"EFFECT OF INJECTION DENOSUMAB IN OSTEOPOROTIC FRACTURE HEALING - A RANDOMIZED CONTROL TRIAL IN TERTIARY CARE HOSPITAL"

BY
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ABSTRACT

Introduction: A significant contributor to morbidity and mortality is osteoporotic fractures, which often result in hospitalization, surgery, and long-term rehabilitation. 1) The existing treatment for osteoporotic fracture healing typically includes fracture fixation, calcium and vitamin D supplementation, bisphosphonates, and anabolic agents like teriparatide to enhance bone healing and reduce fracture risk. The purpose of this investigation is to study the effects of Injection Denosumab in osteoporotic fracture healing and the risk factors of osteoporotic fractures.

Patients and Methods Patients (within age group of 50 – 85 y/o) admitted with fractures will be advised to do a DEXA scan to check osteoporosis. After this, patients diagnosed with osteoporotic fracture "will be randomly divided into 2 groups - control and intervention (sample size - 30 in each group). The intervention group will receive one injection of Denosumab 60 mg subcutaneously along with tablet calcium (1000 mg) with vitamin D3 (600 IU). The control group will be receiving tab calcium (1000 mg) with vitamin D3 (600 IU).

Results: In the intervention group, out of 30 patients, 22 (73.33%) patients showed fracture healing within 3 months, and 8 patients (26.67%) showed fracture healing within 6 months. In control group, out of 30 patients 8 patients (26.67 %) show good fracture healing within 3 months, and 22 patients (73.33 %) show within 6 months. (p value = 0.0001)

Conclusion: According to this study, patients with osteoporotic fractures who received injection denosumab (60 mg subcutaneously) fared better than patients who did not.

Keywords: Osteoporosis, Fracture, Denosumab, Fracture-healing

LIST OF ABBREVIATIONS

Mg	Milligram
IU	International Unit
DEXA	Dual Energy X – Ray Absorptiometry
pDEXA	Peripheral Dual Energy X – Ray Absorptiometry
PTH	Parathyroid Hormone
BMD	Bone Mineral Density
QUS	Quantitative Ultrasound
FRAX	Fracture Risk Assessment Tools
BMI	Body Mass Index
VFA	Vertebral Fracture Assessment

BSAP	Bone-Specific Alkaline Phosphatase
CTX	C – Terminal Telopeptide
SERMs	Selective Estrogen Receptor Modulators
RANK	Receptor Activator Of Nuclear Factor Kappa Beta
RANKL	Receptor Activator Of Nuclear Factor Kappa Beta Ligand
HRT	Hormone Replacement Therapy
CRIF	Close Reduction And Internal Fixation
ORIF	Open Reduction And Internal Fixation
ONJ	Osteonecrosis Of The Jaw
INR	Indian Rupee
LAR	Legally Authorized Representative

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INTRODUCTION

Derived from the Greek words "osteon" (bone) and "poros" (pore), osteoporosis is a skeletal condition marked by weakened bones that increase the risk of fracture. i) Low bone mass, ii) loss of bone tissue, and iii) increased bone fragility are the primary symptoms of osteoporosis, a chronic, progressive skeletal disease. Because of this condition, bones become brittle and more likely to break, even from small or low-impact incidents like coughing, twisting, or falling from a standing height.

People with osteoporosis are susceptible to osteoporotic fractures, additionally called fragility fractures, which are fractures brought on by their weaker bones. Most often, the wrist, hip, and spine are impacted. These fractures can have serious health consequences, including hospitalization, loss of independence, chronic pain, and in rare instances, death. Millions of people worldwide suffer from osteoporosis, a serious public health concern due to its effects on the aging population. [(1)]

Osteoporosis is a very common disorder, particularly in older people. It is thought to impact more than 200 million individuals worldwide, and its prevalence increases with age. Although postmenopausal women are frequently linked to osteoporosis, men can also develop the condition, especially as they get older. As per the estimates “from the World Health Organization (WHO), 1 in 5 men and 1 in 3 women over 50 will suffer an osteoporotic fracture at some point in their lives.

The" widespread occurrence of osteoporosis renders it a major public health issue. The prevalence of osteoporotic fractures is substantial, with millions occurring annually. Hip fractures have been a significant source of morbidity and mortality, frequently leading to hospitalization, surgical intervention, prolonged rehabilitation, and, in numerous instances, fatality. Vertebral fractures, while not

immediately life-threatening, result in persistent pain, spinal abnormalities, and diminished quality of life. Wrist fractures, although frequently less debilitating, can substantially impair upper limb functionality and hinder the execution of daily tasks. [(2)]

The reason osteoporosis is frequently referred to as the "silent disease" is that it develops gradually without any outward signs until a fracture happens. Over many years, bone loss happens gradually and frequently shows no symptoms. Osteoporosis can go untreated until a person sustains a fracture from a low-energy incident, usually something as simple as slipping and falling or even leaning over to pick something up, in contrast to certain disorders that present with pain, edema, or other obvious symptoms. Because of this, many people don't realize they have osteoporosis until it's too late.

The WHO states that “dual-energy X-ray absorptiometry (DEXA)” measurements of “bone mineral density (BMD)” are the basis “for defining osteoporosis. The average peak bone density of a young, healthy adult is compared to a person's BMD using a T-score. A T-score of -1.0 or higher indicates normal bone mass; a T-score of -1.0 to -2.5 indicates osteoporosis; a T-score of -2.5 or less indicates osteoporosis; and a T-score of -2.5 or less with one or more fragility fractures indicates severe osteoporosis. The DEXA scan is the gold standard for osteoporosis diagnosis” because it is rapid, non-invasive, and gives precise bone density readings at important skeletal places, such as the spine and hip. [(3)]

When diagnosing osteoporosis and determining fracture risk, clinical risk factors are taken into account in addition to BMD values. These include age, gender, low body weight, smoking, excessive drinking, personal history of fractures, familial history of osteoporosis, along with long-term use of drugs like corticosteroids that weaken bones. An individual's 10yr. risk of osteoporotic fractures is estimated utilizing instruments that involve the “Fracture Risk Assessment Tool (FRAX)”.

Any drug therapy that enhances bone regeneration, fracture healing, and implant fixation (also known as osseointegration) would be a significant step forward in

lowering osteoporosis-related morbidity. A genetically modified human monoclonal IgG2 antibody called denosumab was produced in hamster ovary cells. Denosumab binds to RANKL and inhibits its receptor, RANK, on the surface of osteoclasts and their precursors. By preventing osteoclast formation, function, and survival, this reduces bone resorption. [(4)]

With a preferable safety and performance credentials, denosumab is a relatively new entity that works to lessen bone turnover, increase bone mineral density, and reduce fracture risks. Very few researches are done over injection denosumab on fracture healing. People with osteoporosis have delayed fracture healing or nonunion. Therefore, the aim of this study is to gain more knowledge and evidence regarding healing in cases of Osteoporotic fracture among patients who received Injection Denosumab with those who did not.

AIMS AND OBJECTIVES

AIMS:

To assess the efficacy and safety of injection denosumab in enhancing osteoporotic fracture healing compared to standard treatment over a period of 6 months in patients treated at a tertiary care hospital.

OBJECTIVES:

Primary Objective:

To evaluate the effect of injection denosumab on the progression and healing of osteoporotic fractures compared to standard treatment over a period of 6 months.

Secondary Objectives:

1. To analyze differences in demographic factors (age, gender, occupation, comorbidities like diabetes and BMI) and their influence on fracture healing outcomes in the two groups.

2. To compare the clinical outcomes (operative vs. conservative management) and their relationship with bone healing progression in both groups.

3. To determine the relationship between Dexa scan results, serum calcium, and vitamin D3 levels and their effects on fracture healing in patients receiving denosumab.

4. To compare the early (6 weeks to 3 months) and late (3 months to 6 months) fracture healing rates between the two groups (denosumab vs. non-denosumab).

5. To assess the impact of injection denosumab on the progression of bone healing at 6 weeks, 3 months, and 6 months.

6. To evaluate the safety and efficacy of injection denosumab in accelerating early bone healing in osteoporotic fractures.

NEED FOR THE STUDY

Denosumab is a relatively new drug that reduces bone turnover, increases BMD, and lowers the risk of fractures. It has better safety and performance credentials. Research on the effects of injectable denosumab on fracture healing is extremely limited. Individuals with osteoporosis need daily drugs in the form of calcium, vitamin D3, and PTH since they experience non-union and delayed fracture repair. Nevertheless, the aim of this particular study is to compare patients who got injection denosumab with those who did not in order to get additional information and evidence regarding healing in cases of osteoporotic fracture.

REVIEW OF LITERATURE

In 2015, Zaheer S, LeBoff M, and Lewiecki EM conducted a study at the New Mexico Clinical Research & Osteoporosis Center in Albuquerque, New Mexico, USA. 49 healthy postmenopausal women were assigned to a single dosage of denosumab (0.01, 0.03, 0.1, 0.3, 1.0, and 3.0mg/kg groups, n = 6/group) in Phase I dose-escalation clinical research at a 3:1 ratio to a placebo. The effectiveness and safety of denosumab in postmenopausal women having low bone mineral density had been assessed in a phase II randomized, placebocontrolled, dose-ranging research. With current data demonstrating sustained fracture risk reduction and bone density improvement up to 8 years of continued use, denosumab is a safe and effective treatment" option for osteoporosis. It has been considered as a novel agent that acts to reduce bone turnover, increase BMD, and lower fracture risk. [(4)]

In 2020, Pang KL, Low NY, Chin KY, department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, The retrospective analysis comprised 92,355 participants aged ≥50 years who were initially prescribed denosumab or alendronate between May 2010 and December 2017 without receiving any antiosteoporosis therapy within a year. As part of the trial, these participants were monitored for hip or other fractures for a maximum of 7.5 years. The long-term effect of denosumab for the prevention of fragility fractures has been proposed in current review, which was prompted by the publication of the FREEDOM study's results and its extension. As a result, they compiled and concluded the clinical studies that demonstrated denosumab's safety and ability to lower fracture risk. [(5)]

A review done by Dutta S. in 2011, in Adis, a Wolters Kluwer Business, Auckland, New Zealand. In the FREEDOM research, postmenopausal women with osteoporosis (n = 7868) had their fracture risk assessed over a 36-month period in relation to denosumab versus placebo. Denosumab therapy improved BMD and reduced bone turnover indicators in postmenopausal individuals with

osteoporosis or low BMD. In contrast to patients who continued taking oral alendronate 70 mg once weekly for 12 months, postmenopausal women with low BMD who switched from alendronate to denosumab in the STAND study experienced an increase in BMD at the total hip of 1.90% following 12 months of denosumab 60mg every 6 months. [(6)]

Research conducted by Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JE, McClung M et al in 2017, San Francisco, A FREEDOM assessment of fracture risk showed that 797 participants who stopped treatment after receiving at least two doses of denosumab did not have an increased risk of a combination of nonvertebral and vertebral fractures over a median of 0.5 years of off-treatment follow-up (hazard ratio ¼ 0.82; 95% CI 0.49–1.38). The effect of cessation on the risk of vertebral fractures, still was not examined separately. [(7)]

A research done by Ferrari S, Eastell R, Napoli N, Schwartz A, Hofbauer LC, Chines A et al in 2020, Switzerland, 508 patients with diabetes (n = 266) out of 7808 participants in FREEDOM were given denosumab or a placebo (n = 242). Of those, BMD elevated considerably with denosumab compared to placebo in FREEDOM, and it continued to rise in long-term (continuing denosumab) and crossover (placebo to denosumab) denosumab" individuals during the Extension. Diabetes patients receiving denosumab in FREEDOM saw a significantly decreased rate of new vertebral fractures (1.6%) compared to those receiving a "placebo (8.0%) (RR: 0.20 [95% CI 0.07 to 0.61]; p =.001). The incidence of nonvertebral fractures was greater with denosumab (11.7%) compared with placebo (5.9%) (HR: 1.94 [95% CI 1.00 to 3.77] p =.046), but denosumab caused fewer hip fractures than placebo. [(8)]

A research done by Saag KG, Pannacciulli N, Geusens P, Adachi JD, Messina OD, Morales-Torres J et al" in 2019, Birmingham, Out of 795 patients, 590 (74.2%) finished the study (109 of 145 patients in the glucocorticoidinitiating group received denosumab treatment, and 117 of 145 patients received risedronate

treatment; 186 of 253 patients received denosumab treatment, and 178 of 252 patients received risedronate treatment in the glucocorticoidcontinuing group). Among individuals starting glucocorticoids, denosumab outperformed risedronate in terms of improving lumbar spine and total hip BMD at all time periods measured. Up until month 24, denosumab outperformed risedronate in terms of gains in hip and spine BMD, and the safety profile was comparable across treatment groups. For individuals receiving glucocorticoids, denosumab may provide a novel osteoporosis therapeutic alternative. [(9)]

Research done by Bell AD, Bell BR in 2011, Toronto, Over the course of 36 months, 7868 women had been randomly assigned to either denosumab or a placebo. The investigation groups' baseline characteristics were comparable. The average total hip T score was -1.9, and the average lumbar T score was -2.8. showed that using denosumab instead of oral alendronate resulted in noticeably higher increases in bone density in the lumbar spine, whole hip, and femoral neck after a year in postmenopausal osteoporosis patients. [(10)]

In 2009, Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR et al. published a study in The New England Journal of Medicine that involved 7868 women aged 60-90yrs. with a BMD T score at the lumbar spine or whole hip that was less than −2.5 but not less than −4.0. Every six months for 36 months, subjects had been randomized to receive either 60mg of denosumab or a placebo subcutaneously". The main outcome was a fresh vertebral fracture. Nonvertebral and hip fractures were secondary end goals noticed when administered subcutaneously twice a year for 36 months, denosumab was linked to a lower risk of hip, nonvertebral, and vertebral fractures in women with osteoporosis. [(11)]

According to a case study conducted in 2021 at PD Hinduja National Hospital and Medical Research Centre in Mumbai, Maharashtra, India, by Agarwala S. and Vijayvargiya M., several osteoporotic drugs, like teriparatide, bisphosphonates, and strontium ranelate, have been tried to enhance fracture healing properties".

Although denosumab has just received approval for treating osteoporosis, it is unclear how it affects fracture repair. [12]

In 2003, Häuselmann HJ and Rizzoli R conducted a review in Switzerland. The study lasted between one and four and a half years. The number of patients enrolled in each research varied significantly, ranging from over 9000 (for risedronate) to 34 (for calcitriol). According to the study, the dropout rate also varied significantly, that range from a lower of 4% for alendronate to a high of 80% for fluoride. Studies where morphometric vertebral fracture was an end-point had mean ages ranging from 60 to 71 years. According to this study, overall BMD changes in comparison to controls were in line with a lower risk of fracture. [13]

Anatomy of Bone

Macroscopic Structure: Bones are composed of "two primary types of tissue:

- Cortical (compact) bone: constitutes the thick outer layer of bones and accounts for almost 80% of the skeletal mass. It is mechanically strong and responsible for protecting internal organs.

- Trabecular (spongy) bone: Located primarily at the ends of long bones and in the vertebrae, this porous, lattice-like structure" is metabolically active and contributes to bone turnover and mineral homeostasis.

Microscopic Structure:

- Osteoblasts: Bone-forming cells that produce osteoid, which is mineralized to form bone.
- Osteoclasts: Multinucleated cells responsible for bone resorption.

- Osteocytes: Mature osteoblasts embedded in the bone matrix; they regulate the bone remodeling process by sensing mechanical strain and coordinating responses.

Bone tissue is organized into functional units known as osteons, which provide structural integrity. (14, 15)

Physiology of Bone Remodeling

Bone Remodeling Process: The process by which new bone tissue is generated (formation) and mature bone tissue is eliminated (resorption) is known as bone remodeling. To maintain bone strength and control calcium and phosphate levels, this process takes place in distinct packets of bone tissue.

Resorption: Osteoclasts break down old bone, releasing calcium and phosphate into the blood.

Formation: Osteoblasts lay down new bone by depositing osteoid, which is then mineralized with calcium and phosphate.

Hormonal Regulation:

- Parathyroid hormone (PTH): It is secreted by parathyroid glands in response to low calcium levels. It increases bone resorption by stimulating osteoclasts, indirectly releasing calcium into the bloodstream.
- Calcitonin: produced by the thyroid gland, calcitonin inhibits osteoclast activity, reducing bone resorption.
- Estrogen: Estrogen inhibits osteoclast-mediated bone resorption, maintaining bone mass. After menopause, the reduction in estrogen levels results in increased bone loss, contributing to the development of osteoporosis. [16, 17]

Pathophysiology of Osteoporosis

Bone loss and structural degradation result from osteoporosis, which is caused by a disruption in the balance between bone creation and resorption. This imbalance can result from multiple factors:

Postmenopausal Osteoporosis: Estrogen deficiency accelerates bone resorption, causing women to experience a quick period of bone loss following menopause.

Age-related Osteoporosis: In both women and men, bone formation decreases with age, causing bone mass to gradually decrease.

Secondary Osteoporosis: This can be caused by other medical conditions like hyperthyroidism, glucocorticoid use, or chronic kidney disease.
Microarchitectural Changes: In osteoporosis, cortical bone gets more porous, and trabecular bone gets thinner. These changes reduce bone strength and increase fracture risk, particularly in areas like the vertebrae, hips, and wrists. [18, 19]

Diagnosis of Osteoporosis: Modalities and Techniques

Osteoporosis is often a silent disease, and the diagnosis typically comes after a fracture occurs. Early detection, especially in at-risk individuals, is essential to prevent fractures and to initiate treatment. Osteoporosis is mostly diagnosed by measuring BMD, but other diagnostic modalities and clinical assessments are also used.

1. Bone Mineral Density (BMD) Testing

BMD assessment is the most accurate way to diagnose osteoporosis. As per the WHO, osteoporosis can be defined by BMD, with particular bone density cutoffs that are related to fracture risk. T-scores are frequently employed to express these cutoffs. [20]

T-score:

- Normal: T-score ≥ -1
- Osteopenia (low bone mass): T-score between -1 and -2.5
- Osteoporosis: T-score ≤ -2.5

1.1. Dual-Energy X-ray Absorptiometry (DEXA)

The most reliable approach for identifying osteoporosis is DEXA. It assesses BMD in important skeletal locations, which include the hip, lumbar spine, and occasionally the wrist, where osteoporotic fractures are most likely to happen. DEXA is preferred because of its accuracy, reproducibility, low radiation dose, and established reference standards.

Advantages:

- Non-invasive and quick (10–15 minutes).
- Low radiation exposure.
- Provides precise measurements for treatment monitoring.

Limitations:

- Cannot assess bone quality or architecture.
- Less accurate in patients with certain spinal conditions (e.g., osteoarthritis, scoliosis). [21]

1.2. Quantitative Computed Tomography (QCT)

QCT is another imaging technique employed to assess "BMD, typically at the spine. Unlike DXA, which measures areal BMD (g/cm^2), QCT measures volumetric BMD (mg/cm^3) and can distinguish between trabecular and cortical bone.

Advantages:

- 3D imaging allows separate analysis of trabecular and cortical bone.
- More sensitive to early changes in bone density.

Limitations:

- Higher radiation dose compared to DEXA.
- More expensive and less available than DEXA.
- Not widely used for routine diagnosis due to cost and radiation. [22]

1.3. Peripheral DEXA (pDEXA)

Peripheral DEXA measures BMD at sites like the forearm, finger, or heel (calcaneus). It is often used in screening settings because of its portability and lower cost.

Advantages:

- Portable and relatively inexpensive.
- Useful in settings where central DXA (spine, hip) is not available.

Limitations:

- Peripheral BMD measurements may not be as predictive of fracture risk as central measurements.
- Not recommended as the primary method for diagnosing osteoporosis but can be used for screening purposes. [23]

2. Quantitative Ultrasound (QUS)

Quantitative ultrasonography is a non-invasive approach employed to compute bone density, generally at the heel (calcaneus). QUS measures the "speed of sound (SOS)" or "broadband ultrasound attenuation (BUA)" through bone, which reflects bone density and structure.

Advantages:

- No radiation exposure.
- Portable and low cost.
- May provide details on both the density and structure of bones.

Limitations:

- Lower predictive value for fractures compared to DEXA.
- Not as accurate for tracking changes in BMD over time.

QUS is not used to formally diagnose osteoporosis but is valuable for initial screening, particularly in community settings or where access to DEXA is limited. [24]

3. Fracture Risk Assessment Tools

To evaluate the 10-year risk of a major osteoporotic fracture (hip, spine, forearm, or shoulder), the World Health Organization (WHO) created the FRAX algorithm. Clinical risk factors are used with or without BMD" tests.

Clinical Risk Factors Included:

- Age, gender, BMI.
- Previous fractures.
- Parental history of hip fracture.
- Smoking, alcohol use, glucocorticoid use, rheumatoid arthritis.

Advantages:

- Provides individualized fracture risk assessment.
- Can be used in conjunction with BMD (T-score) to determine the need for treatment.

Limitations:

- Does not account for factors such as bone quality or architecture.
- The tool's risk estimates are population-specific, which may limit its accuracy in different ethnic groups. [25, 26]

4. Vertebral Fracture Assessment (VFA)

VFA is an imaging technique used to detect vertebral fractures, which are a characteristic of osteoporosis. Vertebral fractures are often asymptomatic and may not be detected until they lead to height loss or kyphosis (spinal curvature). VFA

is performed using lateral spine imaging and can be done simultaneously with DXA.

Advantages:

- Can detect existing vertebral fractures, even those that are asymptomatic.
- Helps to further stratify fracture risk in patients with borderline BMD results.

Limitations:

- Lower image resolution compared to standard radiographs.
- Not typically used as a standalone diagnostic tool. [27]

5. Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover, such as serum "bone-specific alkaline phosphatase (BSAP)" for bone formation and "C-telopeptide (CTX)" for bone resorption, can be utilized as adjuncts to imaging in osteoporosis diagnosis. These markers are particularly useful in assessing response to treatment or understanding the dynamics of bone remodeling.

Advantages:

- Non-invasive and can provide dynamic information about bone turnover.
- May be helpful in assessing fracture risk in conjunction with BMD.

Limitations:

- Considerable variability, affected by circadian rhythm, diet, and other factors.
- Not routinely used for initial diagnosis. [28]

6. Conventional Radiography

While not a primary diagnostic tool for osteoporosis, standard X-rays may reveal fractures that suggest the presence of osteoporosis, especially vertebral compression fractures. Radiographs can show bone thinning and loss of trabecular structure in advanced disease.

Advantages:

- Useful for detecting fractures that may indicate severe osteoporosis.
- Can assess other potential causes of bone pain or fractures (e.g., metastases).

Limitations:

- Not sensitive enough to detect early bone loss.
- Often only reveals osteoporosis after significant bone loss has occurred. [29]

Treatment of Osteoporosis

Non-Pharmacological Interventions:

▪ Exercise: Weight-bearing exercises (e.g., walking, jogging) and resistance training are recommended to improve bone strength.

▪ Dietary Supplements: Adequate intake of calcium and vitamin D is essential in order to maintain bone health. Vitamin D enhances Ca absorption from the gut, while calcium provides the building blocks for bone mineralization.

Pharmacological Interventions:

- Bisphosphonates: First-line therapy for osteoporosis. These drugs inhibit osteoclast activity, reducing bone resorption.

Examples: Risedronate, Alendronate, Zoledronic acid.

- Selective Estrogen Receptor Modulators (SERMs): These mimic the effects of estrogen on bone.

Example: Raloxifene.

- Denosumab: RANKL (receptor activator of nuclear factor kappa-B ligand), a crucial component in osteoclast activity and development, is the target of a monoclonal antibody.
- Parathyroid hormone analogs (e.g., Teriparatide): These drugs stimulate new bone formation and are typically reserved for patients at very high risk of fracture.
- Hormone Replacement Therapy (HRT): While effective, HRT is less commonly used because of associated risks like cardiovascular events and breast cancer. [30, 31]

Pharmacology of Osteoporosis Medications

1. Bisphosphonates:

Mechanism: Inhibiting osteoclast-mediated bone resorption, bisphosphonates attach to the surfaces of bone minerals.

Common drugs: Alendronate (oral), Zoledronic acid (intravenous).

Side effects: osteonecrosis of the jaw (rare), Esophageal irritation, atypical femoral fractures (rare).

2. Denosumab:

Mechanism: RANKL, which is important for osteoclast development, function, and survival, is inhibited by denosumab.

Side effects: risk of infections, Hypocalcemia, osteonecrosis of the jaw (rare).

3. SERMs (e.g., Raloxifene):

Mechanism: These drugs act on estrogen receptors, providing the protective effects of estrogen on bone without stimulating breast or uterine tissue.

Side effects: Increased risk of thromboembolic events, hot flashes.

4. Teriparatide (PTH analog):

Mechanism: Teriparatide stimulates osteoblasts more than osteoclasts, promoting bone formation.

Side effects: Hypercalcemia, dizziness, and leg cramps. [32, 33]

METHODOLOGY

Source of Data: Over the course of a year, from June 1, 2023, to May 31, 2024, data will be gathered from patients undergoing orthopedic surgeries at "KLE's Dr. Prabhakar Kore Hospital & Medical Research Centre and Charitable Hospital in Belagavi".

Study Design: A One-year hospital based Randomized Control Trial (double blind)

Study Period: One Year

From 1st June 2023- 31st May 2024

Sampling design: Probability sampling

Sampling tenchnique: computer – generated random number table

Sample Size:

- The minimum sample size formula based on two proportions is

$$n = \frac{(z_\alpha + z_\beta)^2 \bar{p}(1-\bar{p})}{d^2}$$

- Where p_1 and p_2 are the proportions of the two groups.

$$p = \frac{p_1 + p_2}{2} \text{ and } d = p_1 - p_2$$

- z_α is linked with the level of significance and z_β is linked with the power of the test. For 5% level of the significance $z_\alpha = 1.96$ and $z_\beta = 0.84$ for 80% power of the test.

- Ref: Randomized, Double-Blind, Clinically Controlled Trial of Intranasal Calcitonin Treatment in Patients with Hip Fracture T.M.Huusko, P.Karppi, H.Kautiainen, H.Suominen, V.Avikainen, R.Sulkava[14]

- The parameter considered in the calculation is the percentage of fusion of fracture after 3 months after operation

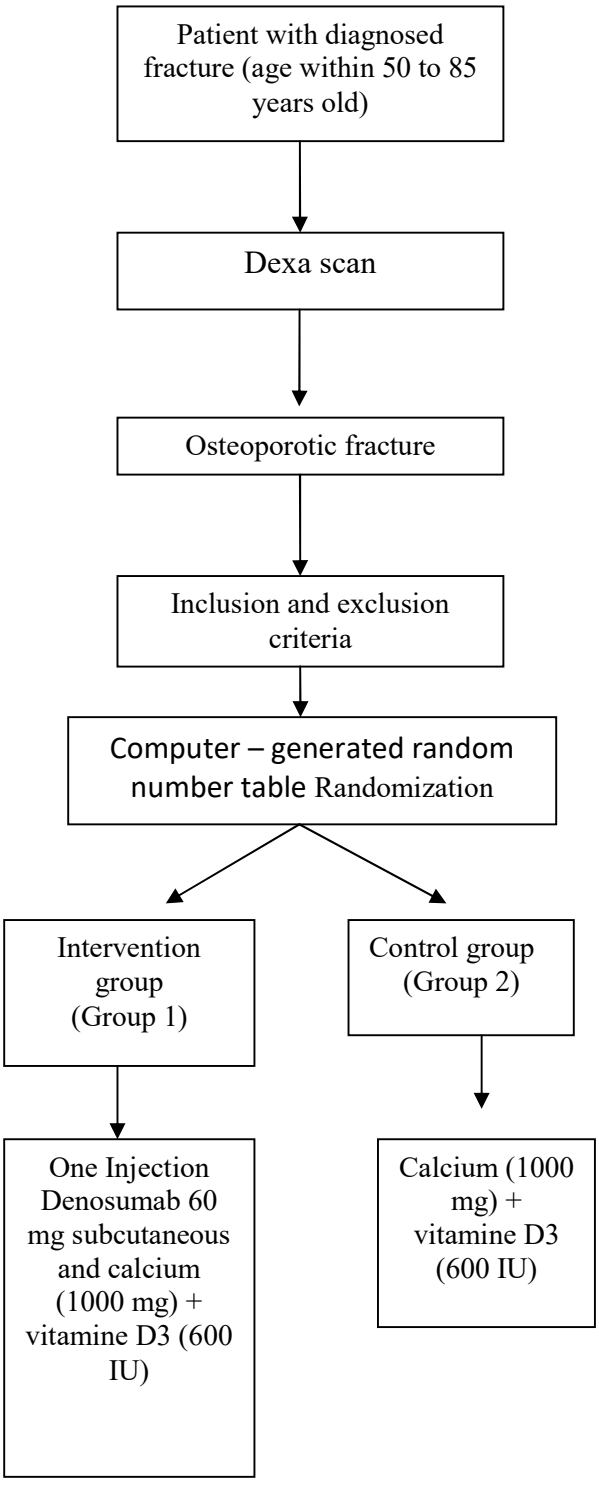
- With p_1 = 89% and p_2 = 53% the sample size obtained is 25.

- There would be two groups with size of 30 (>25) each.

Study protocol:

A randomized controlled study was conducted in a hospital for a year. Patients (within age group of 50 to 85 years old) admitted with diagnosed fracture will be advised to do a Dexa scan to check for osteoporosis. After this, whoever is diagnosed with osteoporotic fracture will be divided into 2 groups, the intervention group and control group. The intervention group will receive one injection of Denosumab 60 mg subcutaneously as well as tablet calcium (1000mg) with vitamin D3 (600IU). The control group will be receiving only tab calcium (1000mg) with vitamin D3 (600IU). This is the best method we have for testing that isn't impacted by our hopes or assumptions. Next, we'll compare the two to see which produces the best outcomes.

Data collection procedure:



Primary efficacy endpoint: fracture healing

Safety endpoint : treatment emergent serious and non serious adverse events

Data processing and analysis/statistical analysis

- The comparison of two groups is the primary emphasis of the research. The mean as well as the standard deviation of the continuous quantitative variables will be determined. The unpaired student's t-test and different appropriate statistical methods are going to be utilized for contrasting the intergroup continuous approaches. "The student's paired t-test can be utilized for comparing two quantitative variables within a group.
- Rates, ratios, and percentages will be utilized to indicate the categorical data. The chi-square test or Fisher's exact test will be employed to analyse the association among the result, clinical, and demographic" factors.
- The median will be utilized for expressing discrete variables.
- Discrete variables will be compared by employing nonparametric testing.
- The relevant graphs will be utilized for showing the comparison.

For every test, a p-value

Does the study require any investigations or interventions to be conducted on patients or other humans or animals? If so, please describe briefly.

- Yes (For patients with fractures)
- Dexa scan, Blood investigations, X rays
- other humans/animals are not involved in this study

Budget analysis:

TITLE: "Effect of Injection Denosumab in Osteoporotic Fracture healing-A Randomized Control Trial in tertiary care hospital"

Principal Investigator	**-**	**Guide**
Dr. Smit D. Upadhyay		Dr. Sameer Haveri
Post graduate Resident,		Professor
Department of Orthopedics,		Department of Orthopedics
J.N. Medical College,		J.N. Medical College,
K.A.H.E.R, Belagavi		K.A.H.E.R, Belagavi
Ph. No.9016469689		Ph. No. 9844333082

A. <u>Direct Cost:</u>

a. Dexa scan: 2500 INR
b. Inj denosumab (60 mg): 17,500 INR
c. Investigations : 10,000 INR
d. Medications - calcium (1000 mg): 654 INR / months

- vitamin D3 (600 IU): 320 INR / months

B. <u>Indirect Cost:</u> 1000 INR

a. Printing and Copying supplies
b. Data Collection and Transport
c. Meeting and other Expenses

C. <u>Miscellaneous:</u> 1000 INR

Total Cost: 32,974 INR

Inclusion Criteria:

1. Adult Males or Females aged between 50 to 85 years of age, both inclusive
2. Able to give consent for participation on their own or through their Legally Authorized Representative (LAR).
3. Patient diagnosed with fracture and Osteoporosis (BONE MASS INDEX <-2.5)

Exclusion Criteria:

1. HIV Positive, HBsAG Positive
2. Refusal of Consent
3. Thyroid dysfunction, hypocalcimia, rheumatoid arthritis, vitamin D deficiency
4. Previous treatment with bisphosphonates in the last 12 months prior to screening.
5. Concomitant head injury with clinically significant abnormality on a head CT
6. Patients with pathological fracture
7. Patient on ventilator or requires ventilator
8. Patients who are currently participating in a clinical trial.

9. Patient who, in the opinion of the investigator, are otherwise unsuitable for this study.
10. Evidence of metabolic bone disease other than osteoporosis such as osteomalacia or osteogenesis imperfect, paget's disease, cushing's disease, hyperprolactinemia

RESULTS

The findings of this study are presented in terms of the demographic characteristics, clinical parameters, fracture characteristics, treatment modalities, and the progression of fracture healing at different time intervals. The findings are described in detail below:

Table 1: Comparison of group 1 and group 2 with age

Age groups	Group 1	%	Group 2	%	Total	%	p-value
51-60yrs	10	33.33	7	23.33	17	28.33	0.3240
61-70yrs	9	30.00	5	16.67	14	23.33	
71-80yrs	6	20.00	11	36.67	17	28.33	
>=81yrs	5	16.67	7	23.33	12	20.00	
Total	30	100.00	30	100.00	60	100.00	
Mean	67.27		71.93		69.60		t=1.8143
SD	10.43		9.47		10.15		P=0.0748

Findings:

The study's participants ranged in age from 51 to more than 81. In Group 1, 33.33% of the participants were between 51–60 years, and 30% were aged between 61–70 years. Comparatively, Group 2 had 23.33% of participants in the 51–60 years age range and 16.67% in the 61–70 years range. Interestingly, a larger proportion of participants in Group 2 belonged to the 71–80 years age group (36.67%), whereas in Group 1, this percentage was 20%. Participants aged 81 years and above accounted for 16.67% in Group 1 and 23.33% in Group 2.

In Group 2, mean age of participants was 71.93 years (SD=9.47), while in Group 1, it was slightly lower at 67.27 years (SD=10.43). Although there was a noticeable difference in age distributions, the statistical analysis revealed that this difference was not significant (p=0.0748), indicating age distribution was comparable between the two groups.

Figure 1: Comparison of group 1 and group 2 with age

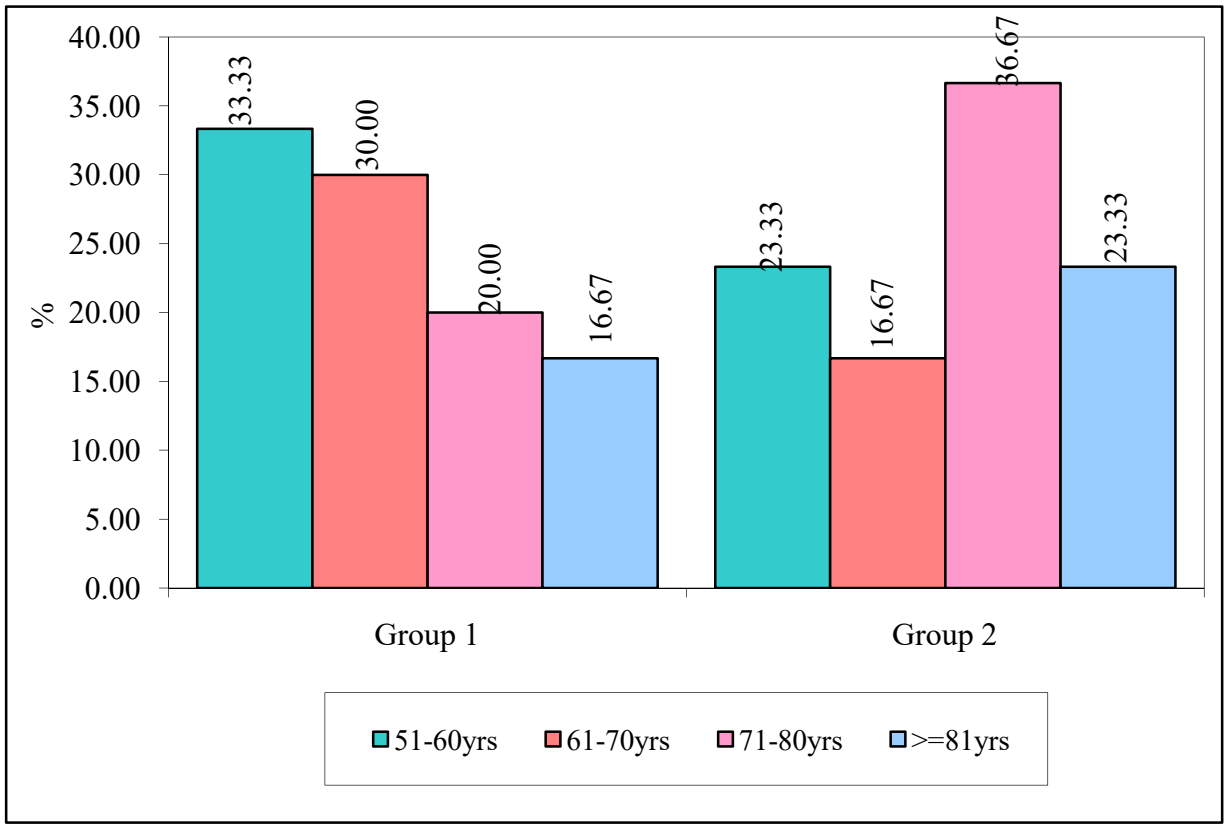


Table 2: Comparison of group 1 and group 2 with gender

Gender	Group 1	%	Group 2	%	Total	%	p-value
Male	12	40.00	16	53.33	28	46.67	0.3010
Female	18	60.00	14	46.67	32	53.33	
Total	30	100.00	30	100.00	60	100.00	

Findings:

The gender distribution in the research demonstrated a predominance of females in Group 1, with 60% female participants and 40% male participants. However, Group 2 had a greater proportion of male participants (53.33%) compared to females (46.67%). Despite these variations, statistical analysis confirmed that gender distribution was not significantly different between groups (p=0.3010).

Figure 2: Comparison of group 1 and group 2 with gender

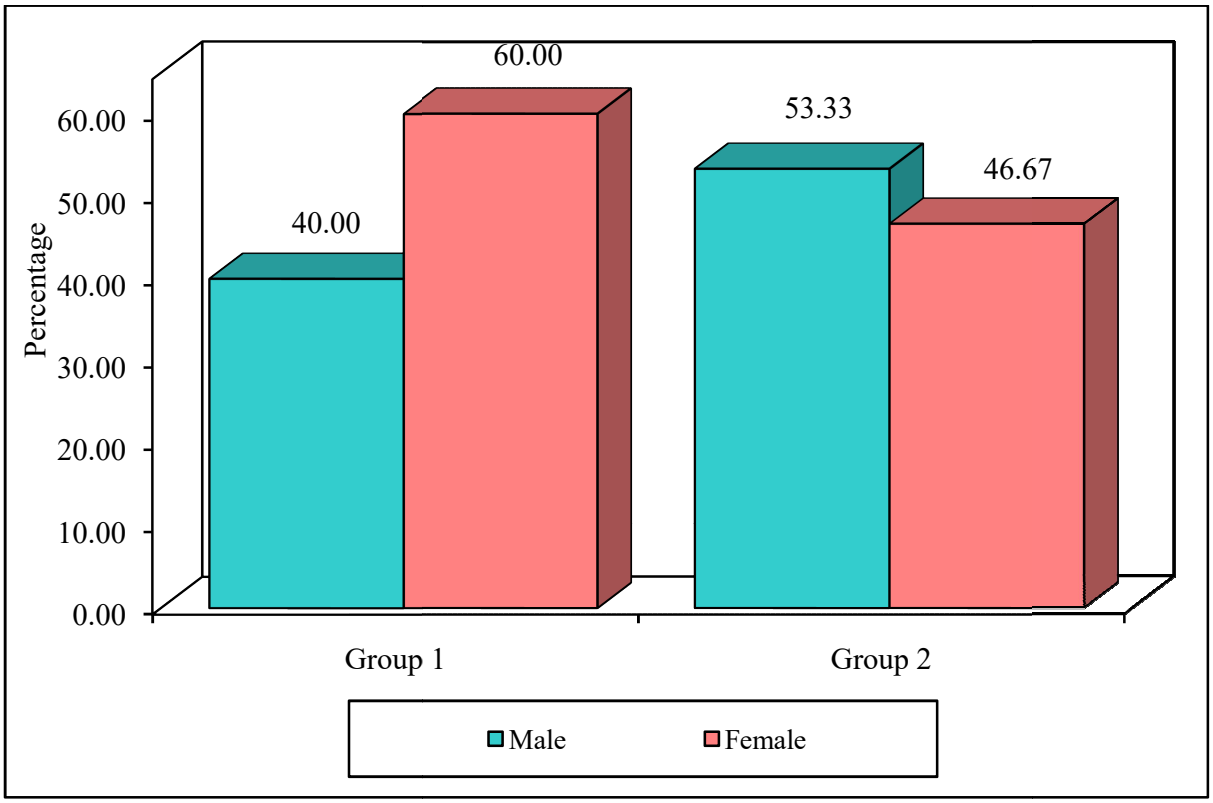


Table 3: Comparison of group 1 and group 2 with occupations

Occupation	Group 1	%	Group 2	%	Total	%	p-value
Sedentary work	29	96.67	30	100.00	59	98.33	1.0000
Heavy work	1	3.33	0	0.00	1	1.67	
Total	30	100.00	30	100.00	60	100.00	

Findings:

The vast majority of participants in both groups were engaged in sedentary occupations. Group 1 had 96.67% of participants with sedentary work and only 3.33% with heavy work. In contrast, all participants in Group 2 were involved in sedentary work. This demonstrates that participants across both groups predominantly led a low-activity lifestyle, likely contributing to their osteoporotic status. Nonetheless, there was no statistically significant difference in the two groups' occupational status (p=1.0000).

Figure 3: Comparison of group 1 and group 2 with occupations

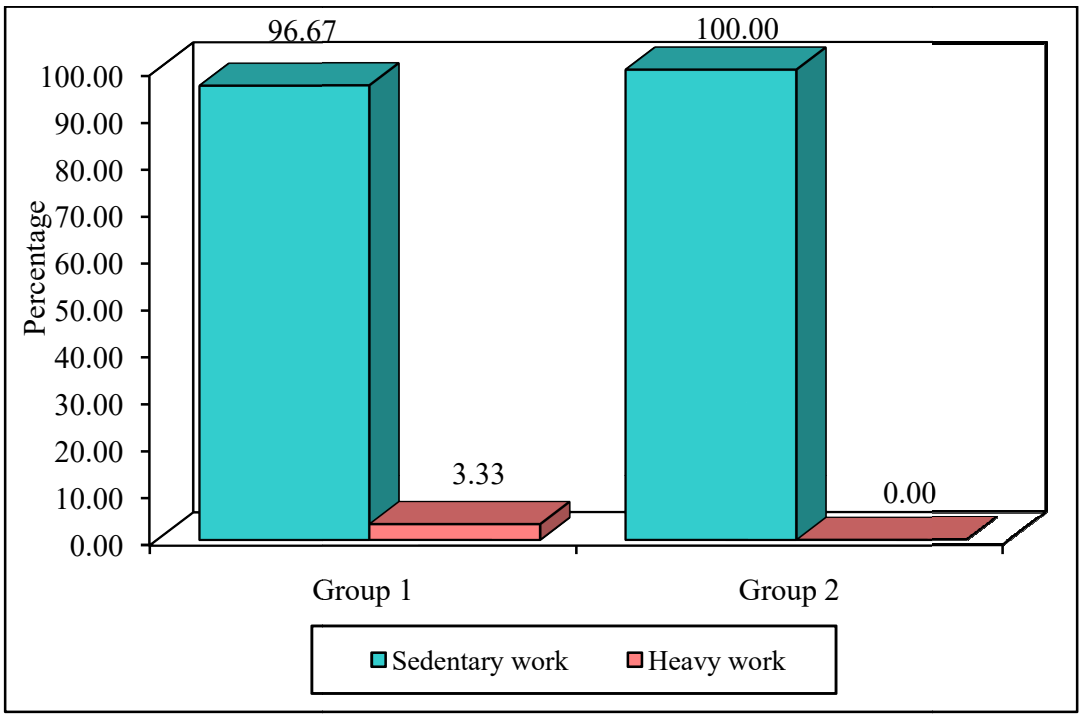


Table 4: Comparison of group 1 and group 2 with smoking status

Smoking	Group 1	%	Group 2	%	Total	%	p-value
No	29	96.67	28	93.33	57	95.00	1.0000
Yes	1	3.33	2	6.67	3	5.00	
Total	30	100.00	30	100.00	60	100.00	

Findings:

In Group 1, 96.67% of participants were non-smokers, while 3.33% were smokers. Group 2 had a similar pattern, with 93.33% non-smokers and 6.67% smokers. This suggests that smoking was not a predominant habit in the study population, and there was no statistically significant difference between the two groups (p=1.0000).

Figure 4: Comparison of group 1 and group 2 with smoking status

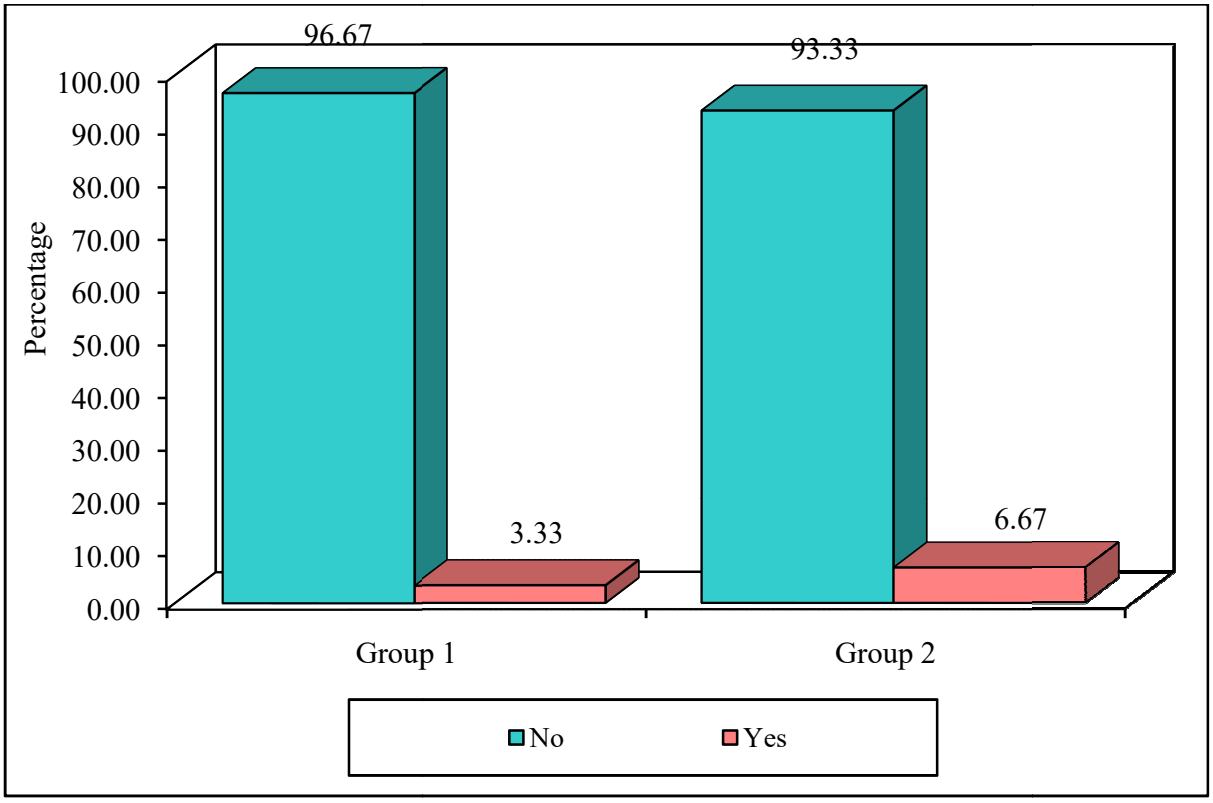


Table 5: Comparison of group 1 and group 2 with alcohol status

Alcohol	Group 1	%	Group 2	%	Total	%	p-value
No	30	100.00	29	96.67	59	98.33	1.0000
Yes	0	0.00	1	3.33	1	1.67	
Total	30	100.00	30	100.00	60	100.00	

Findings:

Alcohol consumption was also rare among participants. None of the participants in Group 1 consumed alcohol, whereas 3.33% of participants in Group 2 reported alcohol use. This slight difference was statistically insignificant (p=1.0000).

Figure 5: Comparison of group 1 and group 2 with alcohol status

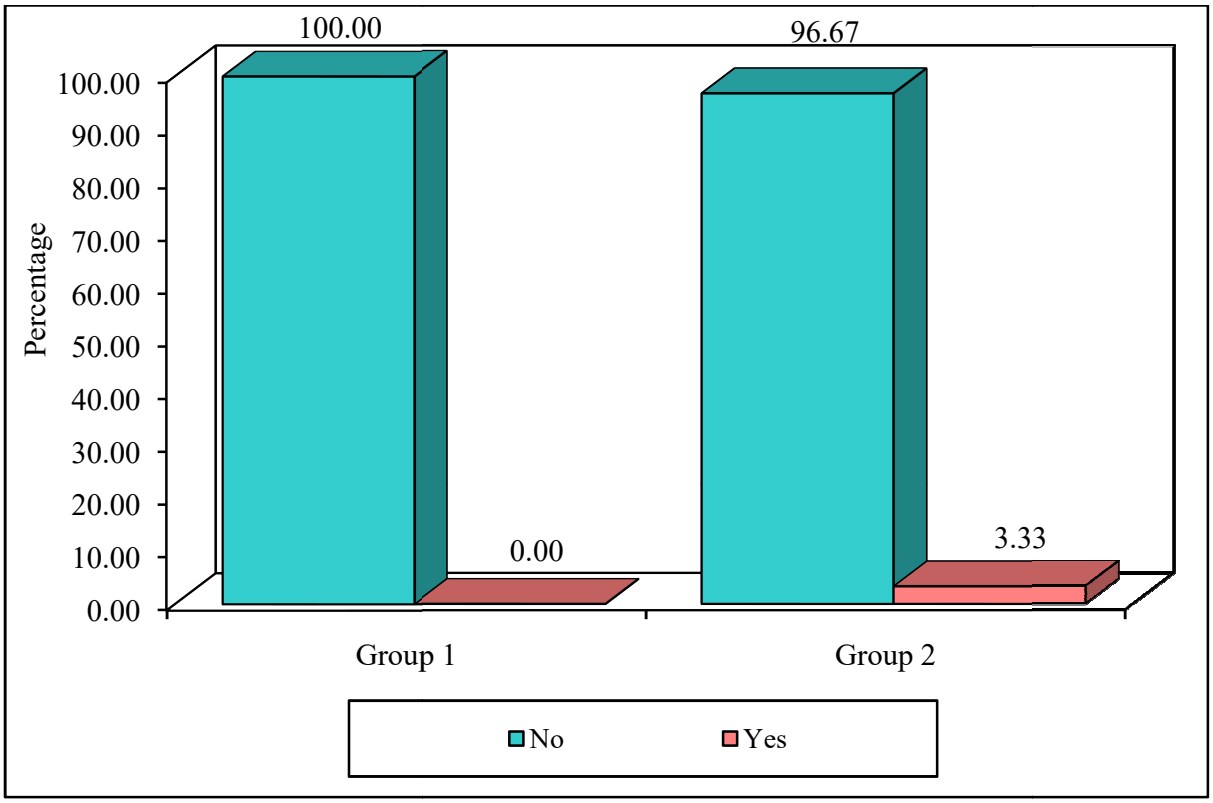


Table 6: Comparison of group 1 and group 2 with diabetic status

Diabetic status	Group 1	%	Group 2	%	Total	%	p-value
No	22	73.33	18	60.00	40	66.67	0.2730
Yes	8	26.67	12	40.00	20	33.33	
Total	30	100.00	30	100.00	60	100.00	

Findings:

Group 1 had a lower proportion of participants with diabetes (26.67%) compared to Group 2 (40%). However, this difference in diabetic status was not statistically significant (p=0.2730).

Figure 6: Comparison of group 1 and group 2 with diabetic status

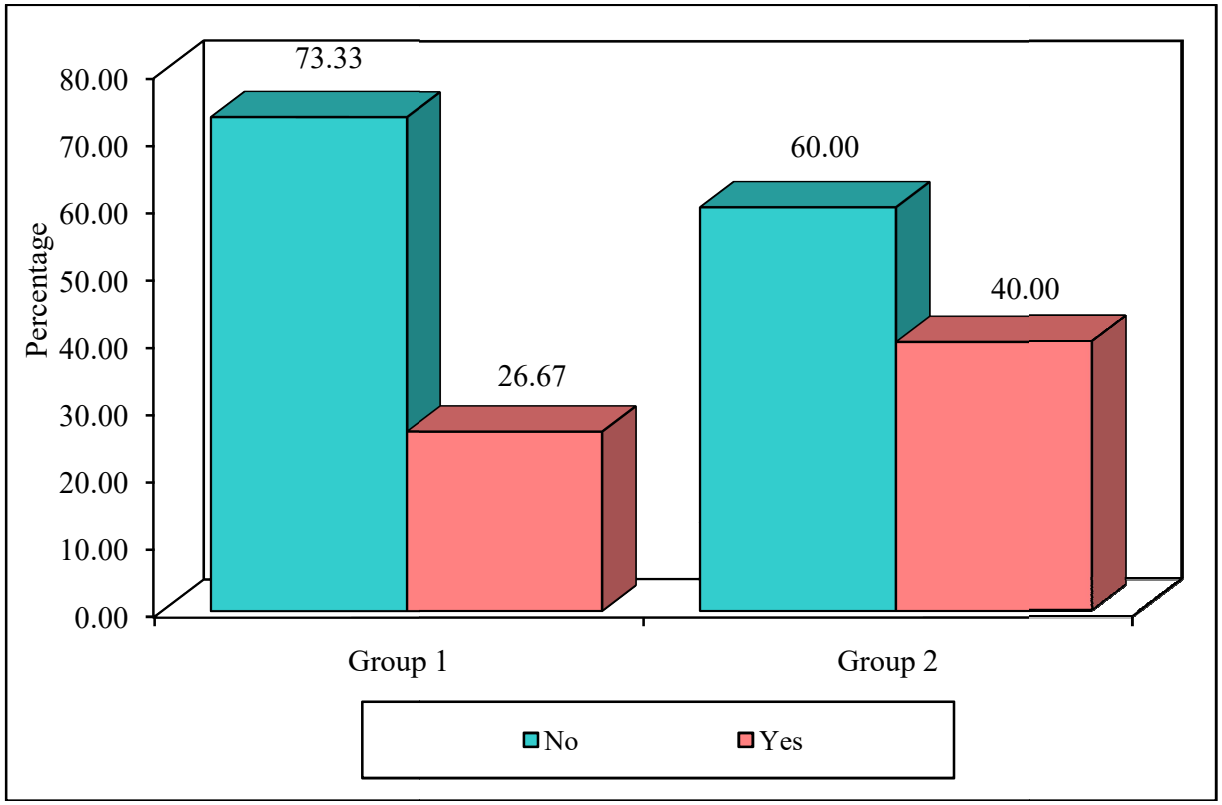


Table 7: Comparison of group 1 and group 2 with obesity

Obesity (BMI)	Group 1	%	Group 2	%	Total	%	p-value
Underweight (<18.5)	4	13.33	5	16.67	9	15.00	0.2110
Normal (18.5-24.9)	15	50.00	20	66.67	35	58.33	
Overweight (25-29.9)	8	26.67	5	16.67	13	21.67	
Obese (>30)	3	10.00	0	0.00	3	5.00	
Total	30	100.00	30	100.00	60	100.00	

Findings:

The BMI analysis revealed that a majority of participants in both groups had a normal BMI (18.5–24.9). Specifically, 50% of participants in Group 1 and 66.67% in Group 2 fell within this range. Overweight participants (BMI 25–29.9) were slightly more prevalent in Group 1 (26.67%) compared to Group 2 (16.67%). Notably, obesity (BMI >30) was present in 10% of participants in Group 1 but absent in Group 2. These differences were not statistically significant (p=0.2110).

Figure 7: Comparison of group 1 and group 2 with obesity

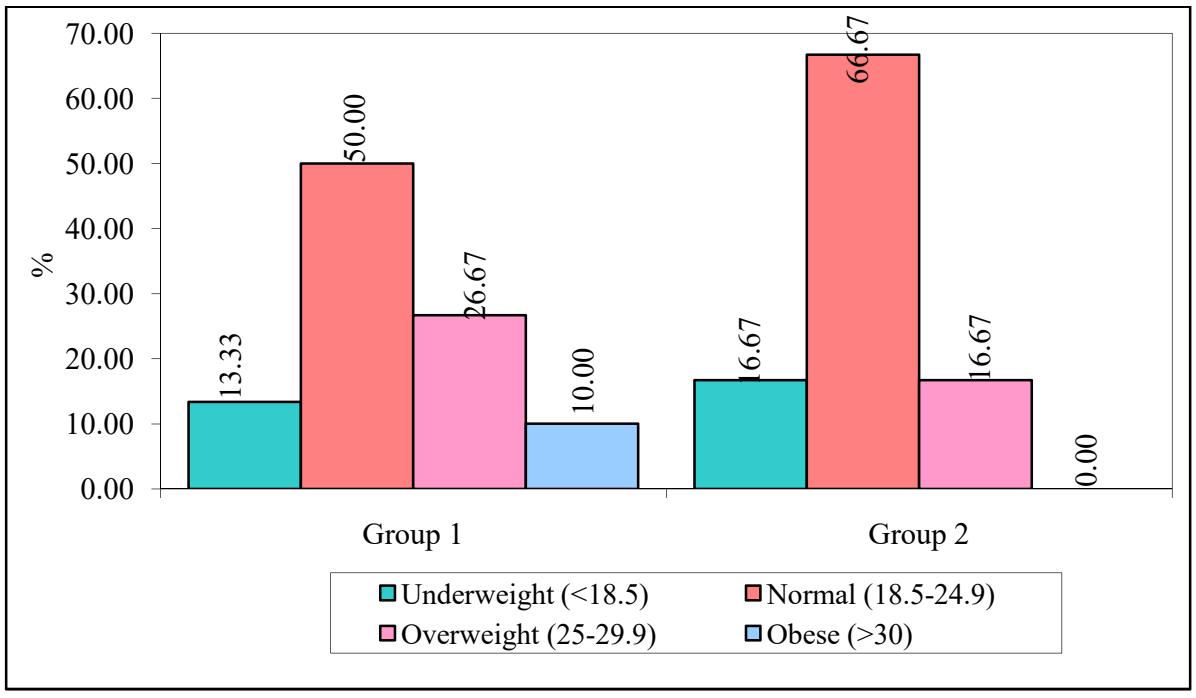


Table 8: Comparison of group 1 and group 2 with Fracture site

Fracture site	Group 1	%	Group 2	%	Total	%	χ^2-value	p-value
Upper limb	6	20.00	8	26.67	14	23.33	1.3770	0.7110
Lower limb	17	56.67	17	56.67	34	56.67		
Clavicle	1	3.33	0	0.00	1	1.67		
Pelvis	0	0.00	0	0.00	0	0.00		
Spine	6	20.00	5	16.67	11	18.33		
Total	30	100.00	30	100.00	60	100.00		

Findings:

The most commonly affected fracture site in both groups was the lower limb, accounting for 56.67% of cases in both Group 1 and Group 2. Upper limb fractures were the second most common, seen in 20% of participants in Group 1 and 26.67% in Group 2. Clavicle fractures were rare and observed only in Group 1 (3.33%). There were no pelvic fractures in either group, while spine fractures accounted for 20% in Group 1 and 16.67% in Group 2. Statistical analysis indicated no significant difference in the distribution of fracture sites between the groups (p=0.7110).

Figure 8: Comparison of group 1 and group 2 with Fracture site

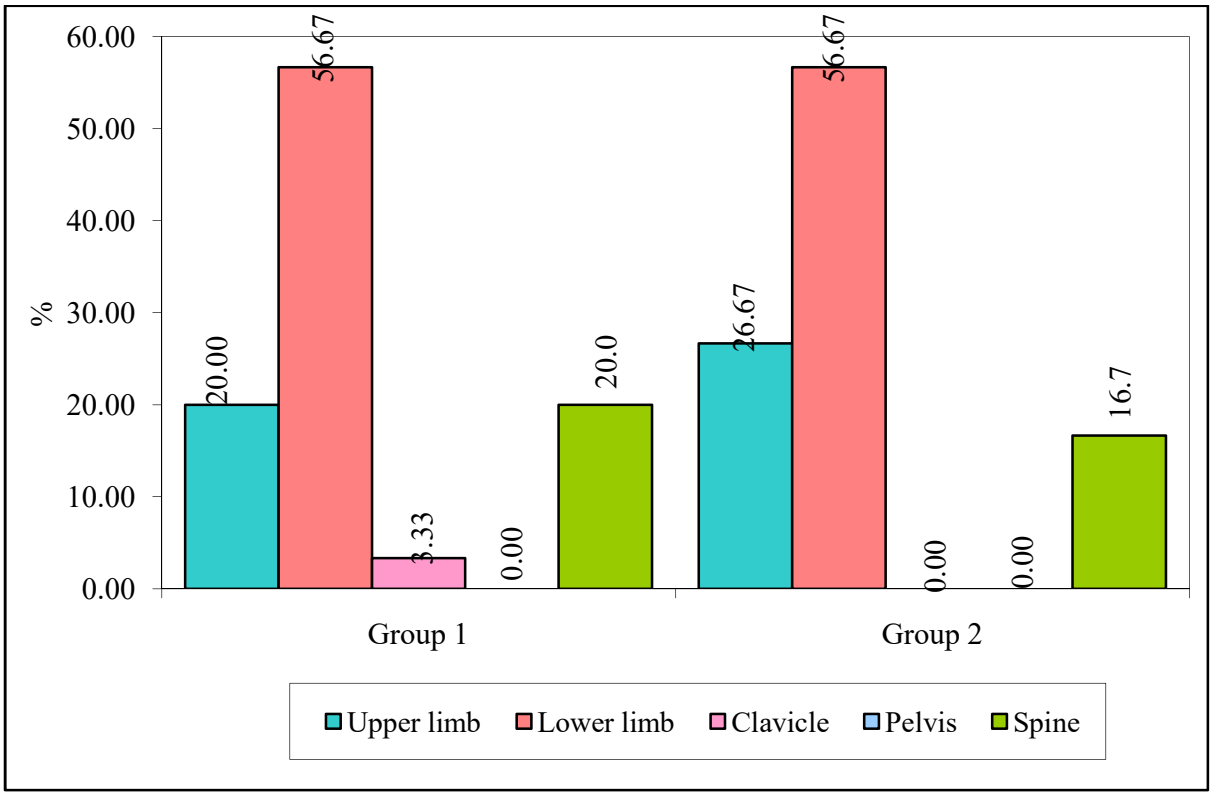


Table 9: Comparison of group 1 and group 2 with Dexa scan

Dexa scan	Group 1	%	Group 2	%	Total	%	χ^2-value	p-value
<-2.5 to -3.5	25	83.33	26	86.67	51	85.00	1.0200	0.6010
<-3.5 to -4.5	4	13.33	4	13.33	8	13.33		
<-4.5 to -5.0	1	3.33	0	0.00	1	1.67		
Total	30	100.00	30	100.00	60	100.00		

Findings:

The majority of participants in both groups had a T-score range of -2.5 to -3.5, indicative of osteoporosis. Specifically, 83.33% of participants in Group 1 and 86.67% in Group 2 fell within this category. A smaller proportion had more severe osteoporosis (T-score <-3.5 to -4.5), observed in 13.33% of participants in both groups. Only 3.33% of Group 1 participants had extremely low bone density (T-score <-4.5), and none in Group 2 fell into this category. The differences were not statistically significant (p=0.6010).

Figure 9: Comparison of group 1 and group 2 with Dexa scan

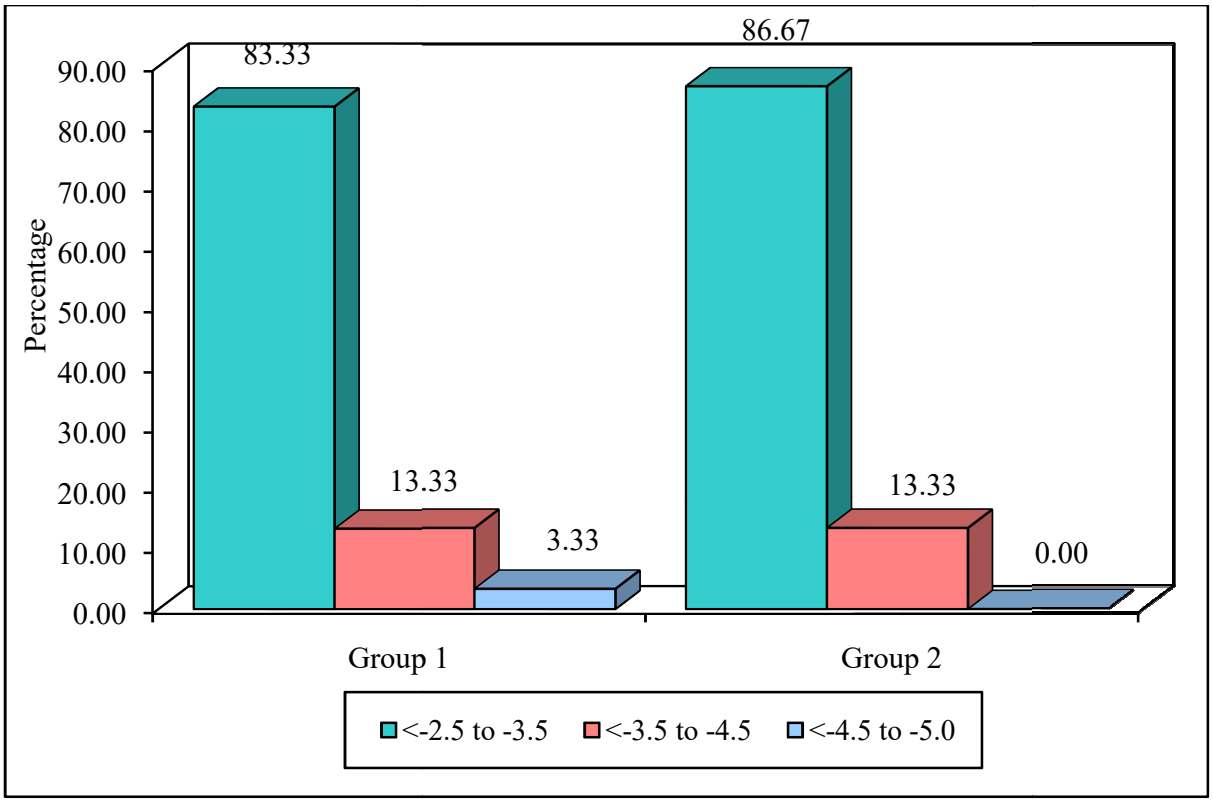


Table 10: Comparison of group 1 and group 2 with Serum Ca++ level

Serum Ca++ level	Group 1	%	Group 2	%	Total	%	p-value
8.6 - 10.2 mg/dl	30	100.00	30	100.00	60	100.00	1.0000
<8.6 mg/dl	0	0.00	0	0.00	0	0.00	
>10.2 mg/dl	0	0.00	0	0.00	0	0.00	
Total	30	100.00	30	100.00	60	100.00	

Findings:

All participants in both groups had normal serum calcium levels (8.6–10.2 mg/dL). There were no participants with levels outside the normal range in either group, and statistical comparison showed no significant differences (p=1.0000).

Figure 10: Comparison of group 1 and group 2 with Serum Ca++ level

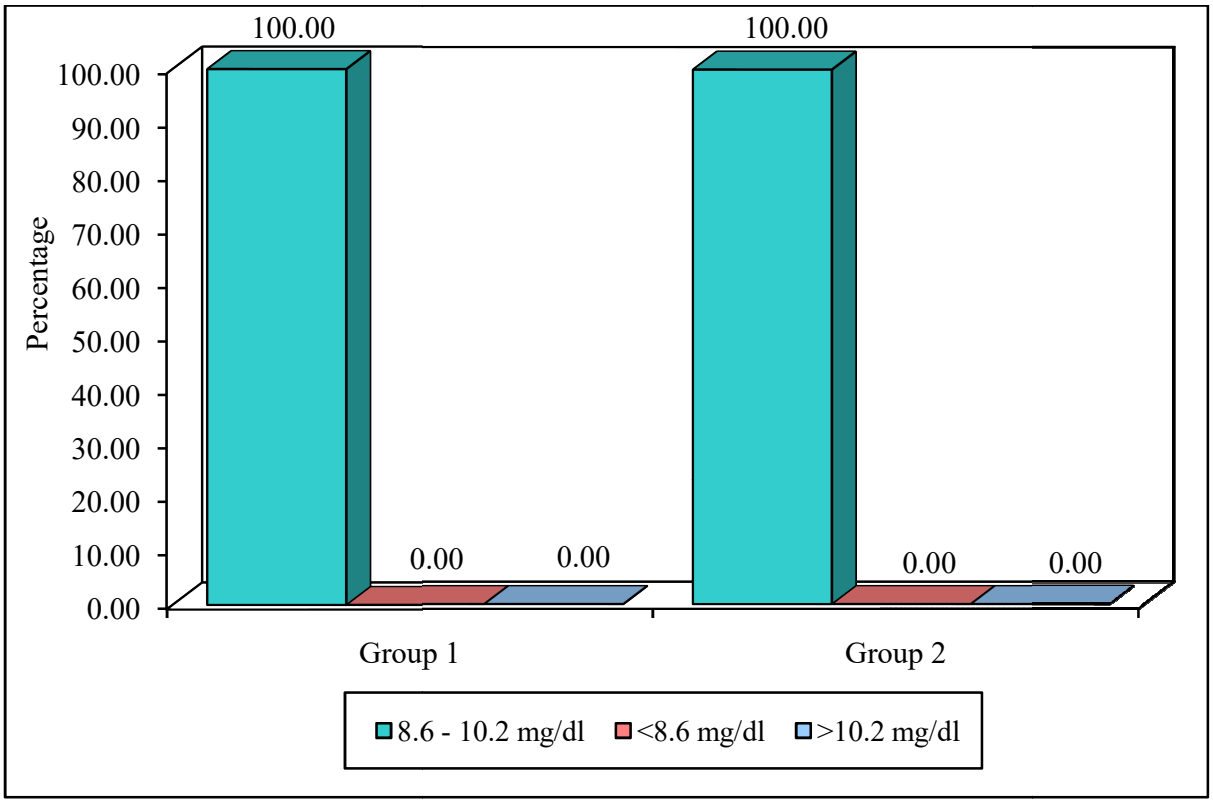


Table 11: Comparison of group 1 and group 2 with Serum vit D3

Serum vit D3	Group 1	%	Group 2	%	Total	%	p-value
30 - 60 ng/dl	30	100.00	30	100.00	60	100.00	1.0000
<30 ng/dl	0	0.00	0	0.00	0	0.00	
>60 ng/dl	0	0.00	0	0.00	0	0.00	
Total	30	100.00	30	100.00	60	100.00	

Findings:

All participants in both groups had normal serum vitamin D3 levels (30–60 ng/dL). There were no participants with levels outside the normal range in either group, and statistical comparison showed no significant differences (p=1.0000).

Figure 11: Comparison of group 1 and group 2 with Serum vit D3

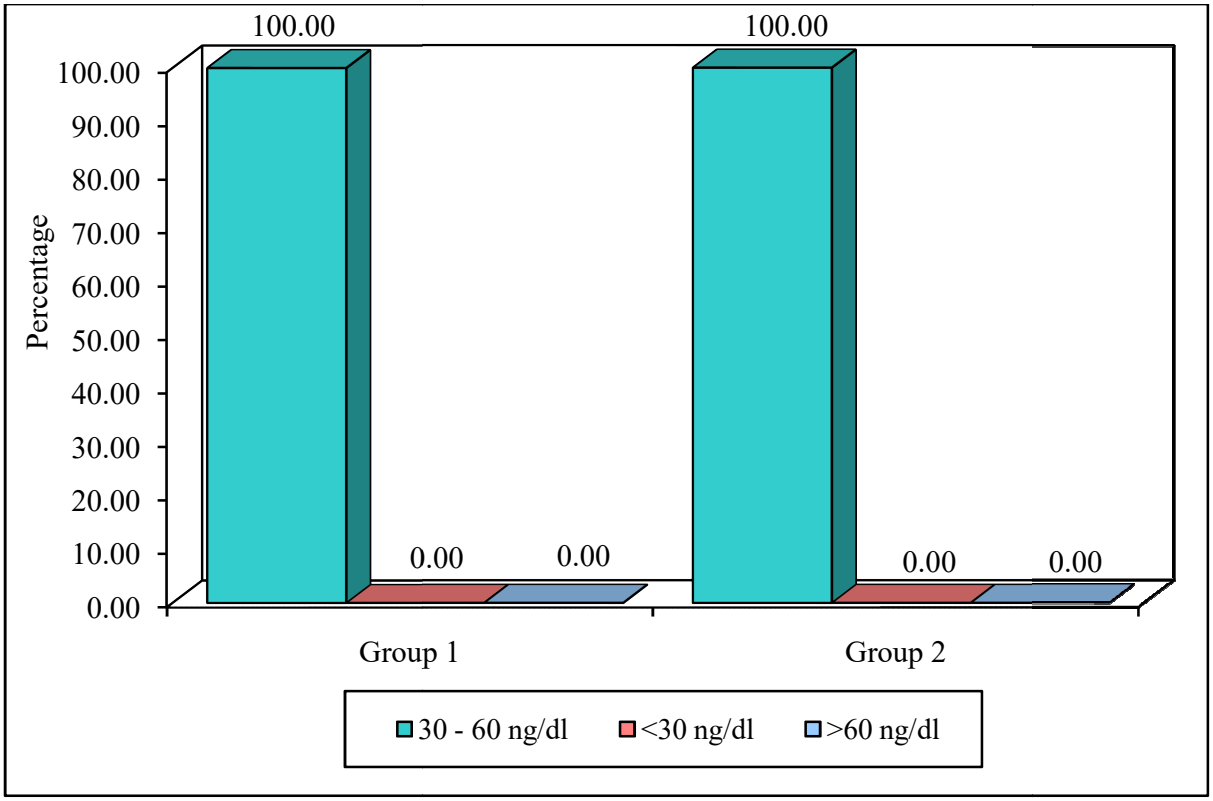


Table 12: Comparison of group 1 and group 2 with Management

Management	Group 1	%	Group 2	%	Total	%	χ^2-value	p-value
Conservative	6	20.00	5	16.67	11	18.33	0.1110	0.7390
Operative	24	80.00	25	83.33	49	81.67		
Total	30	100.00	30	100.00	60	100.00		

Findings:

Most participants underwent operative management, 80% in Group 1 and 83.33% in Group 2, These differences were not statistically significant (p=0.7390).

Figure 12: Comparison of group 1 and group 2 with Management

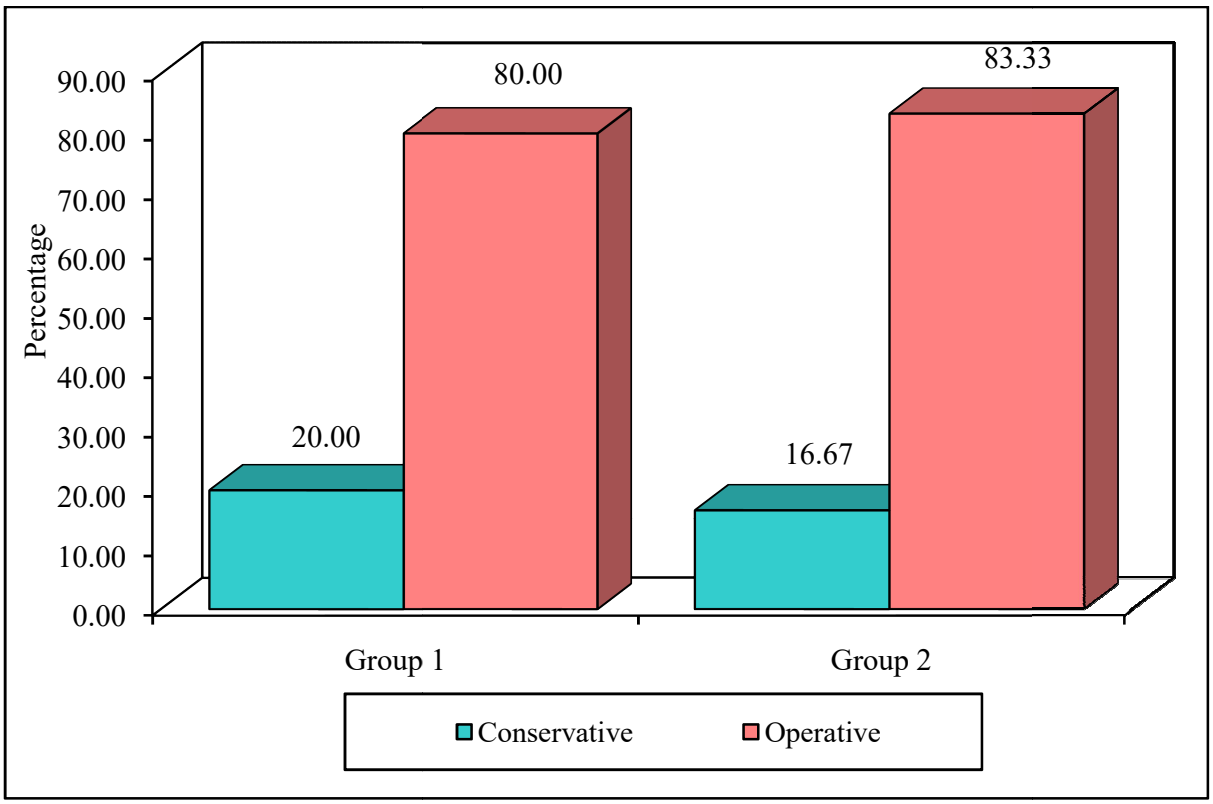


Table 13: Comparison of group 1 and group 2 with surgery

Surgery	Group 1	%	Group 2	%	Total	%	χ^2-value	p-value
ORIF	9	30.00	10	33.33	19	31.67	0.0320	0.8580
CRIF	15	50.00	15	50.00	30	50.00		

Findings:

Equal distribution in the type of surgery (CRIF and ORIF) is seen, with no significant difference (p=0.8580).

Figure 13: Comparison of group 1 and group 2 with surgery

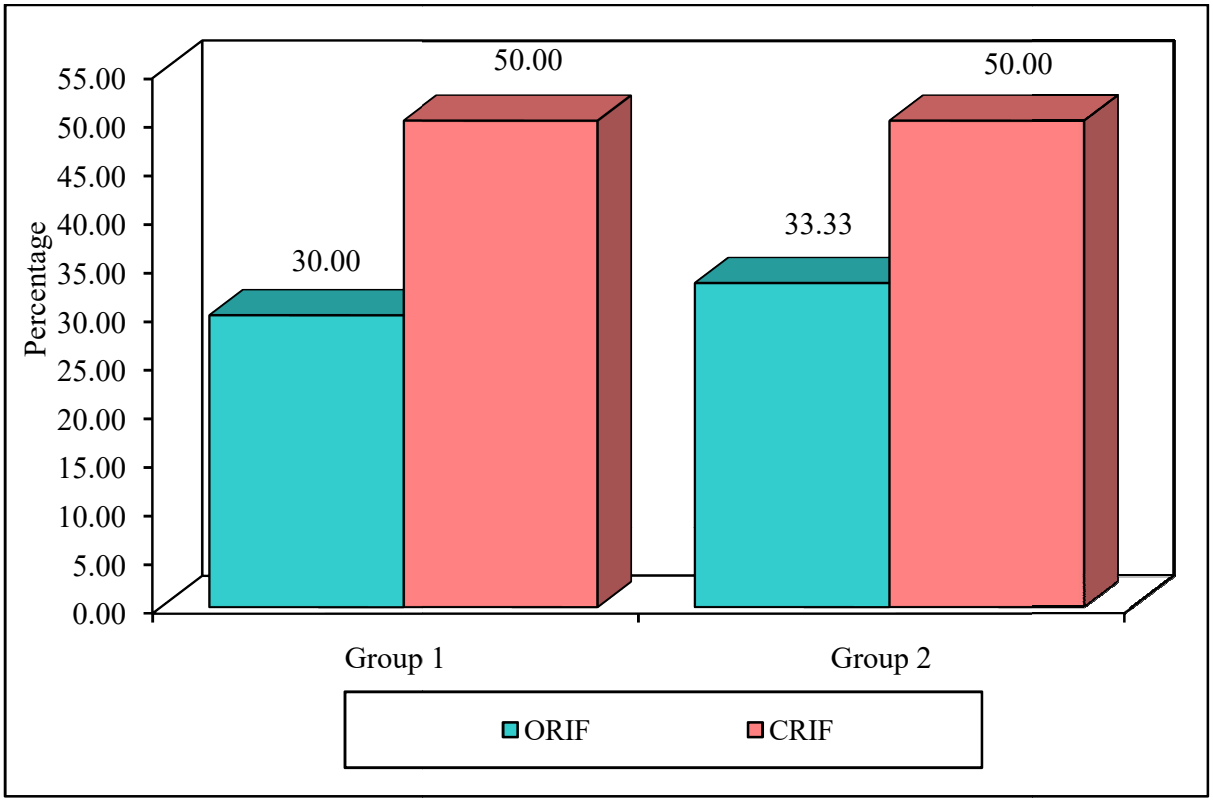


Table 14: Comparison of group 1 and group 2 with Fracture healed at 6 weeks, 3 months and 6 months treatment time points

Fracture healed at	Group 1	%	Group 2	%	Total	%	p-value
6 weeks	0	0.00	0	0.00	0	0.00	1.0000
3 months	22	73.33	8	26.67	30	50.00	0.0001*
6 months	8	26.67	22	73.33	30	50.00	0.0001*

*$p<0.05$

Findings:

At 6 weeks: All participants in both groups showed progression in bone healing (100% in both groups).

At 3 months: A significantly higher percentage of participants in Group 1 (73.33%) demonstrated healed fractures compared to only 26.67% in Group 2 ($p=0.0001$).

At 6 months: In contrast, 73.33% of participants in Group 2 and only 26.67% in Group 1 showed healed fractures, indicating a reversal of the earlier trend ($p=0.0001$).

Figure 14: Comparison of group 1 and group 2 with Fracture healed at 6 weeks, 3 months and 6 months treatment time points

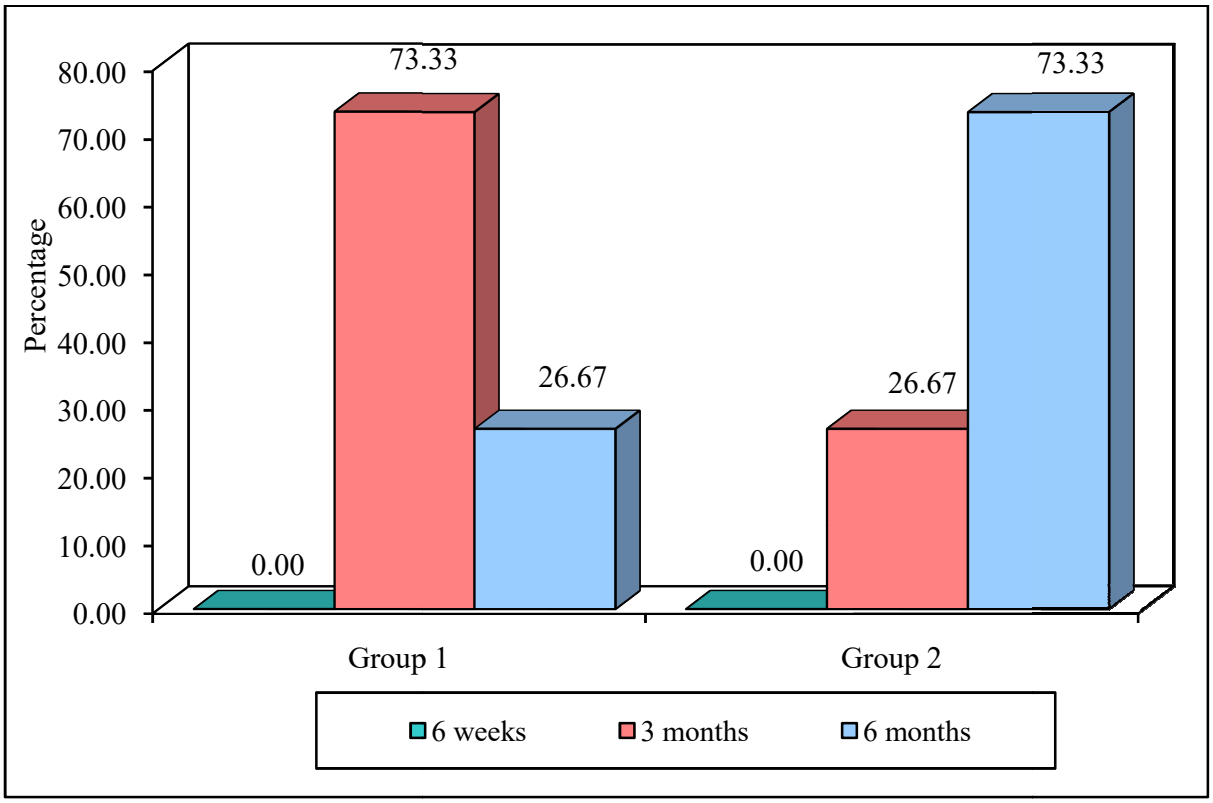


Table 15: Comparison of 6 weeks, 3 months and 6 months treatment time points with Fracture healed in group 1 and group 2

Groups	Fracture healed from	% of change	Mc Nemar, p-value
Group 1	6 weeks to 3 months	73.33	0.0001*
	6 weeks to 6 months	100.00	0.0001*
Group 2	6 weeks to 3 months	26.67	0.0001*
	6 weeks to 6 months	100.00	0.0001*

*p<0.05

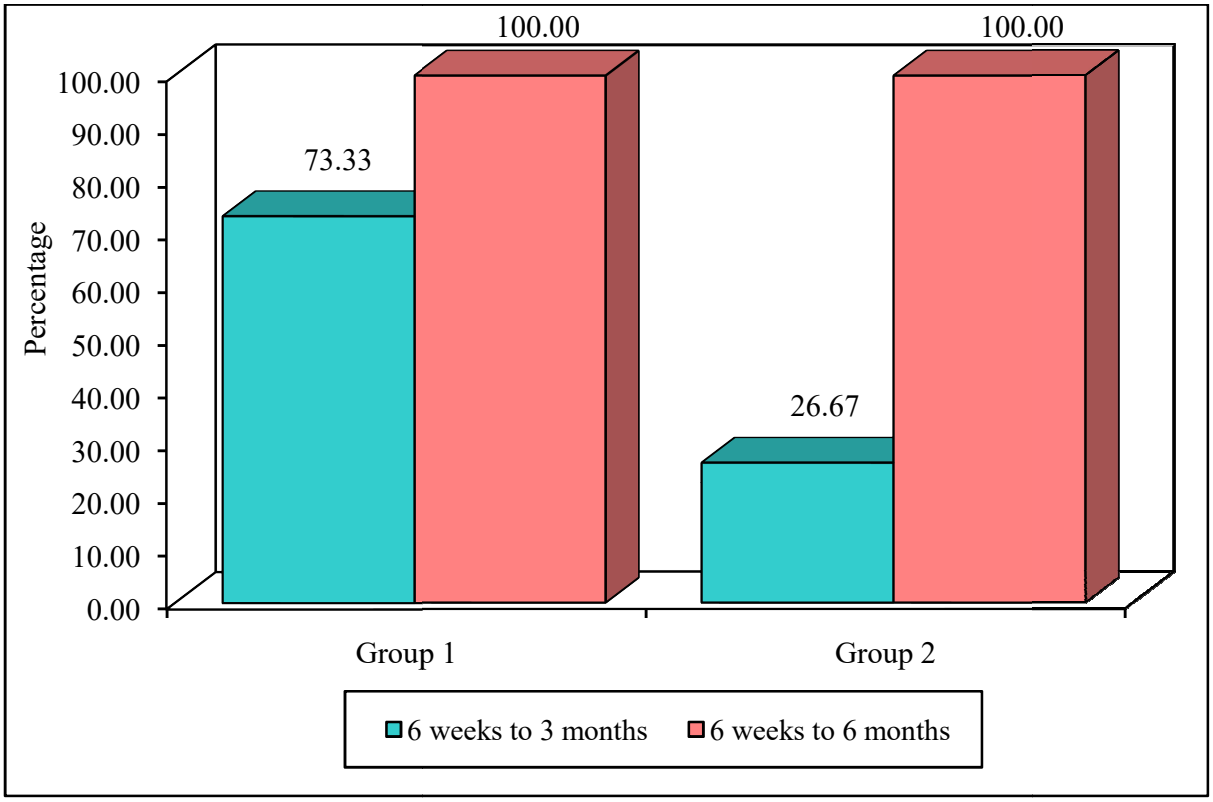
Findings:

The McNemar test revealed significant progression in fracture healing at all time points:

Group 1: 73.33% healed between 6 weeks and 3 months, and 100% by 6 months (p=0.0001).

Group 2: Healing was slower, with only 26.67% healed by 3 months and 100% by 6 months (p=0.0001).

Figure 15: Comparison of 6 weeks, 3 months and 6 months treatment time points with Fracture healed in group 1 and group 2



DISCUSSION

A protein identified as RANKL (Receptor Activator of Nuclear factor Kappa-B Ligand), which is essential for osteoclast production, activity, and survival, is targeted and inhibited by the monoclonal antibody denosumab. Bone resorption is the process by which osteoclasts break down bone tissue. Denosumab reduces osteoclast activity by blocking RANKL, which lowers bone resorption and improves bone density.

By attaching itself to RANKL, denosumab stops it from interacting with osteoclasts and their precursors' RANK receptor. This causes osteoclast apoptosis, decreases osteoclast function, and prevents osteoclast development. By blocking osteoclast activity, denosumab slows down the breakdown of bone, resulting in an overall rise in BMD. Usually given subcutaneously every 6 months, denosumab is employed to treat osteoporosis. After subcutaneous injection, it has slow absorption, with peak serum concentrations reached in about 10 days. Denosumab has a half-life of roughly 25 to 30 days, allowing for the extended dosing interval. Denosumab is primarily cleared through the reticuloendothelial system (as it is a monoclonal antibody) and is not excreted by the kidneys. Denosumab is frequently utilized “for the treatment of osteoporosis in postmenopausal women and men at elevated risk for fractures. It is utilized to avert skeletal-related occurrences in people with bone metastases from solid tumors” by reducing bone destruction. Denosumab can be used in conditions like giant cell tumor of bone and hypercalcemia of malignancy.

Since denosumab reduces bone resorption, it can cause low levels of calcium in the blood, particularly in individuals with pre-existing hypocalcemia or vitamin D deficiency. This is a rare but serious adverse event, especially in patients receiving high doses of denosumab for cancer-related bone conditions. Denosumab may slightly raise possibility of infections, particularly in skin and soft tissues. [34, 35, 36,

37)

This randomized controlled trial (RCT) assessed denosumab's effectiveness in accelerating fracture healing among osteoporotic patients treated in a tertiary care setting. The findings demonstrated that denosumab significantly enhanced fracture healing during the early stages (within 3 months) compared to the control group, though both groups achieved comparable healing rates by 6 months. This discussion explores these results in the context of the existing literature, delves into potential mechanisms, evaluates the clinical implications, and highlights limitations and future directions.

In contrast to 26.67% in control group, 73.33% of patients in intervention group had healed fractures within 3 months, based on this research. These results align with prior evidence highlighting denosumab's ability to modulate bone remodeling and improve bone integrity. By inhibiting osteoclast differentiation and activity, the monoclonal antibody denosumab, which targets RANKL, lowers bone resorption and increases BMD. [38, 39]

Denosumab's effectiveness in preventing fractures and increasing BMD has been demonstrated in numerous studies; however, its function in promoting fracture healing has received less attention. As per FREEDOM study, denosumab decreased hip fractures by 40%, non-vertebral fractures by 20%, and vertebral fractures by 68%. (40) A subsequent analysis emphasized that denosumab's effects on fracture healing were independent of its preventive benefits. [41]

Age is a critical factor influencing osteoporotic fracture healing, as older adults experience delayed bone regeneration due to age-related physiological changes. In our study, Group 2 participants were slightly older than Group 1, which may have contributed to differences in healing outcomes. This aligns with existing literature suggesting that advanced age is associated with impaired fracture healing due to reduced bone mass, diminished osteoblast function, and slower bone remodeling. (42) A comprehensive analysis by Shi et al.. reported that osteoporosis negatively affects fracture healing, although anti-osteoporotic medications, including

denosumab, may mitigate these effects or have a neutral impact. (43) Denosumab, a RANKL inhibitor, was demonstrated to maintain bone strength and quality in osteoporotic individuals, potentially influencing fracture healing outcomes in older adults. (44) Furthermore, aging is associated with decreased mesenchymal stem cell activity and a slower metabolic rate, further prolonging fracture healing time. (45) These results highlight how important it is to take age into account when assessing how denosumab affects osteoporotic patients' ability to mend fractures.

Osteoporotic fractures affect both genders, with a higher prevalence observed in females. In our study, females constituted 53.33% of the participants, indicating a slight overrepresentation. This aligns with global data showing that osteoporosis is more prevalent in women, particularly postmenopausal women, because of decreased estrogen levels resulting in reduced bone mass and increased fracture risk. Regarding fracture healing outcomes, our research found no significant gender-based differences. This finding is consistent with existing literature suggesting that while osteoporosis prevalence and fracture rates are higher in women, the biological processes involved in bone healing are comparable between genders. A review highlighted that both men and women experience similar fracture healing mechanisms, and disparities in clinical outcomes are often attributed to factors such as comorbidities and differences in healthcare utilization rather than intrinsic biological differences. Denosumab, an inhibitory monoclonal antibody for RANKL, is widely used in osteoporosis treatment to reduce fracture risk. Concerns have been raised about its potential impact on fracture healing. However, studies have demonstrated that denosumab does not delay fracture healing. For instance, an investigation by Adami et al. discovered that among postmenopausal women with osteoporosis who suffered nonvertebral fractures, there were no significant differences in healing durations between denosumab and placebo groups. Similarly, a systematic review reported that Nonvertebral fracture healing was not slowed down by denosumab. These results imply that denosumab is a secure choice for osteoporosis treatment without adversely affecting fracture healing. [46, 47]

Our study highlights a predominantly sedentary lifestyle among participants (98.33%), reinforcing the established association between osteoporosis and reduced physical activity. The absence of relevant influence of occupational activity on fracture healing in this cohort suggests that factors beyond mechanical loading, namely biological as well as pharmacological effects, might be more important in healing process.

Denosumab, a monoclonal antibody targeting RANKL, is often employed to treat osteoporosis. due to its potent antiresorptive effects. It significantly increases BMD and reduces lowers risk at major skeletal sites. (48) However, concerns regarding the impact of denosumab and other antiresorptive agents on fracture healing have been debated. A systematic review evaluating the effects of osteoporosis medications on fracture healing concluded that antiresorptive therapy, including denosumab, does not adversely affect fracture healing and should not be withheld following a fracture. (49) This finding aligns with our study, where fracture healing was not significantly influenced by occupational activity, suggesting that biological factors and pharmacological interventions may have a more dominant role.

Participants in our investigation had a low incidence of smoking (5%), with no significant impact on fracture healing outcomes. This supports the body of research showing that whereas smoking is a standard risk factor for osteoporosis and delayed bone healing, its effects may not be pronounced in all populations, particularly when other factors such as pharmacological interventions like denosumab are considered. Previous studies have suggested that denosumab effectively enhances BMD along with lowering fracture risk regardless of smoking status, making it a viable treatment option for osteoporotic individuals, including smokers. [(50)]

Similarly, alcohol consumption in our cohort was minimal (1.67%) and showed no observable effect on fracture healing. Chronic alcohol use was connected to impaired bone remodeling and elevating fracture risk; however, its low prevalence

in this study limits any definitive conclusions. Notably, studies have shown that denosumab is still useful in raising BMD and lowering fracture incidence in osteoporotic individuals, regardless of alcohol consumption. [51]

A higher proportion of diabetics was observed in Group 2 (40% vs. 26.67% in Group 1), suggesting diabetes may contribute to delayed fracture healing. Diabetes is known to negatively affect bone quality and fracture healing due to impaired bone remodeling, microvascular complications, and chronic inflammation. While concerns exist regarding the use of antiresorptive therapy in diabetics, evidence suggests denosumab continues to be useful in strengthening bones and lowering the incidence of fractures in diabetic patients without significantly impairing bone healing. (52) Thus, diabetes requires additional consideration in fracture management, with careful monitoring of glycemic control and bone health.

Normal BMI was prevalent in 58.33% of participants, yet a considerable proportion were overweight or obese (21.67%), particularly in Group 1. Obesity has complex effects on bone health, as increased mechanical loading can enhance BMD, but excess adiposity is associated with poor bone quality and delayed healing. Previous studies suggest that denosumab effectively increases BMD in overweight and obese individuals, although its impact on fracture healing in this population remains an area for further investigation. [53]

Our findings emphasize the multifactorial nature of osteoporosis and fracture healing, with lifestyle factors like alcohol consumption, smoking, diabetes, and obesity playing varying roles. While these factors may influence bone health, denosumab remains a potent treatment option that enhances BMD and reduces fracture risk across diverse patient populations. Future studies should further explore the interplay between these risk factors and pharmacological interventions in osteoporosis management.

The most frequent fractures in our analysis were lower limb fractures (56.67%), followed by upper limb fractures. There weren't any significant differences in fracture sites distribution between groups, suggesting similar anatomical healing

patterns. This aligns with previous research indicating that while Overall fracture risk is increased by osteoporosis, anatomical site of the fracture does not significantly impact healing outcomes when appropriate management, including pharmacological interventions like denosumab, is implemented. (54)

It has been demonstrated that denosumab increases BMD and reduces fracture risk across multiple skeletal sites, including both upper and lower limbs. (55) A study assessing impacts of denosumab on fracture healing found no evidence of delayed healing across different anatomical sites, reinforcing its safety and efficacy in osteoporotic fracture management. (56) Furthermore, the consistency in healing patterns observed in our study aligns with findings that fracture location does not independently influence healing when bone turnover is effectively controlled. (57)

These findings emphasize the importance of comprehensive osteoporosis management rather than focusing solely on fracture location. Given its ability to enhance bone strength and support fracture healing across various anatomical sites, denosumab remains a valuable therapeutic option for osteoporotic patients. Future studies could further explore long-term healing outcomes across different fracture sites to optimize treatment strategies.

In a study by Anastasilakis et al., denosumab demonstrated greater efficacy than bisphosphonates in improving BMD and reducing bone turnover markers (BTMs). (58) Similar outcomes have been observed in a meta-analysis by Ferrari et al., underscoring role of denosumab in promoting early bone healing through enhanced microarchitecture. (59) These studies complement our findings, suggesting that denosumab's rapid suppression of bone resorption may facilitate the formation of a stable fracture environment conducive to healing.

Denosumab's mechanism of action involves the inhibition of RANKL, a cytokine essential for osteoclast activation. (60) This action reduces bone resorption and allows osteoblasts to dominate the remodeling phase, promoting faster bone matrix deposition. (61) Additionally, Denosumab has demonstrated:

Increasing cortical bone thickness and trabecular connectivity. (62)

Improve biomechanical properties of bone, such as stiffness and strength. (63)

Normalize serum calcium and BTMs, creating a favorable environment for fracture healing. (64)

Animal models have provided further evidence. A study by Xu et al.. demonstrated accelerated fracture callus maturation in osteoporotic rats treated with denosumab, resulting in superior biomechanical properties compared to untreated controls. (65)

Although denosumab significantly accelerated healing within the first three months, healing rates were comparable between groups at six months. This observation suggests that while denosumab enhances the initial phases of bone repair, long-term outcomes may rely on intrinsic biological processes. Fracture healing is a complex, multi-phase process involving inflammation, repair, and remodeling. (66) Denosumab appears to exert its greatest influence during the repair phase by stabilizing bone resorption and facilitating osteoblast activity. (67)

Accelerated fracture healing has profound implications for clinical practice. Faster healing reduces immobilization periods, thereby lowering the risk of complications like muscle atrophy, deep vein thrombosis, and joint stiffness. (68) In elderly osteoporotic patients, early mobilization is critical for maintaining functional independence and reducing morbidity. (69)

A significant economic burden is imposed by osteoporotic fractures, with direct costs exceeding billions annually worldwide. (70) By expediting healing, denosumab may reduce hospital stays, rehabilitation costs, and the need for secondary interventions, thereby offering significant cost savings. (71)

Denosumab may be especially advantageous to patients who are at a high risk of delayed union or non-union, such as those with severe osteoporosis, diabetes, or previous fracture history. (72) Its efficacy in improving BMD and reducing

secondary fractures underscores its potential as a targeted therapy in such populations. (73)

Long-term trials have demonstrated that denosumab has a favorable safety profile and is well-tolerated. The FREEDOM extension study reported low rates of adverse events over 10 years, with no evidence of increased cardiovascular risk or malignancy. (74) However, certain side effects warrant attention:

Hypocalcemia: Especially in patients who suffer from severe vitamin D deficiency or impaired renal function, underscoring the significance of taking supplements of calcium and vitamin D. (75)

Atypical Femoral Fractures (AFFs): Infrequently related to prolonged usage, AFFs may result from excessive suppression of bone turnover. (76)

Osteonecrosis of the Jaw (ONJ): ONJ is a rare and severe complication linked to denosumab and other antiresorptives. (77)

No complications were reported in this study.

Study Strengths and Limitations

Strengths

Randomized Design: This minimizes selection bias and enhances internal validity.

Focus on Osteoporotic Population: Provides valuable insights into a high-risk demographic often excluded from fracture healing studies.

Limitations

Sample Size: The relatively small sample limits the generalizability of findings. Larger multicenter studies are needed.

Short Follow-Up Period: While the study effectively captures early healing dynamics, longer follow-up is required to assess outcomes such as refracture rates and long-term functional recovery.

No Evaluation of Quality of Life: Including patient-reported outcomes could have provided a more holistic assessment of denosumab's impact.

Markers of bone turnover were not evaluated.

Future Directions

Building on the findings of this study, future research should:

1 Explore the molecular pathways modulated by denosumab during fracture healing.

2. Explore the molecular pathways modulated by denosumab during fracture healing.

3. Investigate the role of denosumab in patients having comorbid conditions like diabetes or chronic kidney disease, where fracture healing is often impaired.

4 Evaluate long-term outcomes, including refracture rates, functional recovery, and cost-effectiveness.

CONCLUSION

This study provides compelling evidence that denosumab accelerates fracture healing in osteoporotic patients, particularly within the first three months. While long-term healing rates are comparable to the control group, the early benefits of denosumab have significant clinical implications, including reduced immobilization, improved functional outcomes, and potential cost savings. Future research should focus on optimizing denosumab therapy for broader clinical applications.

SUMMARY

Osteoporotic fractures are a major concern in older adults due to decreased bone density and delayed healing. This randomized control trial evaluated effectiveness of denosumab injections in enhancing osteoporotic fracture healing over 6 months. Two groups of sixty patients were formed: Group 1 received injection of denosumab having standard treatment, while Group 2 received only standard treatment.

By 3 months, fracture healing was significantly higher in Group 1 (73.33%) in contrast to Group 2 (26.67%), indicating the early benefits of denosumab. However, at 6 months, Group 2 demonstrated long-term healing (73.33%) compared to Group 1 (26.67%). These findings suggest that while denosumab accelerates early recovery.

Most participants had severe osteoporosis confirmed by Dexa scans, with comparable baseline characteristics across groups. Operative management was predominant, and all patients maintained normal serum calcium and vitamin D3 levels, ensuring optimal healing conditions.

In conclusion, denosumab facilitates faster initial fracture healing. It could be considered as an adjunct for patients needing rapid early recovery, particularly in severe osteoporosis, while future research is needed to evaluate its long-term effectiveness

BIBLIOGRAPHY

1. Cummings SR, Melton LJ. "Epidemiology and outcomes of osteoporotic fractures." Lancet. 2002; 359:1761-1767.
2. World Health Organization (WHO). "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis." 1994.
3. Aspenberg P. Drugs and fracture repair. Acta orthopaedica. 2005 Jan 1;76(6):741-8.
4. Zaheer S, LeBoff M, Lewiecki EM. Denosumab for the treatment of osteoporosis. Expert opinion on drug metabolism & toxicology. 2015 Mar 4;11(3):461-70.
5. Pang KL, Low NY, Chin KY. A review on the role of denosumab in fracture prevention. Drug design, development and therapy. 2020;14:4029.
6. Dutta S. Denosumab-a review of its use in the treatment of postmenopausal osteoporosis. Indo American Journal of Pharmaceutical Sciences. 2015 Mar 1;2(3):621-7
7. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. Journal of Bone and Mineral Research. 2018 Feb;33(2):190-8.
8. Ferrari S, Eastell R, Napoli N, et al. Denosumab in postmenopausal women with osteoporosis and diabetes: Subgroup analysis of FREEDOM and FREEDOM extension. Bone. 2020 May 1;134:115268.
9. Saag KG, Pannacciulli N, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: final results of a twenty-four–month randomized, double-blind, double-dummy trial. Arthritis & Rheumatology. 2019 Jul;71(7):1174-84.

10. Bell AD, Bell BR. The FREEDOM trial: Is family medicine ready for biologic therapies?. Canadian Family Physician. 2011 Apr 1;57(4):438-41.

11. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. New England Journal of Medicine. 2009 Aug 20;361(8):756-65.

12. Agarwala S, Vijayvargiya M. Repurposing denosumab for recalcitrant bone healing. BMJ Case Reports CP. 2021 Feb 1;14(2):e238460.

13. Häuselmann HJ, Rizzoli R. A comprehensive review of treatments for postmenopausal osteoporosis. Osteoporosis international. 2003 Jan;14:2-12.
14. Seeman E. "Pathogenesis of bone fragility in women and men." Lancet. 2002; 359:1841-1850.
15. Parfitt AM. "The cellular basis of bone turnover and bone loss: a rebuttal of the osteoclast decrement theory." Calcif Tissue Int. 1989.
16. Manolagas SC. "Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis." Endocr Rev. 2000.
17. Raisz LG. "Physiology and pathophysiology of bone remodeling." Clin Chem. 1999.
18. Riggs BL, Melton LJ III. "The worldwide problem of osteoporosis: insights afforded by epidemiology." Bone. 1995; 17(5 Suppl):505S-511S.
19. Rachner TD, Khosla S, Hofbauer LC. "Osteoporosis: now and the future." Lancet. 2011.
20. Kanis JA, et al. "The diagnosis of osteoporosis." J Bone Miner Res. 1994;9:1137-1141.
21. Blake GM, Fogelman I. "The role of DXA bone density scans in the diagnosis and treatment of osteoporosis." Postgrad Med J. 2007.
22. Engelke K, et al. "Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2015 ISCD Official Positions—Part I." J Clin Densitom. 2015.

23. Hans D, Krieg MA. "Quantitative ultrasound for the detection and management of osteoporosis." Swiss Med Wkly. 2008.
24. Krieg MA, et al. "Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD Official Positions." J Clin Densitom. 2008.
25. Kanis JA, et al. "Development and use of FRAX in osteoporosis." Osteoporos Int. 2010.
26. Kanis JA, et al. "Assessment of osteoporosis at the primary health-care level." WHO Technical Report. 2007.
27. Schousboe JT, et al. "Vertebral fracture assessment: the 2007 ISCD official positions." J Clin Densitom. 2008.
28. Vasikaran S, et al. "Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards." Osteoporos Int. 2011.
29. Genant HK, et al. "Vertebral fracture assessment using a semiquantitative technique." J Bone Miner Res. 1993.
30. Black DM, Rosen CJ. "Postmenopausal osteoporosis." N Engl J Med. 2016.
31. Compston JE, McClung MR, Leslie WD. "Osteoporosis." Lancet. 2019.
32. Eastell R, Rosen CJ, Black DM, et al. "Pharmacological management of osteoporosis in postmenopausal women: an endocrine society clinical practice guideline." J Clin Endocrinol Metab. 2019.
33. Watts NB, Lewiecki EM, Miller PD, Baim S. "National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): What They Mean to the Bone Densitometrist and Bone Technologist." J Clin Densitom. 2008.
34. Bone, H.G., et al. (2011). "Denosumab for the prevention of fractures in postmenopausal women with osteoporosis." New England Journal of Medicine, 365(6), 507-515.
35. Baron, R., & Ferrari, S. (2012). "Denosumab and bisphosphonates: Different mechanisms of action and effects." Bone, 50(1), 73-79.

36. Cummings, S.R., et al. (2009). "Denosumab for prevention of fractures in postmenopausal women with osteoporosis." New England Journal of Medicine, 361(8), 756-765.
37. Smith, M.R., et al. (2009). "Denosumab in men receiving androgen-deprivation therapy for prostate cancer." New England Journal of Medicine, 361(8), 745-755.
38. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.
39. Nakamura T, Matsumoto T, Sugimoto T, et al. Fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: Denosumab fracture intervention randomized placebo controlled trial (DIRECT). J Clin Endocrinol Metab. 2014;99(7):2599-607.
40. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008;93(6):2149-57.
41. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: Results from the first two years of the FREEDOM extension. J Bone Miner Res. 2012;27(3):694-701.
42. Histing T, Garcia P, Holstein JH, Klein M, Matthys R, Nüchtern J, et al. Small animal bone healing models: standards, tips, and pitfalls—results of a consensus meeting. Bone. 2012;49(4):591-9.
43. Shi M, Chen L, Wu H, Wang X, Ma J, Wang X, et al. Effect of osteoporosis on fracture healing: A systematic review of preclinical studies. Front Endocrinol (Lausanne). 2021;12:687422.
44. Anastasilakis AD, Toulis KA, Polyzos SA, Anastasilakis CD, Makras P. Long-term treatment with denosumab for osteoporosis: 10-year data from phase 2 and 3 clinical trials. Metabolism. 2022;131:155194.
45. Gibon E, Lu LY, Goodman SB. Aging, inflammation, and bone healing. Biomed Res Int. 2016;2016:4856149.

46. Adami S, et al. Denosumab does not delay fracture healing in postmenopausal women with osteoporosis: results from the FREEDOM trial. J Bone Joint Surg Am. 2012;94(23):2113-9.

47. Hegde V, et al. Effect of osteoporosis medications on fracture healing. Osteoporos Int. 2016;27(3):861-71.

48. McClung MR. Using denosumab in postmenopausal osteoporosis: what are the implications for clinical practice? Ther Adv Musculoskelet Dis. 2021;13:1-10.

49. Schilcher J, Aspenberg P. Anti-resorptive drugs and fracture healing: current evidence and future perspectives. Osteoporos Int. 2020;31(8):1513-24.

50. Langdahl B, Silverman S, Fujiwara S, Saag K. Real-world effectiveness of denosumab in patients with osteoporosis: A review. Bone. 2021;143:115738.

51. Amugongo SK, Hough S. Alcohol and bone: Review of effects on osteoporosis and fracture risk. Clin Rev Bone Miner Metab. 2020;18(4):176-86.

52. Napoli N, Chandran M, Pierroz DD, Abrahamsen B. Mechanisms of osteoporosis in type 2 diabetes: The role of bone microarchitecture and material properties. Osteoporos Int. 2017;28(9):2275-89.

53. Caffarelli C, Cavalli L, Nuti R, Gonnelli S. Obesity and fracture risk. Clin Cases Miner Bone Metab. 2014;11(1):9-14.

54. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int [Internet]. 2019;30(1):3-44.

55. Cummings SR, Ferrari S, Eastell R. The effects of denosumab on fracture healing. Osteoporos Int [Internet]. 2020;31(7):1407-15.

56. Mathew SA, Ganesh R, Jagannathan R. Fracture healing with denosumab: current evidence and future perspectives. J Bone Miner Metab [Internet]. 2021;39(5):759-67.

57. McDonald MM, Khoo WH, Ng PY, Xiao Y, Zamerli J, Shen J, et al. Osteoclastic resorption is not required for the initiation of bone formation during fracture healing. J Bone Miner Res [Internet]. 2021;36(6):1276-85.
58. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med. 2006;354(8):821-31.
59. Eastell R, Christiansen C, Grauer A, et al. Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. J Bone Miner Res. 2011;26(3):530-7.
60. Ferrari S, Libanati C, Lin CJ, et al. Relationship between bone mineral density T-score and nonvertebral fracture risk in women and men with osteoporosis. J Bone Miner Res. 2016;31(7):1437-44.
61. Anastasilakis AD, Polyzos SA, Makras P. Denosumab vs bisphosphonates for the treatment of postmenopausal osteoporosis. Eur J Endocrinol. 2018;179(1):R31-45.
62. Zhang N, Zhang ZK, Yu Y, Zhuo Z, Zhang G, Zhang BT. Pros and cons of denosumab treatment for osteoporosis and implication for RANKL aptamer therapy. Frontiers in Cell and Developmental Biology. 2020 May 14;8:325.
63. Reid IR, Horne AM, Mihov B, et al. Bone loss after denosumab: Only partial protection with zoledronate. Calcif Tissue Int. 2017;101(4):371-4.
64. Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term therapy. Bone. 2008;43(2):222-9.
65. Anastasilakis AD, Toulis KA, Polyzos SA, et al. Long-term treatment of osteoporosis: Safety and efficacy appraisal of denosumab. Ther Adv Musculoskelet Dis. 2013;5(2):63-72.
66. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: A randomized, blinded, phase 3 trial. J Bone Miner Res. 2009;24(1):153-61.
67. Lewiecki EM. New and emerging concepts in the use of denosumab for the treatment of osteoporosis. Ther Adv Musculoskelet Dis. 2018;10(12):209-23.

68. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46-56.
69. Compston J, Cooper A, Cooper C, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43.
70. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.
71. Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465-75.
72. Xu S, Lin H, Liu Q, et al. Effects of denosumab on fracture healing: An animal study. Int J Clin Exp Med. 2017;10(6):10137-44.
73. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3-44.
74. Hiligsmann M, Ethgen O, Richy F, et al. Cost-effectiveness of denosumab compared with current treatment strategies for postmenopausal osteoporosis. Value Health. 2012;15(4):485-94.
75. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and denosumab alone or in sequence on bone mineral density and bone turnover in postmenopausal women: The DATA-Switch study. Lancet. 2014;383(9916):1327-35.
76. Lorentzon M, Cummings SR. Osteoporosis: The evolution of a diagnosis. J Intern Med. 2015;277(6):650-61.
77. Reginster JY, Burlet N. Osteoporosis: A still increasing prevalence. Bone. 2006;38(2):4-9.

ANNEXURE I - INFORMED CONSENT FORM

TITLE OF THE STUDY: "Effect of Injection Denosumab in Osteoporotic Fracture healing"

PRINCIPAL INVESTIGATOR: [redacted]

PG Resident, JAWAHARLAL NEHRU MEDICAL COLLEGE, Belagavi

GUIDE: [redacted]

Professor, Department of Orthopaedics,

J.N. Medical College, K.A.H.E.R, Belagavi, Karnataka.

This Informed Consent Form is for men and women who attend Dr PRABHAKAR KORE HOSPITAL AND RESEARCH CENTRE and who we are inviting to participate in Randomised controlled trial on osteoporotic fracture healing. The title of The Randomised controlled trial is "Effect of Injection Denosumab in Osteoporotic Fracture healing"

This Informed Consent Form has two parts:

• Information Sheet (to share information about the research with you) • Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction:

I am [redacted] PG Resident, JAWAHARLAL NEHRU MEDICAL COLLEGE, Belagavi. We are doing Randomized controlled trial on the effect of Injection Denosumab in Osteoporotic Fracture healing, which is very

common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide today. whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you may not understand. Please contact me for more information as needed. If you have questions later, you can ask them of me, the study doctor or the staff.

Purpose of the research:

Numerous low-energy fractures occur as a result of osteoporosis, which is thought to affect 200 million people globally.

Osteoclast development, activity, and survival are inhibited by denosumab via preventing the interface of RANKL with RANK, the osteoclasts' receptor.

With a preferable safety and performance credentials, denosumab is a relatively new entity that works to lessen bone turnover, increase bone mineral density, and reduce fracture risks.

Very few Indian researches are done over injection denosumab on fracture healing on Indian population. Therefore, the aim of this study was to investigate healing in cases of Osteoporotic fracture among patients who received Inj. Denosumab with those who did not.

Participant selection

Adults with Age more than 50 years and less than 85 years, who are identified as Cases of osteoporotic fracture ie diagnosed fracture with dexa scan <-2.5

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to

participate in this research project, you will be offered the treatment that is routinely offered in this clinic/hospital for osteoporotic fracture, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

A one-year hospital based Randomized controlled study. Patients (within age group of 50 to 85 years old) admitted with diagnosed fracture will be advised to do Dexa scan to check osteoporosis. After which whoever diagnosed with osteoporotic fracture will be divided into 2 groups, the intervention group and control group. The intervention group will receive one injection denosumab 60 mg subcutaneously along with tablet calcium (1000 mg) with vitamin D3 (600 IU).The control group will be receiving only tablet calcium (1000 mg) with vitamin D3 (600 IU). This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.

The Principal investigator will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

B. Description of the Process:

One Injection Denosumab 60 mg subcutaneously along with tablet calcium (1000 mg) with vitamin D3 (600 IU), followed by follow up 6 weeks, 3 months and 6 months post treatment.

We will also ask you a few questions about your general health and measure in the form of questionnaire.

Duration

This is a 1 year Randomized controlled study.

Risks

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes.

Benefits

There may not be any benefit for you but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Reimbursements

You will not be given any other money or gifts to take part in this research

Confidentiality

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no- one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone.

Sharing the Data and results

The knowledge that we get from doing this research will be shared with you through journal publications. Confidential data & information will not be shared.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may

also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

[redacted] PG resident JNMC, Belagavi – Ph no: [redacted] or

[redacted] Professor, Dept of Orthopaedics,JNMC, Belagavi-Ph [redacted]

Incase you have any questions regarding the ethical clearance of this study, Contact Dr Harsha Hegde, Chairperson JNMC, IEC and Scientist D, ICMR, National Institute of Traditional Medicine, Belagavi, 94804225280

This proposal has been reviewed and approved by [ETHICS COMMITTEE JNMC, Belagavi], which is a committee whose task it is to make sure that research participants are protected from harm.

PART II: Certificate of Consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign. A researcher or the person going over the informed consent must sign each consent. The certificate of consent should avoid statements that have "I understand...." phrases. The understanding should perhaps be better tested

through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____ Day/month/year

If illiterate

Aliterate witness must sign (if possible, this person should be selected by the participant and should have no connection to-the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, andthe individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____
Thumb print of participant

Signature of witness _____

Date _____ Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____ Day/month/year

VOLUNTARY PARTICIPATION / WITHDRAWAL:

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. 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 identify 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:

[redacted]

Post-graduate resident, Department of Orthopaedics, J.N. Medical College, K.A.H.E.R, Belagavi 10.

[redacted]

[redacted]

Professor Dept of Orthopaedics, J.N. Medical College, K.A.H.E.R, Belagavi 10

[redacted]

CONSENT STATEMENT

I am making a voluntary decision to participate in the study **"Effect of Injection Denosumab in Osteoporotic Fracture healing-A Randomized Control Trial"**. My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

Date:

Place:

ANNEXURE II - PROFORMA

EFFECT OF INJECTION DENOSUMAB IN OSTEOPOROTIC FRACTURE HEALING-A RANDOMIZED CONTROL TRIAL IN TERTIARY CARE HOSPITAL

Patient Number- I.P. Number-

Patient Name-

Age-

Sex-

Address-

Phone Number-

Visit 1

Question Numbers	Predictor	Response	Tick on the Box	Response in terms of option number
Q1	Age of the Patient		1)50-85 years ☐ 2)60-69 years ☐ 3)70-79 years ☐ 4)80-85 years ☐	
Q2	Gender of Patient		1) Male ☐ 2) Female ☐	
Q3	Occupation of the Patient		1)Sedentary Work ☐ 2)Heavy Work ☐	
Q4	Does the Patient Smoke?		1)Yes ☐ 2)No ☐	
Q5	Does the patient drink Alcohol?		1)Yes ☐ 2)No ☐	

Q6	Is the patient Diabetic		1)Yes .. 2)No ..	
Q7	BMI of the patient		1)Underweight (<18.5) .. 2)Normal (18.5-24.9) .. 3)Overweight (25-29.9) .. 4)Obese (>30) ..	
Q8	Diagnosis			
Q9	Fracture Site		1)Upper Limb .. 2)Lower Limb .. 3)Clavicle .. 4)Pelvis .. 5)spine ..	
Q10	Dexa scan lumber/femur		1)<-2.5 to -3.5 .. 2)<-3.5 to -4.5 .. 3)<-4.5 to -5.0	
Q11	Serum calcium level		1)8.6-10.2 mg/dl .. 2)<8.6 mg/dl .. 3)>10.2 mg/dl ..	
Q12	Serum vitamin D3		1)30-60 ng/dl .. 2)<30 ng/dl .. 3)>60 ng/d ..	
Q13	Management		1)conservative .. 2)operative ..	
Q14	If operative then type Of Surgery		1)ORIF .. 2)CRIF ..	
Q15	Inj Denosumab 60 mg		1)given .. 2)not given ..	
Q16	Calcium 1000 mg + 400 IU vitamin D3		1)given .. 2)not given ..	
Q17	Pre op x ray			
Q18	Post op x ray			

Visit 2 (6 weeks)

X ray

Intervention

Progression in bone healing (compare with last X ray)

1) Yes ..
2) No ..

Fracture healed

1) Yes ..
2) No ..

Visit 3 (3 months)
X ray
Intervention
Progression in bone healing (compare with last X ray)

1) Yes ☐
2) No ☐

Fracture healed

1) Yes ☐
2) No ☐

Visit 4 (6 months)
X ray
Intervention
Progression in bone healing (compare with last X ray)

1) Yes ☐
2) No ☐

Fracture healed

1) Yes ☐
2) No ☐

ANNEXURE III – MASTER CHART

INTERVENTIONGROUP

NO.	AGE	SEX	VISIT1 OCCUPATION		SMOKING		ALCOHOL		DIABETIC		BMI				DIAGNOSIS	FRACTURESITE					DEXASCAN			S. Ca++			S.VIT D3			MANAGEMENT		SURGERY		INJ.DENOSUMAB 60mg		Ca++1000mg+400IU VIT D3		PREOPXRAY	POST OPXRAY	VISIT2 PROGRESSIONINBONE HEALING		FRACTUREHEALED		VISIT3 PROGRESSIONINBONE HEALING		FRACTUREHEALED		VISIT4 PROGRESSIONINBONE HEALING		FRACTUREHEALED	
			SEDENTARYWORK	HEAVYWORK	YES	NO	YES	NO	YES	NO	UNDERWEIGHT(<18.5)	NORMAL(18.5-24.9)	OVERWEIGHT(25-29.9)	OBESE(>30)		UPPERLIMB	LOWERLIMB	CLAVICLE	PELVIS	SPINE	<-2.5 TO -3.5	<-3.5 TO -4.5	<-4.5 TO -5.0	8.6 - 10.2mg/dl	<8.6 mg/dl	>10.2 mg/dl	30-60ng/dl	<30ng/dl	>60ng/dl	CONSERVATIVE	OPERATIVE	ORIF	CRIF	GIVEN	NOT GIVEN	GIVEN	NOT GIVEN			YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
1	77	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
2	84	M	1	0	0	1	0	1	0	1	1	0	0	0	RIGHT SUBTROCH#	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
3	57	M	1	0	0	1	0	1	0	1	0	1	0	0	L1WEDGE COMPRESSION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
4	75	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
5	65	F	1	0	0	1	0	1	1	0	0	0	0	1	LRFT TRIMELLEOLAR#	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
6	71	F	1	0	0	1	0	1	1	0	0	0	1	0	DISTAL END OF FEMUR #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
7	85	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
8	62	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_

9	57	F	1	0	0	1	0	1	0	1	0	0	1	0	L1WEDGE COMPRESSION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
10	69	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
11	57	F	1	0	0	1	0	1	0	1	0	0	1	0	LEFT IT #	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
12	83	M	1	0	0	1	0	1	0	1	1	0	0	0	RIGHT ULNA #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
13	53	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHT TIBIA#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
14	82	F	1	0	0	1	0	1	1	0	0	1	0	0	L2-L3 WEDGE COMPRESSION#	0	0	0	0	1	0	1	0	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
15	58	M	0	1	0	1	0	1	0	1	0	0	0	1	POLY TRAUMA	1	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
16	70	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFT IT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
17	70	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
18	75	F	1	0	0	1	0	1	0	1	1	0	0	0	D12 & L3 WEDGE COMPRESSION#	0	0	0	0	1	0	0	1	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
19	75	F	1	0	0	1	0	1	1	0	0	0	1	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
20	65	F	1	0	0	1	0	1	1	0	0	0	1	0	RIGHT SUPRACONDYLAR #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
21	60	M	1	0	0	1	0	1	0	1	0	0	1	0	RIGHT DER#	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
22	65	F	1	0	0	1	0	1	0	1	0	0	0	1	L1WEDGE COMPRESSION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
23	60	F	1	0	0	1	0	1	1	0	0	0	1	0	LEFT IT	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0

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24	84	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHT DER#	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
25	72	F	1	0	0	1	0	1	0	1	0	1	0	0	LEFT IT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
26	69	F	1	0	0	1	0	1	1	0	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
27	62	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHT TIBIA#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
28	52	F	1	0	0	1	0	1	0	1	0	1	0	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
29	53	F	1	0	0	1	0	1	1	0	0	0	1	0	LEFT IT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
30	51	M	1	0	1	0	0	1	0	1	1	0	0	0	L2-L3 WEDGE COMPRES S SION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	1	0	1	0	1	_	1	0	0	1	1	0	0	1	1	0	1	0
CONTROL GROUP																																																			
1	83	F	1	0	0	1	0	1	1	0	1	0	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
2	60	M	1	0	0	1	0	1	1	0	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
3	84	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
4	59	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHT SUB TROCHA N TERIC#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
5	70	M	1	0	0	1	0	1	1	0	0	1	0	0	LEFT IT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
6	76	F	1	0	0	1	0	1	0	1	0	0	1	0	T12 WEDGE COMPRE S SION#	0	0	0	0	1	0	1	0	1	0	0	1	0	0	1	0	_	_	0	1	1	0	1	_	1	0	0	1	1	0	0	1	1	0	1	0
7	58	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
8	58	M	1	0	1	0	0	1	0	1	1	0	0	0	L1WEDG E COMPRE S SION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	0	1	1	0	1	_	1	0	0	1	1	0	0	1	1	0	1	0
9	82	F	1	0	0	1	0	1	1	0	0	0	1	0	RIGHT DER#	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0

10	67	F	1	0	0	1	0	1	1	0	0	1	0	0	RIGHTIT#	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
11	78	F	1	0	0	1	0	1	1	0	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
12	76	F	1	0	0	1	0	1	0	1	0	1	0	0	L1WEDGE COMPRESSION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	0	1	1	0	1	_	1	0	0	1	1	0	0	1	1	0	1	0
13	74	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
14	84	F	1	0	0	1	0	1	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
15	73	M	1	0	0	1	0	1	1	0	0	1	0	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
16	83	M	1	0	0	1	0	1	1	0	1	0	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
17	78	F	1	0	0	1	0	1	1	0	1	0	0	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
18	63	F	1	0	0	1	0	1	0	1	0	0	1	0	RIGHT DER#	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
19	72	M	1	0	1	0	0	1	0	1	1	0	0	0	L2WEDGE COMPRESSION#	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	0	1	1	0	1	_	1	0	0	1	1	0	0	1	1	0	1	0
20	78	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
21	85	F	1	0	0	1	0	1	1	0	0	0	1	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
22	67	M	1	0	0	1	1	0	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	0	1	1	0	1	0
23	70	M	1	0	0	1	0	1	0	1	0	1	0	0	T12 WEDGE COMPRESS S #	0	0	0	0	1	1	0	0	1	0	0	1	0	0	1	0	_	_	0	1	1	0	1	_	1	0	0	1	1	0	1	0	_	_	_	_
24	72	F	1	0	0	1	0	1	1	0	0	1	0	0	LEFT DER #	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
25	57	F	1	0	0	1	0	1	0	1	0	1	0	0	RIGHT DER#	1	0	0	0	0	1	0	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
26	58	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
27	82	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFT DER #	1	0	0	0	0	0	1	0	1	0	0	1	0	0	0	1	1	0	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
28	74	M	1	0	0	1	0	1	0	1	0	1	0	0	LEFTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_
29	80	F	1	0	0	1	0	1	1	0	0	0	1	0	RIGHTIT#	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_

30	57	M	1	0	0	1	0	1	0	1	0	1	0	0	RIGHTIT #	0	1	0	0	0	1	0	0	1	0	0	1	0	0	0	1	0	1	0	1	1	0	1	1	1	0	0	1	1	0	1	0	_	_	_	_