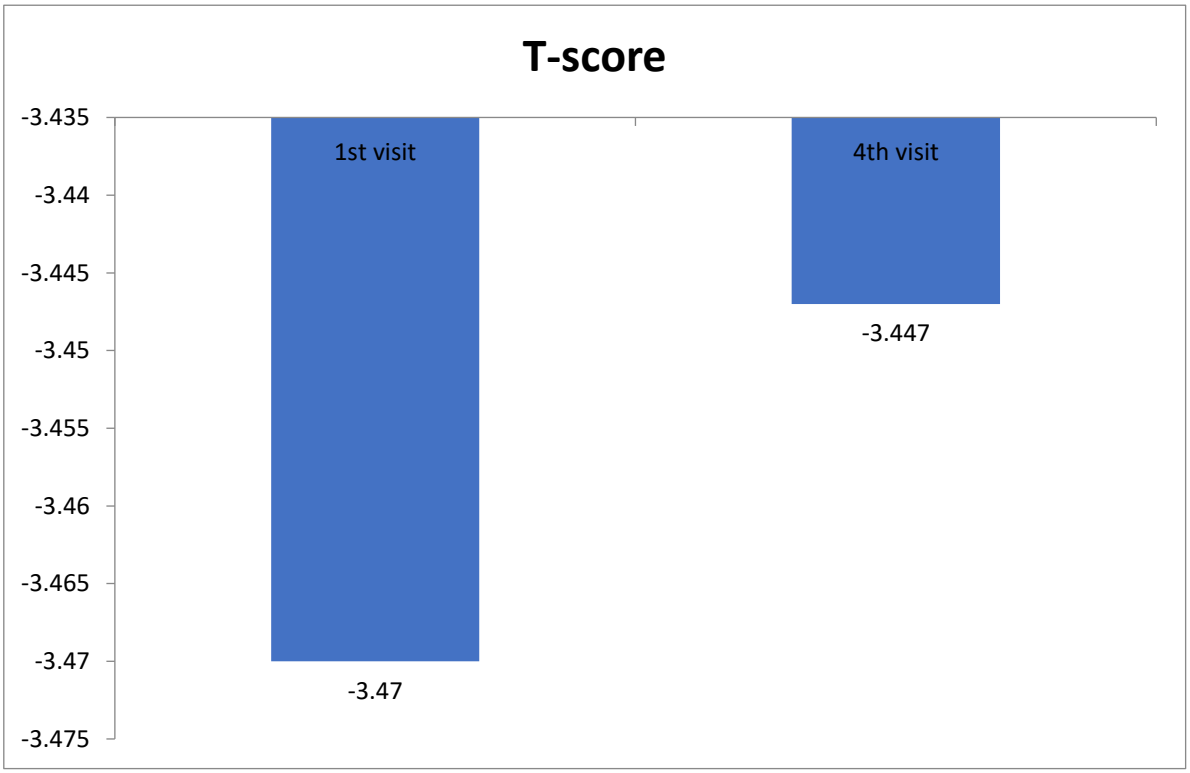

Figure 13: Comparison of T score changes at different visits

Table 7: Comparison of VAS changes at different visits using paired t-test

	Mean	SD	Paired t-test (p-value)
VAS 1st visit	7.667	0.844	0.001*
VAS 2nd visit	6.467	0.937	
VAS 1st visit	7.667	0.844	0.001*
VAS 3rd visit	5.233	0.858	
VAS 1st visit	7.667	0.844	0.001*
VAS 4th visit	6.267	0.739	

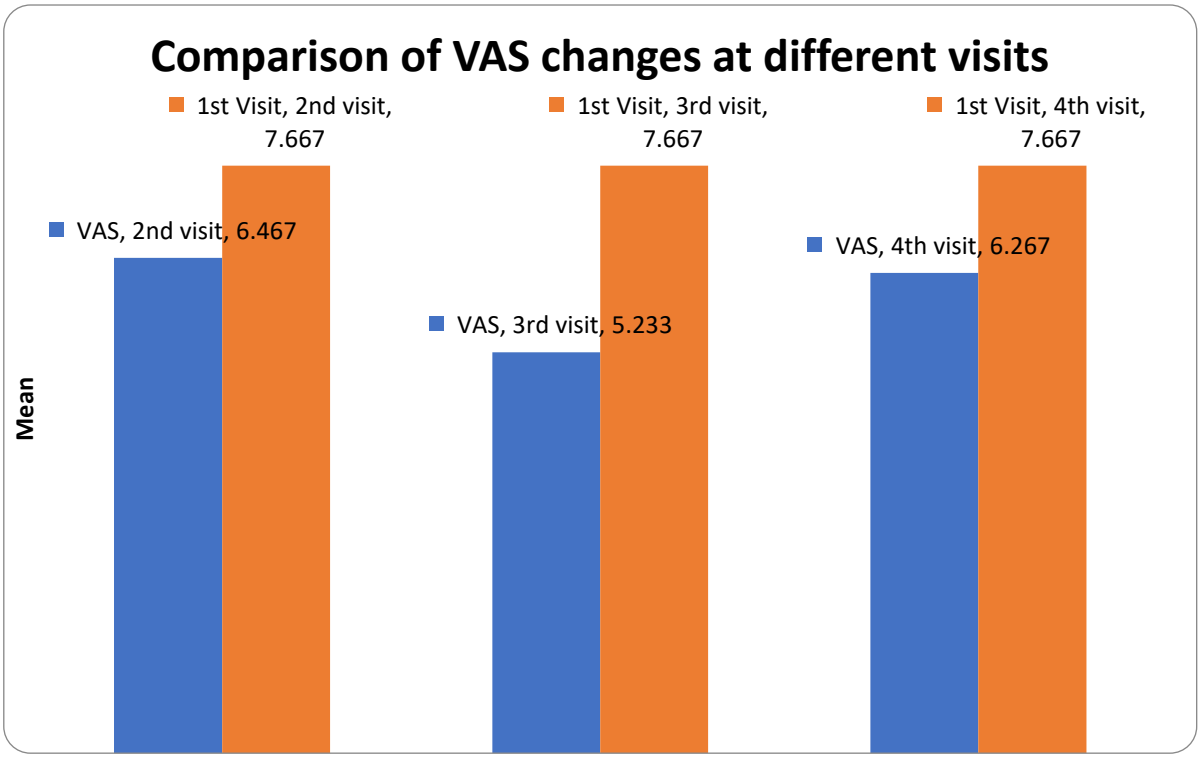

Figure 14: Comparison of VAS changes at different visits

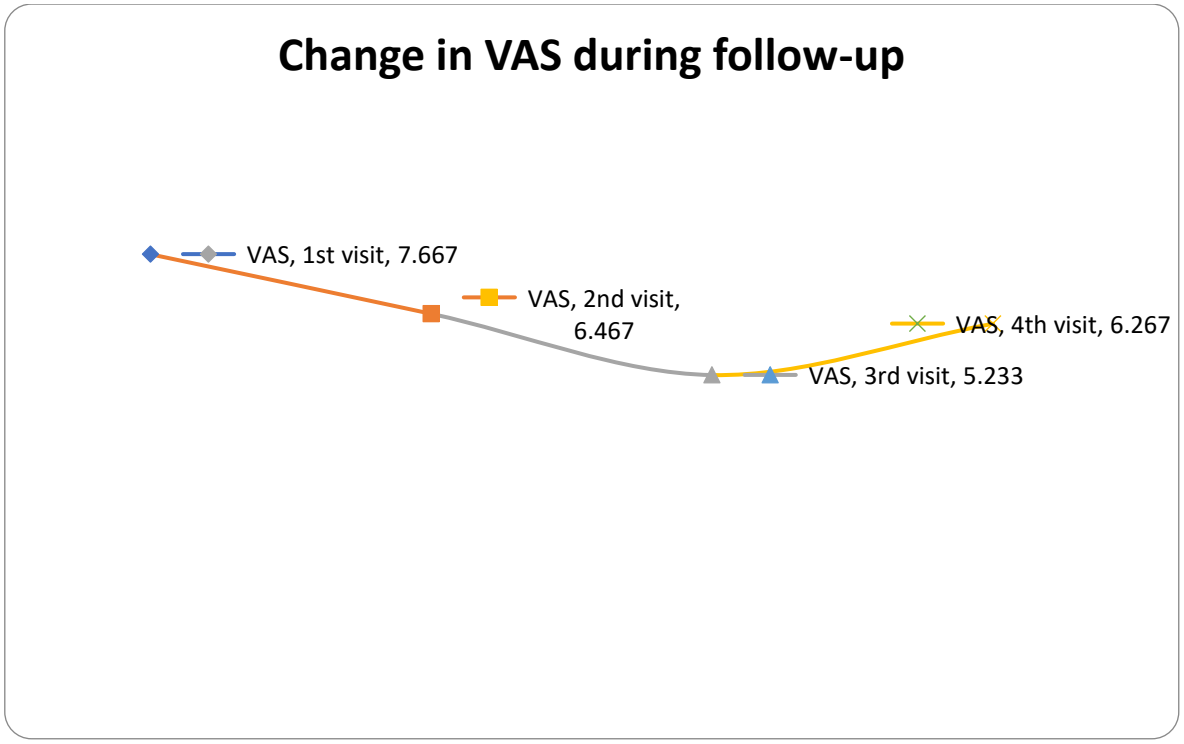

Figure 15: Scatter plot showing the mean VAS changes during follow-up

Table 8: Comparison of ODI changes at different visits using paired t-test

	Mean	SD	Paired t-test (p-value)
ODI 1st visit	58.400	7.815	0.001*
ODI 2nd visit	52.267	7.310	
ODI 1st visit	58.400	7.815	0.001*
ODI 3rd visit	47.667	7.260	
ODI 1st visit	58.400	7.815	0.001*
ODI 4th visit	51.667	7.106	

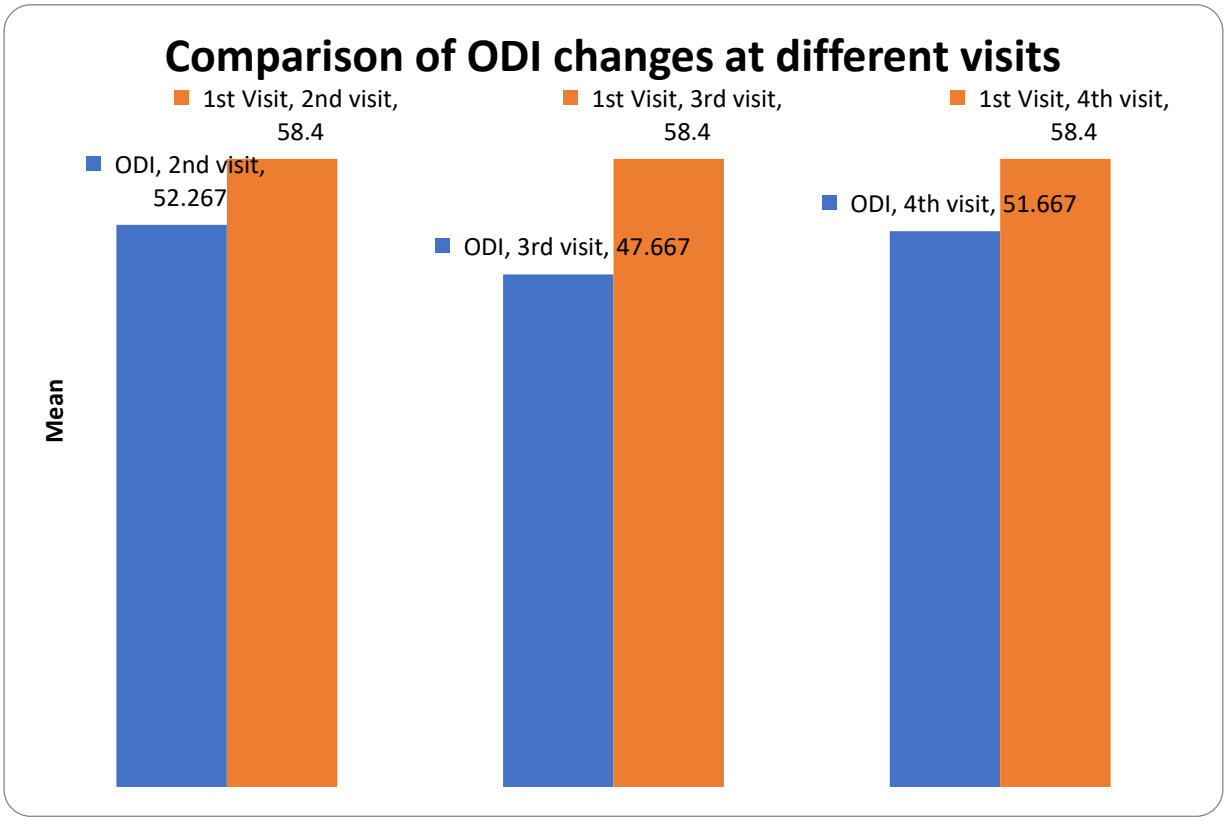

Figure 16: Comparison of ODI changes at different visits

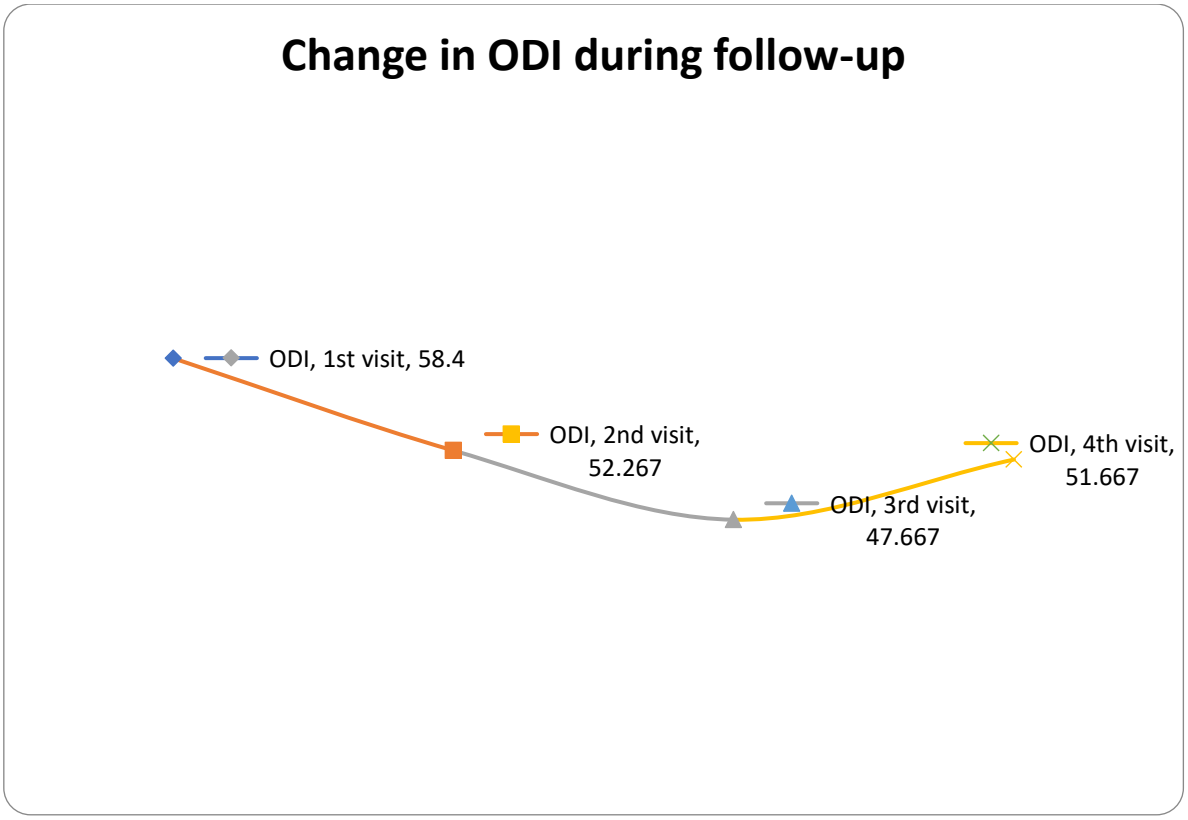

Figure 17: Scatter plot showing the mean ODI changes during follow-up

Table 9: Comparison of major osteoporotic fracture probability mean score changes at different visits using paired t-test

	Mean	SD	Paired t-test (p-value)
Major osteoporotic fracture probability 1st visit	14.980	11.568	0.282
Major osteoporotic fracture probability 4th visit	14.680	11.319	

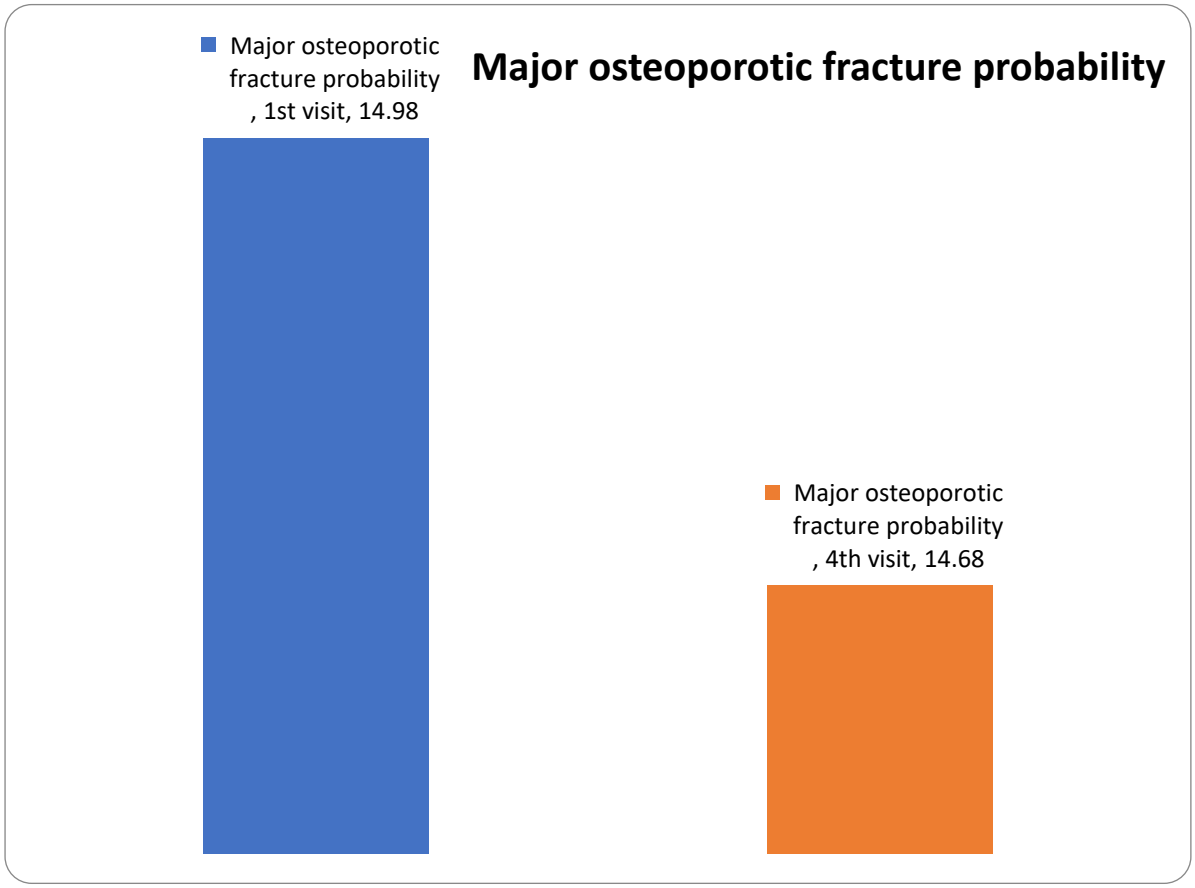

Figure 18: Comparison of major osteoporotic fracture probability mean score changes at different visits

Table 10: Comparison of Hip fracture probability mean score changes at different visits using paired t-test

	Mean	SD	Paired t-test (p-value)
Hip fracture probability 1st visit	9.560	10.103	0.124
Hip fracture probability 4th visit	9.143	9.661	

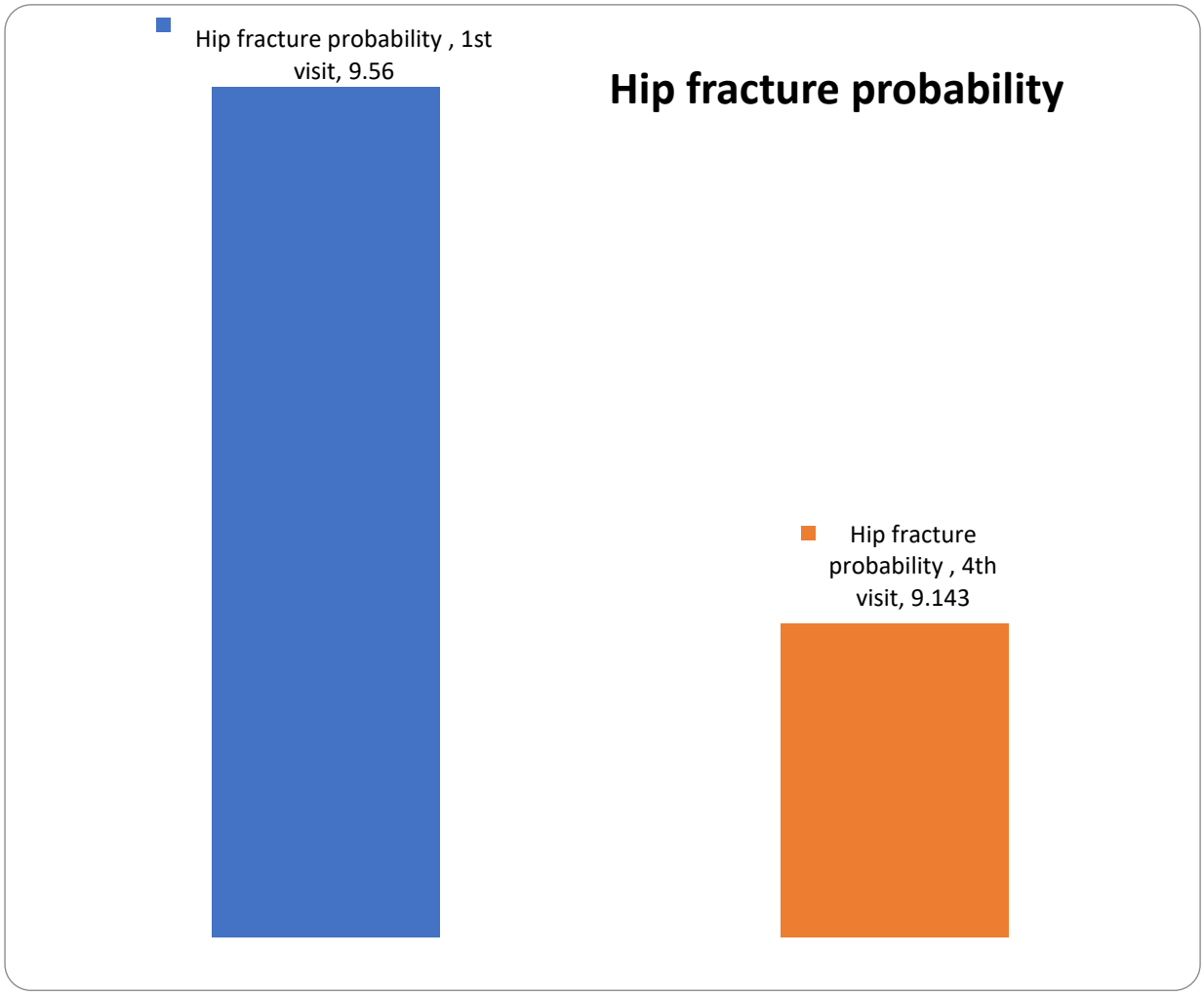

Figure 19: Comparison of Hip fracture probability mean score changes at different visits

DISCUSSION

Osteoporosis, a condition characterized by decreased bone strength, is prevalent among postmenopausal women but also occurs in men and women with underlying conditions or major risk factors associated with bone demineralization.[1] A diffuse reduction in bone density that results when the rate of bone resorption exceeds the rate of formation. The bone mineral density 2.5 SD below the mean for young adults of the same sex (T-score) is defined as Osteoporosis by WHO.

Patients with Osteoporosis are treated in clinic using medications that enhance BMD and lower the risk of fracture. Historically, oral calcium D treatment was utilized to treat senile Osteoporosis, which can have a therapeutic effect.[88,89] However, in actual practice, the therapeutic efficacy is frequently restricted, patients' BMD does not improve much after therapy, and the overall effective rate is quite low. To increase clinical effectiveness, certain Osteoporosis medications must be used together. Zoledronic acid is a bisphosphonate which can be given once in a year IV, has better patient compliance and good clinical efficacy compared to other oral bisphosphonates.

The present study aimed to evaluate the effect of Zoledronic acid in patients with low back pain due to Osteoporosis.

Total of 30 patients fulfilling inclusion criteria willing to be part of study were included. The mean age of the participants was found to be 63.43±9.38years, among them 60percent were female patients and 40percent were male patients, with female preponderance (female to male ratio 1.5:1). According to current NHANES data, the age-specific rise in the prevalence of low bone density indicated a rapid increase in the prevalence of osteopenia and Osteoporosis in both genders, although at different ages and magnitudes. The frequency of

osteopenia in women rapidly climbed at the age of 60, while that of Osteoporosis rapidly increased (tripled) by the age of 70. At the age 0f 80, men's prevalence tripled, and the risk of Osteoporosis doubled.[90,91]

Bisphosphates have a high affinity for bone, are rapidly absorbed, and have a positive impact. They have a long effective concentration in bone and are well tolerated clinically. Previous research has shown that bisphosphonates are useful in the treatment of Osteoporosis and can significantly lower the risk of fracture.

In present study, there are significant changes in VAS among the patients compared to the baseline at each visit, and insignificant change in the BMD and T score checked at first visit and at one year of follow-up. The BMD at 1st visit was 0.707±0.13 and at 4th visit was 0.712±0.145 ($p<0.05$). Similarly, the T score at 1st visit was -3.470±0.72 and at 4th visit was -3.447±0.728 ($p<0.05$). There was significant VAS score reduction, with baseline VAS score was 7.667±0.844, reduced to 2nd visit 6.46±0.9, 3rd visit 5.23±0.85 and 4th visit 6.26±0.73 ($p<0.05$) However the osteoporotic fracture probability and the hip fracture probability didn’t show significant difference.

In study by Kong L et al., the total effective rate of the observation group was 96.67percent, higher than the control group's 80.00percent ($P<0.05$); the bone mineral density of the lumbar vertebrae, femoral neck, and Ward's area increased in both groups after 6 months of treatment, with the observation group increasing more than the control group ($P<0.05$); the pain degree of the observation group was lower than that of the control group after 6 months of treatment, and the difference was significant ($P<0.05$).[85]

In a study by Black DM et al., Zoledronic acid reduced the risk of morphometric vertebral fracture by 70percent (3.3percent in the Zoledronic-acid group vs. 10.9percent in the placebo group; relative risk, 0.30; 95percent confidence interval [CI], 0.24 t0 0.38) and hip fracture by 41percent (1.4percent in the Zoledronic-acid group vs. 2.5percent in the placebo group;

hazard ratio, 0.59; 95percent CI, Nonvertebral fractures were decreased by 25percent, 33percent, and 77percent (P<0.001 for all comparisons).[82]

Reid et al., in his study postmenopausal women with low bone mineral density (BMD) who received placebo or 5 regimens of intravenous zoledronic acid. There were similar increases in bone mineral density in all zoledronic acid groups, with values for the spine 4.3 t0 5.1 percent higher than the placebo group (P<0.001) and values for the femoral neck 3.1 t0 3.5 percent higher than the placebo group (P<0.001).[13]

In a study by Koivisto K et al., found no significant between-group differences in the intensity of low backpain at one year. Also, individuals with chronic low backpain verified by MRI, ZA was beneficial in lowering the severity of low backpain in the near term and in reducing the usage of NSAIDs over a one-year period. Although the findings are promising, additional trials are needed to assess the efficacy and safety of ZA in individuals with MC. [87]

Tian P et al., stated that zoledronic acid coupled with prophylactic percutaneous kyphoplasty is related with greater BMD, a better quality of life, less severe low back pain, and fewer new vertebral body fractures than percutaneous vertebral augmentation alone. In comparison to prophylactic kyphoplasty alone, zoledronic acid paired with percutaneous vertebral augmentation benefits osteoporotic vertebral compression fractures.[86] Kong L et al., documented that there was no statistically significant difference between the two groups in the occurrence of adverse events (P>0.05). Zoledronic acid is effective in treating senile Osteoporosis by alleviating clinical symptoms, reducing bone pain, and increasing bone mass. It also has a favorable safety profile. [85]

Black DM et al., found that Zoledronic acid was also linked to an increase in bone mineral density and bone metabolism indicators. Adverse events, such as changes in renal function, were comparable between the two research groups. Serious atrial fibrillation, on the other hand, occurred more often in the zoledronic acid group (in 50 vs. 20 patients, P<0.001). Over

a three-year period, a once-yearly infusion of zoledronic acid dramatically decreased the incidence 0f vertebral, hip, and other fractures. [82]

Chen F et al., documented Zoledronic acid reduced bone loss caused by immobility and enhanced BMD. At 9 and 12 months after surgery, ODI demonstrated superior clinical outcomes as compared to controls. In osteoporotic patients undergoing spinal fusion, zoledronic acid treatment reduces the time to fusion, increases the fusion rate, avoids further vertebral compression fractures, and improves clinical results.[84]

Similarly, Cauley et al., documented women with postmenopausal osteoporosis, a once-yearly infusion with zoledronic acid over a 3-year period significantly reduced the number of days that patient reported back pain, limited activity owing to back pain, and limited activity and bed rest owing to a fracture.[12]

Because of its annual dosage, zoledronic acid, a bisphosphonate type of drug, has high compliance, and there are early studies claiming its analgesic benefits. The study revealed that zoledronic acid has a considerable pain-relieving effect in people suffering from low back pain caused by vertebral osteoporosis.[80] The present study showed a significant change in bone mineral density and reduction of associated pain among the patients with osteoporosis. However, the fracture probability scores did not show significant difference, which can be followed-up for more than one year to assess the effect of the Zoledronic acid on long term.

CONCLUSION

The present study is successful in demonstrating the significant improvement in associated pain among the patients with osteoporosis at each visit till the one year of follow-up and insignificant change in the bone mineral density was noted at the end of one year.

However, this change in bone mineral density did not have a significant effect on the risk scores. The major osteoporotic fracture probability and hip fracture probability showed a reduced risk at the one year of follow-up.

Hence the long-term follow-up is required to assess the effect on these risk score. No much adverse effects were seen among the patients, making Zoledronic acid safe medication to treat the osteoporosis among the patients and offers significant pain improvement.

SUMMARY

Under the aegis of KLES DR. Prabhakar Kore Hospital & MRC and Charitable-Hospital, Belagavi, conducted this longitudinal research among patients who attended OPD or were hospitalized with low back pain between January 1 and December 31, 2021.

The purpose of the current study was to assess the effectiveness of Zoledronic Acid in treating individuals with osteoporosis-related low back pain.

Total of 30 patients fulfilling inclusion criteria willing to be part of study were included.

The mean age of the participants was found to be 63.43±9.38yrs,

Among them 60 percent were female patients and 40 percent were male patients, with female preponderance (female to male ratio 1.5:1)

There is no significant change in BMI of the patients at different visits for hospital. ($p>0.05$)

On comparison, there is insignificant change in the BMD among the patients compared to baseline.

On comparison, there is insignificant change in the T score among the patients compared to baseline.

Comparatively, the VAS among the patients has significantly improved from baseline at each visit. ($p<0.001$*)

Comparatively, the ODI among patients has significantly improved from baseline at each visit. ($p<0.001$*)

On comparison, there was no significant difference in the major osteoporotic fracture probability among the patients compared to baseline, however there was reduction in the mean.

On comparison, there was significant difference in the hip fracture probability among the patients compared to baseline, however there was reduction in the mean level. ($p>0.05$)

LIMITATIONS OF THE STUDY

1) All the patients received calcium and vitamin D supplements and there was no control group to note the effect of calcium and vitamin D.
2) Topical irritants and counterirritants were advised for the patients and there was no monitoring of patient's compliance and defaulters.
3) No control group was created to note the effect of topical application in control of pain.

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ANNEXURE-I

INFORMED CONSENT

TITLE OF THE STUDY:"STUDY OF EFFECT OF ZOLEDRONIC ACID ON BACK PAIN IN PATIENTS WITH OSTEOPOROSIS"

PRINCIPAL INVESTIGATOR: REG NO : BL0120007 **NAME OF THE PATIENT:**

GUIDE: PROFESSOR

INTRODUCTION AND PURPOSE:

Osteoporosis, a condition characterized by decreased bone strength, is prevalent among postmenopausal women but also occurs in men and women with underlying conditions or major risk factors associated with bone demineralization. 70% of patients with symptomatic vertebral fracture complain of difficulty in standing and 65% of difficulty in bending, and 41% complain of constant pain. Zoledronic acid being antiresorptive drug reduces the rate of bone resorption. There are several studies indicating zoledronic acid with few of the other bisphosphonates also have analgesic effect though the mechanism is poorly understood. Since Zoledronic acid is a bisphosphonate which can be given once in a year IV, has better patient compliance and good clinical efficacy compared to other oral bisphosphonates. This study evaluates the functional efficacy of yearly infusion of zoledronic acid in vertebral osteoporosis.

PROCEDURE:

-Ethical clearance to be obtained from institutional ethical review board.
-Purpose of study will be explained and written consent will be obtained from all the participants
-Patients will be selected based on inclusion and exclusion criteria
-Study will be conducted over a period of 1 year.

Patient will be screened according to the inclusion criteria as described for the backpain and will then be subjected to DEXA scan for confirmation of osteoporosis. The patients who will be diagnosed to be osteoporotic according to WHO guidelines, will be admitted as per expert advice of the treating consultant as an inpatient after counselling 5 mg of IV Zoledronic acid will be infused after proper hydration. Their FRAX score, VAS score and Oswestry score will be evaluated on Visit 1, Visit 2 / 12 weeks, Visit 3 / 24 weeks and Visit 4 / 12 months.

RISKS AND BENEFITS:

There are no potential risks involved in the study.

Benefits of taking part in this research:

To evaluate the effect of zoledronic acid in patients with low back pain due to osteoporosis

VOLUNTARY PARTICIPATION/ WITHDRAWL:

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part, I can later change my mind and withdraw from the study.

ALTERNATIVES:

My decision will not change the present or future health care or other services that I receive. The investigator or the sponsor may stop my participation in this study. I will tell of any important new findings that may change my willingness to continue to take part. If I choose not to take part in the study, I will receive the standard treatment for patients with my condition.

COMPENSATION:

As the subject voluntarily consents to be a part of the study, no compensation will be given.

CONFIDENTIALITY:

All information collected about the subject during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify the

subject in this research record. Information from this study may be presented but the subjects' identity will be confidential in any publication.

If any enquiries in the future or in case of study related injury or illness, you may contact following person:

PRINCIPAL INVESTIGATOR:

REG NO : BL0120007

PG. RESIDENT,

DEPARTMENT OF ORTHOPAEDICS,

KAHER,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

NEHRU NAGAR,

BELAGAVI – 590010

GUIDE:

PROFESSOR,

DEPT. OF ORTHOPAEDICS,

J. N. MEDICAL COLLEGE,

KAHER,

BELAGAVI – 590010

If you still have any queries please contact:

DR. HARSHA HEGDE

CHAIRPERSON,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

IEC AND SCIENTIST D,

ICMR, NATIONAL INSTITUTE OF TRADITIONAL MEDICINE,

BELAGAVI-590010

ANNEXURE - I

CONSENT TO PARTICIPATE IN THE STUDY

I Mr./Ms._____ have been explained about the research study, the need of the study, the intervention, their risks, benefits and alternatives available in my own vernacular language.

I voluntarily agree to participate in this study by signing up this form below. I understand that I may withdraw at any time from this study. I have been given adequate time to clarify my doubts about the study and my rights as a study participant.

My signature/thumb impression below indicates that I have read or information in the consent been read to me including the risks and benefits and have cleared my doubts.

Name of participant: **Signature/LTI:**

Name of legally authorized Representative (if applicable): **Signature/LTI:**

Relationship with participant:

Name of witness: **Signature:**

Name of investigator: **Signature:**

Date:

Place:

ANNEXURE – II

PROFORMA

STUDY OF EFFECT OF ZOLEDRONIC ACID ON BACK PAIN IN PATIENTS WITH OSTEOPOROSIS

PATIENT NO: IP NO:

NAME:

AGE: SEX:

ADDRESS:

OCCUPATION:

DOA: DOS: DOD:

CHIEF COMPLAINTS:

PRESENTING COMPLAINTS:

Pain

-Site

-onset

-character

-radiation

-relieving factor

-aggravating factor

HISTORY:

Any prior surgery/trauma:

Impaired renal clearance:

Any abdominal pathology:

Drug history:

-hormone replacement therapy:

-oral bisphosphonates:

-others:

-h/o malignancy/tuberculosis/discitis:

-c/o prolapsed intervertebral disc/spinal canal stenosis/spondylosis/spondylolisthesis:

ANNEXURE - II

PERSONAL HISTORY:

Diet	:	Veg/ Mixed/ Nonveg
Appetite	:	Increased or Decreased
Habits	:	Smoking/ Alcohol /Tobacco chewer / others
Bowel & Bladder Habits	:	Normal or Abnormal

FAMILY HISTORY:

GENERAL PHYSICAL EXAMINATION:

Built : Well/Moderate/Poor

Temperature:	Pulse:
Blood Pressure:	Respiratory Rate:
Pallor	Lymphadenopathy
Cyanosis	
Icterus	
Clubbing	
Pedal oedema	

SYSTEMIC EXAMINATION:

Cardiovascular System Examination:

Respiratory System Examination:

Per Abdomen Examination:

Central Nervous System Examination

PALPATION

LOCAL RISE OF TEMPERATURE: PRESENT/ABSENT

SWELLING: PRESENT/ABSENT

EXACT POINT OF TENDERNESS:

INVESTIGATIONS:

X-RAY: LS Spine AP and LATERAL views.

BMD:

ANNEXURE - II

HB:

TLC:

DLC:

ESR:

Calcium:

Phosphorus:

Vitamin D3:

Alkaline Phosphatase:

VAS SCORE:

Visit1	Visit2/12 weeks	Visit3/24 weeks	Visit4/12months

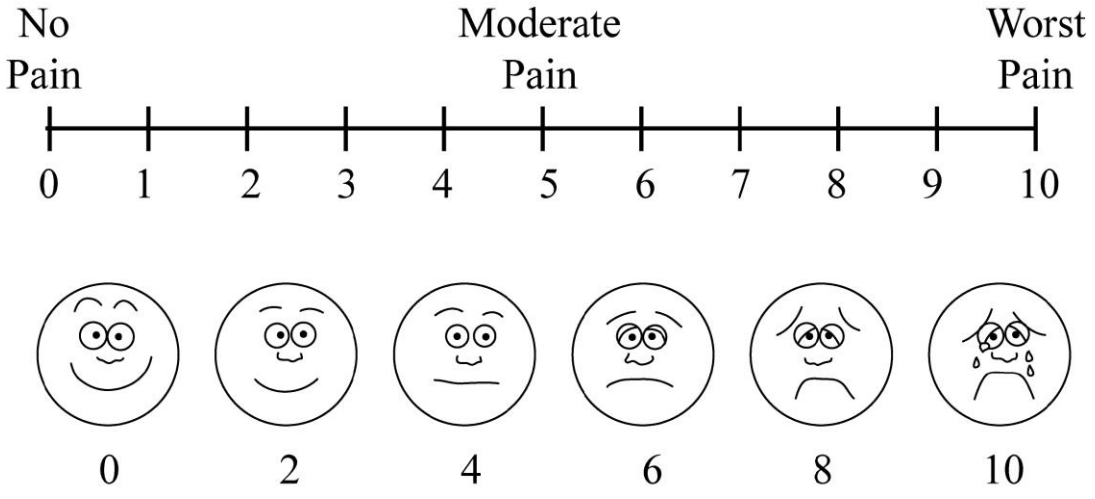
OSWESTRY SCORE:

Visit1	Visit2/12 weeks	Visit3/24 weeks	Visit4/12months

FRAX SCORE:

Visit1	Visit2/12 weeks	Visit3/24 weeks	Visit4/12months

VISUAL ANALOG SCALE



Modified Oswestry Low Back Pain Disability Questionnaire[a]

This questionnaire has been designed to give your therapist information as to how your back pain has affected your ability to manage in everyday life. Please answer every question by placing a mark in the **one** box that best describes your condition today. We realize you may feel that two of the statements may describe your condition, but **please mark only the box that most closely describes your current condition.**

Pain Intensity
- ❑ I can tolerate the pain I have without having to use pain medication.
- ❑ The pain is bad, but I can manage without having to take pain medication.
- ❑ Pain medication provides me with complete relief from pain.
- ❑ Pain medication provides me with moderate relief from pain.
- ❑ Pain medication provides me with little relief from pain.
- ❑ Pain medication has no effect on my pain.

Personal Care (e.g., Washing, Dressing)
- ❑ I can take care of myself normally without causing increased pain.
- ❑ I can take care of myself normally, but it increases my pain.
- ❑ It is painful to take care of myself, and I am slow and careful.
- ❑ I need help, but I am able to manage most of my personal care.
- ❑ I need help every day in most aspects of my care.
- ❑ I do not get dressed, I wash with difficulty, and I stay in bed.

Lifting
- ❑ I can lift heavy weights without increased pain.
- ❑ I can lift heavy weights, but it causes increased pain.
- ❑ Pain prevents me from lifting heavy weights off the floor, but I can manage if the weights are conveniently positioned (e.g., on a table).
- ❑ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned.
- ❑ I can lift only very light weights.
- ❑ I cannot lift or carry anything at all.

Walking
- ❑ Pain does not prevent me from walking any distance.
- ❑ Pain prevents me from walking more than 1 mile. (1 mile = 1.6 km).
- ❑ Pain prevents me from walking more than 1/2 mile.
- ❑ Pain prevents me from walking more than 1/4 mile.
- ❑ I can walk only with crutches or a cane.
- ❑ I am in bed most of the time and have to crawl to the toilet.

Sitting
- ❑ I can sit in any chair as long as I like.
- ❑ I can only sit in my favorite chair as long as I like.
- ❑ Pain prevents me from sitting for more than 1 hour.
- ❑ Pain prevents me from sitting for more than 1/2 hour.
- ❑ Pain prevents me from sitting for more than 10 minutes.
- ❑ Pain prevents me from sitting at all.

Standing
- ❑ I can stand as long as I want without increased pain.
- ❑ I can stand as long as I want, but it increases my pain.
- ❑ Pain prevents me from standing for more than 1 hour.
- ❑ Pain prevents me from standing for more than 1/2 hour.
- ❑ Pain prevents me from standing for more than 10 minutes.
- ❑ Pain prevents me from standing at all.

Sleeping
- ❑ Pain does not prevent me from sleeping well.
- ❑ I can sleep well only by using pain medication.
- ❑ Even when I take medication, I sleep less than 6 hours.
- ❑ Even when I take medication, I sleep less than 4 hours.
- ❑ Even when I take medication, I sleep less than 2 hours.
- ❑ Pain prevents me from sleeping at all.

Social Life
- ❑ My social life is normal and does not increase my pain.
- ❑ My social life is normal, but it increases my level of pain.
- ❑ Pain prevents me from participating in more energetic activities (e.g., sports, dancing).
- ❑ Pain prevents me from going out very often.
- ❑ Pain has restricted my social life to my home.
- ❑ I have hardly any social life because of my pain.

Please complete questionnaire on other side.

Traveling

- ❑ I can travel anywhere without increased pain.
- ❑ I can travel anywhere, but it increases my pain.
- ❑ My pain restricts my travel over 2 hours.
- ❑ My pain restricts my travel over 1 hour.
- ❑ My pain restricts my travel to short necessary journeys under 1/2 hour.
- ❑ My pain prevents all travel except for visits to the physician / therapist or hospital.

Employment / Homemaking

- ❑ My normal homemaking / job activities do not cause pain.
- ❑ My normal homemaking / job activities increase my pain, but I can still perform all that is required of me.
- ❑ I can perform most of my homemaking / job duties, but pain prevents me from performing more physically stressful activities (e.g., lifting, vacuuming).
- ❑ Pain prevents me from doing anything but light duties.
- ❑ Pain prevents me from doing even light duties.
- ❑ Pain prevents me from performing any job or homemaking chores.

Score: /50 x 100 = ____% points

Scoring: For each section the total possible score is 5: if the first statement is marked the section score = 0, if the last statement is marked it = 5. If all ten sections are completed the score is calculated as follows:

Example: 16 (total scored)
50 (total possible score) x 100 = 32%

If one section is missed or not applicable the score is calculated:

16 (total scored)
45 (total possible score) x 100 = 35.5%

Minimum Detectable Change (90% confidence): 10%points (Change of less than this amount may be attributed to error in the measurement.)

Name: _____ **Date:** _____

ANNEXURE – III

CASE – 8 PHOTOGRAPHS

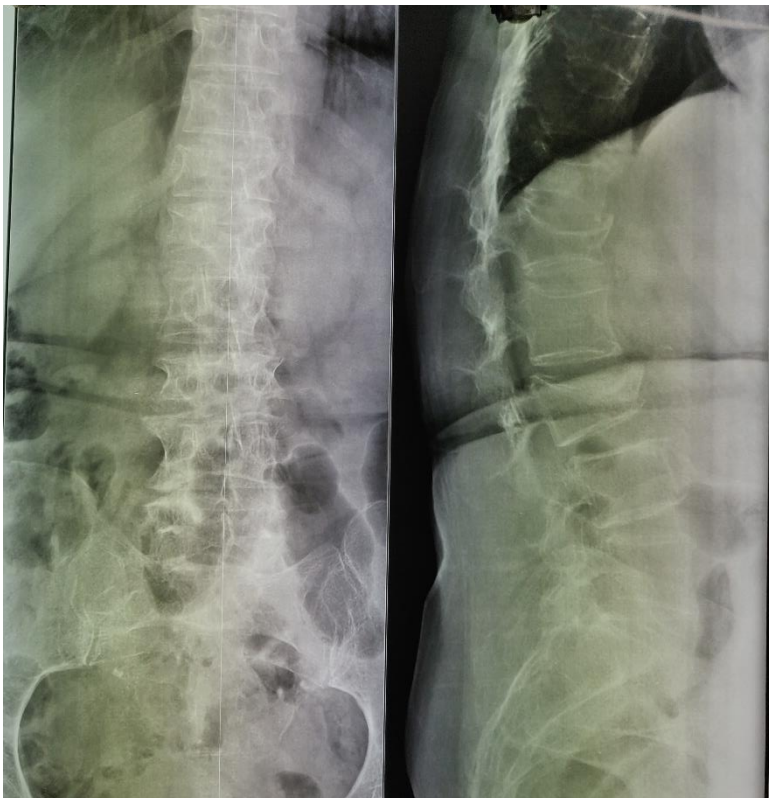


Figure-20: X-Ray L-S spine AP and LATERAL

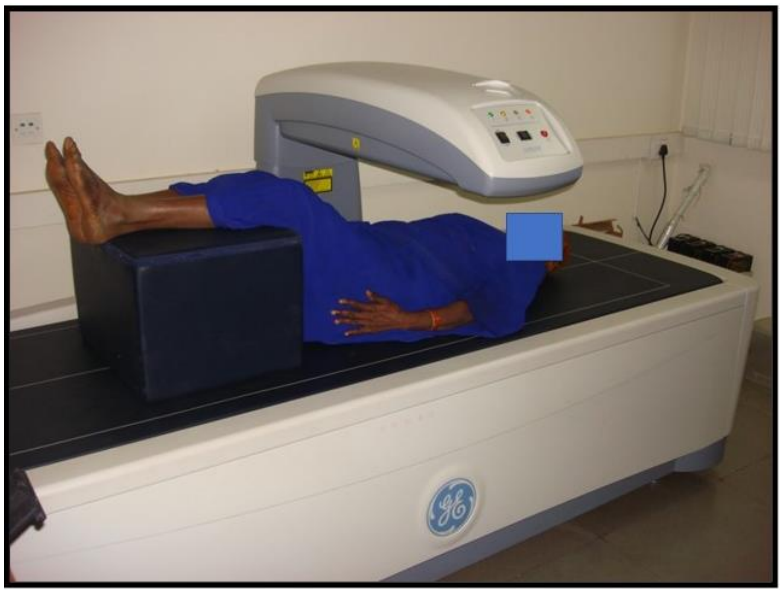


Figure 21: DEXA SCAN OF LUMBAR SPINE ON GE LUNAR PRODIGY DEXA BMD SCAN MACHINE

Figure 22: Injection ZOLEDRONIC ACID being administered intravenously

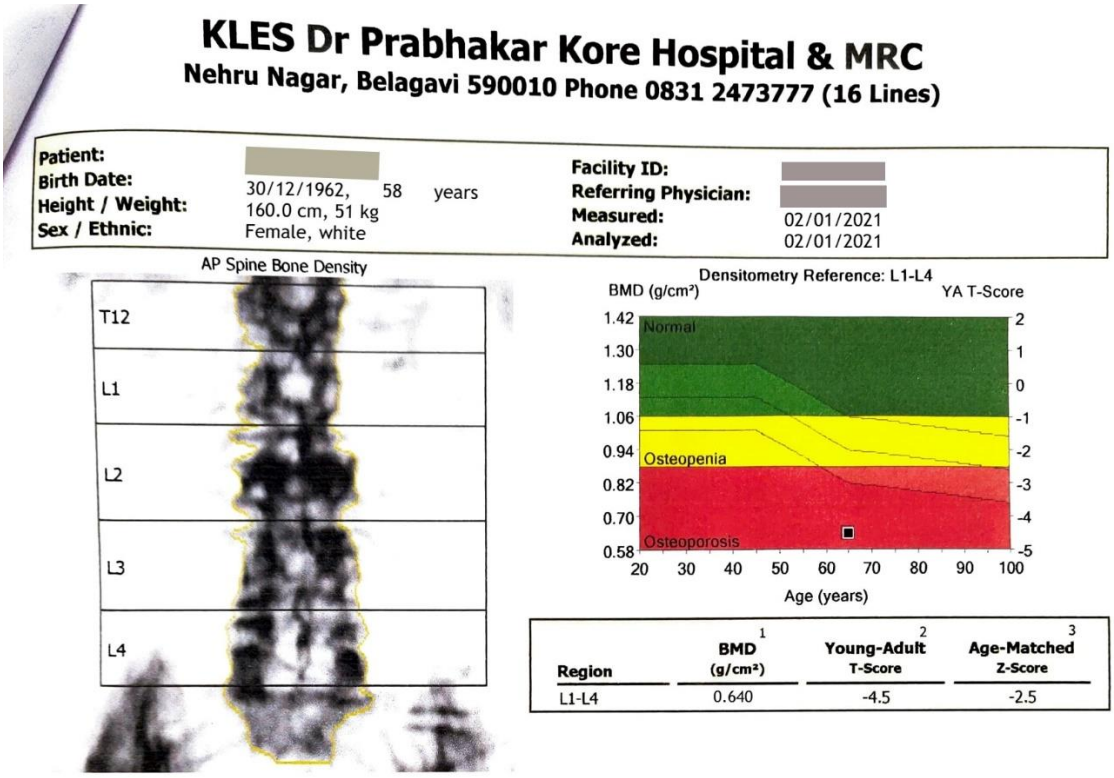


Figure 23: DEXA scan report of the patient on the first visit

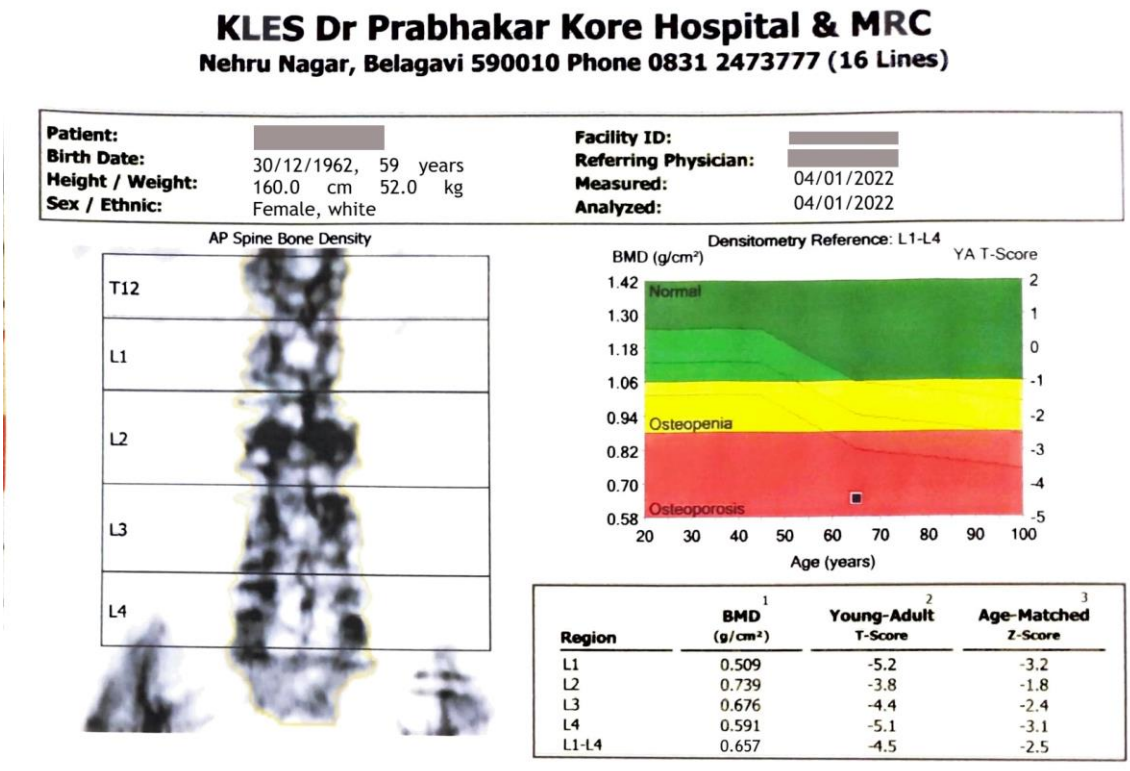


Figure 24: Figure: DEXA scan report of the patient on the final follow-up

ANNEXURE - IV

MASTERCHART

Sr No.	AGE	SEX	BMD-1	BMD-2	T-SCORE #1	T-SCORE #2	VAS-1	VAS-2	VAS-3	VAS-4	ODI-1	ODI-2	ODI-3	ODI-4	CALCIUM	VIT D	PHOSPHORUS	ALP	DM	Vertebral fracture	Major osteoporotic fracture	Major osteoporotic fracture	Hip fracture probability-1	Hip fracture probability-2	BMI-1	BMI-2	HIP fracture
1	63	F	0.624	0.644	-2.6	-2.6	8	7	6	7	66	50	42	56	7.8	9.37	3	92	NO	NO	7.1	7.6	2.6	2.8	24.4	24.4	NO
2	60	F	0.605	0.625	-3.2	-3.2	7	6	5	6	50	44	40	46	8.7	12.16	2.8	82	NO	YES	15	16	7.9	8.4	25.1	25.1	NO
3	75	M	0.751	0.781	-3.2	-3.2	6	5	4	5	42	38	36	40	7.8	18.93	3.5	116	NO	NO	8.8	8.7	4.9	4.9	26.5	25.8	NO
4	70	F	0.783	0.811	-3.3	-3.2	8	7	5	6	60	56	54	50	9.1	38.39	3	92	NO	YES	21	20	9.4	8.5	35.1	34.2	NO
5	66	M	0.63	0.653	-3.4	-3.3	8	8	6	7	66	64	58	62	8.8	12.96	2.9	102	NO	YES	16	15	10	9.1	22.5	22.5	NO
6	60	M	0.878	0.892	-4.2	-4.2	7	6	5	6	52	48	46	50	10	98.24	4	98	YES	NO	15	16	13	13	22.8	23.1	NO
7	69	F	0.528	0.538	-5.4	-5.4	8	7	6	7	50	46	42	46	9	33.37	2.6	150	YES	NO	45	39	39	32	20	19.6	NO
8	58	F	0.64	0.657	-4.5	-4.5	6	6	4	5	46	42	38	40	9.1	17.82	3.2	106	YES	YES	32	33	26	27	20.3	20.3	NO
9	75	M	0.826	0.861	-2.8	-2.6	8	7	5	7	68	60	56	60	8	15.45	3.6	102	YES	NO	7.4	6.6	3.8	3.2	24.8	24.8	NO
10	56	F	0.78	0.799	-3.3	-3.3	9	8	7	6	72	66	60	64	8.2	18.93	2.8	101	YES	NO	6.6	7.1	3.4	3.6	27.9	28.8	NO
11	46	F	0.641	0.641	-2.9	-2.9	7	6	5	6	56	52	46	50	7.1	17.82	2.6	104	YES	YES	7.7	7.6	2.7	2.7	21.1	20.1	YES
12	65	M	1.023	1.086	-2.6	-2.6	8	7	5	7	60	54	48	52	9	13.57	4	98	YES	YES	11	11	5.3	5.3	27.6	27.6	YES
13	76	M	0.528	0.584	-4.5	-4.5	7	6	5	6	62	60	56	58	8.7	14.16	3.6	74	YES	NO	16	15	11	11	25.5	25.5	NO
14	55	F	0.751	0.769	-3.3	-3.3	8	7	5	7	64	60	56	58	9	30.08	2.6	92	YES	YES	11	11	6.3	5.9	23.6	23.6	NO
15	74	F	0.546	0.579	-3.7	-3.5	7	6	5	6	56	50	46	50	8.8	12.24	2.8	88	YES	NO	18	16	9.6	8	22.8	22.8	NO
16	70	M	1.013	1.099	-2.6	-2.6	8	6	5	6	64	60	54	58	10.1	38.37	3	102	NO	NO	7	6.8	3.4	3.2	26.7	28.4	NO
17	76	M	0.568	0.593	-3.5	-3.5	8	6	5	6	60	52	50	54	7.2	16.78	2.9	96	YES	NO	8.2	7.9	5	4.8	21.6	21.6	NO
18	53	F	0.751	0.779	-3.2	-3.2	9	8	6	7	66	60	56	60	8.2	28.99	3.2	58	YES	YES	11	12	7	7.3	28.9	28.9	NO
19	58	F	0.578	0.588	-5	-5	7	5	4	6	50	46	40	42	8.8	15.45	2.8	152	YES	YES	56	58	45	46	27.4	27.4	YES
20	53	M	0.89	0.899	-3.4	-3.4	8	7	6	6	56	46	38	42	8.7	13.25	2.4	78	NO	NO	5.3	5.3	3.1	2.9	21.2	21.2	NO
21	53	M	0.578	0.596	-2.5	-2.5	7	6	5	6	54	50	46	50	8.4	16.38	4	78	YES	YES	5.6	5.9	2.8	3	23.5	23.5	NO
22	53	F	0.78	0.795	-3.3	-3.3	9	8	7	8	70	64	60	62	8.2	12.96	3.6	77	YES	YES	5.1	5.5	2.7	2.9	28.9	28.9	NO
23	73	F	0.605	0.634	-3.2	-3	7	6	5	5	56	50	44	50	10.1	100	3.9	118	YES	YES	18	16	8.2	6.8	20	20	NO

24	42	M	0.65	0.674	-4.2	-4	8	7	5	6	62	54	48	52	7.1	16.35	3.3	108	NO	NO	12	9	10	7.6	25.2	25.2	NO
25	64	F	0.888	0.899	-2.8	-2.8	8	6	4	6	60	52	46	50	9.1	18.93	3.5	82	YES	NO	8.7	9.2	3.6	3.7	23.1	23.1	NO
26	65	M	0.78	0.797	-2.9	-2.9	8	5	6	7	58	50	44	48	8.3	33.73	2.7	110	YES	NO	7.9	8.2	3.6	3.7	16.7	16.7	NO
27	70	F	0.63	0.667	-3.1	-3.1	6	5	4	5	42	38	36	38	8.6	17.2	3.8	96	YES	NO	13	13	5.6	5.6	28.9	28.9	NO
28	60	F	0.552	0.556	-3.5	-3.5	8	6	5	7	56	50	42	50	8.9	24.4	3	106	YES	NO	10	11	5.9	6.4	21.9	21.9	NO
29	75	F	0.711	0.722	-3.9	-3.9	9	8	7	7	68	50	54	60	7.5	14.28	2.8	100	NO	NO	20	19	11	10	32.9	32.9	NO
30	70	F	0.731	0.734	-4.1	-4.1	8	6	5	6	60	56	48	52	9	17.82	2.6	104	YES	NO	24	24	15	15	26.5	26.5	NO