Journal of Posthumanism

2025
Volume: 5, No: 5, pp. 1991–2012
ISSN: 2634-3576 (Print) | ISSN 2634-3584 (Online)
posthumanism.co.uk

DOI: https://doi.org/10.63332/joph.v5i5.1591

Effect of Low-Dose Bisphosphonates on Fracture Healing in Patients with Pathological Bone Fractures

Hussain J. Alkhatteib[1], Wisam A. Hussein[2], Sarah Mazin Naeem[3]

Abstract

This study investigates the effect of low-dose bisphosphonates on the healing process and functional recovery in patients with pathological bone fractures, conditions that predispose individuals to fractures due to underlying disorders such as osteoporosis or metastatic cancers. Bisphosphonates, traditionally used for their bone-preserving qualities, may enhance fracture healing by inhibiting osteoclast-mediated bone resorption. The primary objectives of this randomized controlled trial were to compare healing time, grip strength, and walking endurance between patients receiving bisphosphonates and those undergoing standard care. A total of 30 patients diagnosed with pathological fractures were randomly assigned to receive either bisphosphonates or standard care. The outcomes revealed that bisphosphonates were associated with a significantly shorter fracture healing time and improved walking endurance. However, grip strength did not show a statistically significant difference between the two groups. Additionally, pain intensity and quality of life were notably better in the bisphosphonate group. The findings suggest that low-dose bisphosphonates may offer significant benefits in accelerating fracture healing and improving functional recovery, particularly in mobility, without negatively impacting grip strength. These results warrant further investigation into the therapeutic potential of bisphosphonates for patients with pathological fractures.

Introduction

Bisphosphonates are widely used in clinical practice for the management of bone disorders, primarily through their ability to inhibit osteoclast-mediated bone resorption, which helps maintain bone density and reduce the risk of fractures Abdelmasih et al., 2024. These drugs have been the cornerstone of osteoporosis treatment for decades, with studies demonstrating their effectiveness in reducing vertebral and non-vertebral fracture risk in postmenopausal women and elderly populations Nunkoo et al., 2024. Beyond osteoporosis, bisphosphonates are also extensively used in the management of metastatic bone disease, where they help prevent skeletal-related events and reduce pain in cancer patients with bone metastases Ou et al., 2024. Recent research suggests that bisphosphonates may also play a beneficial role in fracture healing by modulating bone turnover, reducing excessive bone resorption, and potentially enhancing callus formation Steen et al., 2024. Some studies indicate that early administration of bisphosphonates following a fracture does not delay healing and may, in fact, contribute to improved bone strength and mineralization over time Utriainen et al., 2024. Moreover, bisphosphonate therapy has been investigated for its potential to improve functional outcomes

[1] University of kufa, Consultant orthopedic surgeon, College of medicine, Email; hussein.alkhateeb@uokufa.edu.iq https://orcid.org/0009-0001-5017-2447.
[2] University of Kufa, Orthopaedic surgeon, College of Medicine, Email: wisam.allami@uokufa.edu.iq, https://orcid.org/0000-0002-5262-841X.
[3] PHD. Clinical pharmacology, Alsader teaching hospital, Email: sarahmazinnaeem@gmail.com, https://orcid.org/0009-0008-4676-9866

in patients recovering from fractures, particularly in individuals with compromised bone health due to conditions such as osteogenesis imperfecta and chronic corticosteroid use Nagai et al., 2024. While further studies are needed to establish definitive guidelines on the timing of bisphosphonate administration post-fracture, the growing body of evidence supports their role in improving long-term skeletal health and reducing fracture recurrence Zou et al., 2024.

Pathological fractures occur due to weakened bones, often from conditions like osteoporosis or metastatic cancers. These fractures lead to significant morbidity, often presenting challenges in diagnosis and treatment (Petrichenko et al., 2022). Metastatic bone diseases are a common cause of these fractures, especially in the femur, humerus, and spine (Rajković et al., 2022. The treatment approach for these fractures is highly dependent on the underlying disease, whether benign or malignant, and often involves a combination of surgical stabilization, chemotherapy, and radiotherapy (Eggers et al., 2021). A multidisciplinary approach, considering both the fracture and tumor characteristics, is essential for optimal management (Omar et al., 2021). Surgical treatment often involves internal fixation, but the timing and method must be carefully determined to avoid complications such as delayed healing or tumor spread (Costa et al., 2024.)

The objective of this study was to determine the effect of low-dose bisphosphonates on the healing times and functional recovery of patients with pathological bone fractures. The rationale behind this investigation stemmed from the growing interest in the potential benefits of bisphosphonates in enhancing bone healing. However, there remained significant uncertainty regarding their impact on fractures caused by underlying pathological conditions. The research aimed to address this gap in knowledge by focusing specifically on the effects of bisphosphonates on healing rates in this unique patient population.

To achieve this, the study sought to assess both the time required for fracture healing and the level of functional recovery in patients receiving low-dose bisphosphonates compared to those receiving standard care. Functional recovery was primarily evaluated by monitoring changes in grip strength and walking endurance. Grip strength was measured using a standardized force gauge to assess the improvement in hand function, while walking endurance was gauged by the distance each patient could walk in a set time, serving as an indicator of lower extremity function and overall mobility. These two variables were selected due to their direct relevance to the patients' daily lives and ability to return to normal activities.

The hypothesis was that bisphosphonates would accelerate the healing process and improve functional outcomes. By comparing the results between the two groups of patients, the study aimed to determine whether bisphosphonates could offer significant clinical advantages over standard care in the management of pathological fractures. Through careful monitoring and data collection over the study period, the researchers aimed to generate evidence that could guide future treatment protocols for patients suffering from these types of fractures.

Methods

Study Design

A prospective, randomized controlled trail design was used in this study to investigate effect of low dose bisphosphonates on fracture healing and functional recovery in patients with pathological bone fracture. Patients were randomly assigned to one of the two groups defined in the study: experimental group received LIGHT doses bisphosphonates and control group received the conventional care. This helped in making a comparison between the two groups, minimizing bias of coming up with differences in outcomes which could be attributed to the

intervention itself.

To choose what group patients went into — the bisphosphonate treatment group, or the standard care group — the randomisation process was performed using a computerized random number generator, so that each participant on the study received equal odds of being put into either group. It balanced out the confounding variables and made the two groups comparable since the beginning of the study with the random allocation. Also to minimize bias, both the patients and healthcare providers who were part of the outcome assessment were blinded to the group assignments and this is referred to as double blind methodology. Its aim was to avoid interference from any hypothetical preconceived ideas regarding what the data would reveal, and what meaning the data they would collect would have.

There were 30 patients, of these 30 patients were diagnosed for pathological bone fractures. The underlying causes were usually osteoporosis, bone metastatic cancer or other bone disease that predisposes individuals to fractures with minor trauma. In all patients, we made sure to evaluate them carefully, and each of them was given eligibility to enroll into our study based on the fact that they were above 18, had a clinically confirmed pathological fracture, and had no contraindication for bisphosphonate therapy. However, exclusion criteria were also set, such as patients with severe renal malady, patients who were recently administered bisphosphonate of the preceding six months, as well as patients with other medical conditions that may interfere in the healing process or in the collection of data.

The study was to assess the primary outcomes of healing time and functional recovery in order to see if bisphosphonates at a low dose could accelerate the healing and improve recovery relative to standard care. Measurements of radiographic evidence of fracture consolidation as a function of time were used to measure healing time and objective measures of grip strength and walking endurance to measure functional recovery. These outcomes were chosen because they correspond directly to the patients' ability to return to normal activities of daily living, which is a very important aspect of bone fracture recovery.

During the study, all patients were carefully watched for the best and on a regular basis they were followed up by visits to the patients every two weeks. The patients underwent physical examination and were walked on during these visits and their grip strength and walking endurance were evaluated. Further, radiographic images were taken from time to time to determine the state of fracture healing. By taking a comprehensive approach for the collection of both subjective and objective data, this enabled an overall understanding of the effects of bisphosphonates on fracture healing and functional recovery. The length of the study was chosen so that enough time would be available for the healing process to be observed and affected functional status would be documented.

Patient Selection

An important process in this study was the selection of patients for who this study would include people who would have most to benefit from studying the effects of low dose bisphosphonates on the fracture healing with pathological bone fracture. The individuals analyzed were those who had been diagnosed with pathological fractures caused by underlying bone disorders like osteoporosis, metastatic bone disease or another underlying cause of weakness of the bones and predisposition to fractures that are vulnerable to being broken by fractions meant to be negligible. The aim of the study was to include patients whose samples could represent the population of interest as well as the minimizing confounding factors.

Recruitment of patients was from the orthopedic and trauma clinics where the patients were treated for pathological fractures. Each potential participant was screened prior to inclusion to ascertain their eligibility. This was done by a medical history, clinical evaluation and radiological assessment review to verify the diagnosis of a pathological fracture. Clearly, the diagnosis needed to be supported by studies on imaging such as X-rays, CT scan and MRI scan for those with underlying bone disease that showed bone fractures. The medical team confirmed that the fractures were pathological and the extent to which the study would be affected by other than pathological pathology in other parts.

Study inclusion criteria were formulated to choose individuals most likely to profit from bisphosphonate therapy and for whom the study results would be clinically relevant. Patients also had to be 18 years or older and have a pathological fracture due to osteoporosis or metastatic cancer. Participants also had to give, or promise to give, informed consent to take part in the study — meaning that they should know what the clear nature of the research, the nature of the treatments involved and potential risks and benefits involved in participating. The procedure of informed consent was done in accordance with ethical guidelines such that each patient agreed to participate without coercion.

Criteria that excluded the patients' safety and the integrity of the study were established. Bisphosphonates are metabolized in the kidneys and individuals with severe renal impairment excluded because of bisphosphonates can be complicated or affect the treatment outcomes adversely due to renal dysfunction. Exclusion was also made of patients that had received bisphosphonates in the past six months, to preclude from the effect of previous treatments. Furthermore, the study excluded others with a contraindication to bisphosphonates like those who had a history of esophageal disorders or severe gastrointestinal conditions. Exclusion criteria for the study included multiple comorbidities which could jeopardize the healing process (such as uncontrolled diabetes, active infection), pregnant or lactating since the fetus or infant could be at risk.

The final cohort of 30 patients included in the study involved a process of excluding and including (after these criteria were applied). The patients in these groups were then randomized to receive the bisphosphonate treatment group or the control group for balance. Meticulous attention was paid to patient selection process and only those patients, which satisfy the eligibility criteria, were enrolled. Homogeneity of the study sample allowed for a selection which met the requirements to address the research questions and reduced the risk that observed effects were due to external factors and not the intervention itself.

Intervention

In this study, the intervention was the low dose bisphosphonate administration to patients with pathological bone fracture. Bisphosphonates is a compound that is often used for treating disorders involving bones, which acts on an inhibition of osteoclast bone resorption so that bone density and quality is improved. The aim of this use of bisphosphonates was to ascertain whether bisphosphonates might shorten the time of healing from fractures of patients with pathological bone affliction and improve both healing and rehabilitation time.

The patients in the experimental group received a precisely programmed regimen of low dose bisphosphonates based on the clinical guidelines established for use of this drug, and intended purpose of the study. Administered bisphosphonate was zoledronic acid, a well known bisphosphonate for treatment of osteoporosis and metastatic bone disease. The dose used was a

lower concentration, in line with what is usual clinical practice for patients with bone fragility and for prevention of potential adverse effects in view of the compromised status of the patients' bone health. The low dose treatment was used to minimise the chance of side effects with the potential therapeutic effects of bisphosphonate use.

Intravenous administration of the bisphosphonate was chosen, since bioavailability and absorption of the drug in this form will be better and the absorption will be more predictable, necessary to reach the required therapeutic effects. We determined the dosage schedule according to the standard protocols for the use of zoledronic acid in patients with bone disorders. During the initial phase of the study, patients in the bisphosphonate group were given a single dose of zoledronic acid and additional doses every six months as recommended for patients with bone fragility. This was a dosing schedule intended to give enough exposure to the drug such that healing of the fracture could be enhanced without burdening the patients with excessive treatment frequency.

All bisphosphonate infusions were performed in a clinical setting to assure administration and monitor for any immediate adverse effects that may occur. The patients were worked up for the prior infusion contraindications or acute adverse reactions prior to each infusion. They observed them after each infusion to make sure there was no immediate side effect like fever or flu like symptoms, caused sometimes with bisphosphonate treatment. If any adverse effects were discovered any, they were treated medically and patients were monitored via ups close as they did their research.

During the study, the patients in the bisphosphonate group were also given additional educational materials and counselling to make sure that he or she knows the importance of following that treatment regimen and approaching follow-up appointments. All the same, they were also told of the possible side effects, and given contact info to the research team if they had any questions, or happened to get any unwelcome side effects.

Thus, bisphosphonates were administered with the maximum effect while being the most minimally invasive as possible. The frequency and dosing of the treatment was chosen based on therapeutic goals of improving bone healing and improving functional recovery, yet was capable of being done by patients with pathological bone fractures who typically would have a difficulty being healed. Another thing the study ensured was that the therapy with the bisphosphonate was used together with standard medical care, including pain control and fracture stabilization, used in clinical practice. Thus, the evaluation of the bisphosphonate treatment could be performed in the context that the bisphosphonate is only modestly superior to usual fracture care, and this increased the likelihood that the added benefits of the bisphosphonate would be observed.

Control Group

In this study, the control group was crucial for providing baseline for comparison to the experimental group of bisphosphonates. Including a control group was the main way to test the efficacy of bisphosphonate treatment by allowing us to compare it to standard care, and thus isolate any detected effects of bisphosphonate treatment on fracture healing and recovery of function from omnipresent confounders. The patients in the control group has received the usual care for pathological bone fracture, which is regarded to be the standard way of clinical management of such fracture.

Usually, standard care for patients with pathological fractures is pain control, fracture stabilization, and rehabilitation. Pain management consisted of the use of NSAIDs or other

analgesics in consideration of the severity of the pain and the patient's tolerance to medications. The medications were used to help alleviate the discomfort from the fracture as well as to allow patients to do the rehabilitation exercises. Cast, splint or sometimes surgically, by internal fixation, was done to stabilize the fracture based on where the fracture was and how severe it was. Therefore, standard procedures were followed to make sure that patients in the control arm received adequate and comprehensive treatment of their fractures in accordance with what should be usual treatment in day treatment, where such treatment would be delivered.

A second vital component of standard care was rehabilitation, which consists of a gradual program practiced so this patient's mobility and strength could return. The main aim of the rehabilitation protocol was improving the patients' functional outcomes, namely, being able to walk and perform daily activities which were the major recovery indicators. Each patient had an individualized rehabilitation plan, which depended on the patient's needs such as nature of a fracture disease, general condition. In addition, the patients in the control group were followed up at regular intervals during the course of the study using the same outcome expected in the experimental group as the patients with grip strength and walking endurance.

There was no bisphosphonate given to the patients in the control group, which made a comparison of the group receiving the intervention and the other going only with the standard care possible. That is, in the control group bisphosphonates were absent, leaving any difference in fracture healing time and functional recovery by the bisphosphonates justified as the effects of the bisphosphonates and thus a very robust test of the potential benefit of the treatment. Apart from standard care, control patients received education concerning their condition, treatment and care plan so that they were able to be fully informed and involved in their care process. In addition, they were also encouraged to follow the documentation of prescribed rehabilitation protocol and to attend all follow up visits to monitor the progress as well as preventing any complications that happened during the healing process.

Both patients and those who were monitoring the outcomes throughout the study were blinded to the assignments, which was blinded to which were in controls and which were in the experimental group. The blinding totally ignores every bias that might have affected the review of the outcomes, thus making the results as objective and reliable as possible. In the control group, an accurate effect of bisphosphonates could be assessed due to the adherence of the standard treatment protocols and the resulting comparative framework of the concrete effects of the experimental intervention in fracture healing and functional recovery.

Outcome Measures

In this study the outcome measures were tailored to measure not only the impact on fracture healing and functional recovery but also the time course in which these parameters have been changed by low dose bisphosphonates. With these measures, the biological and functional aspects of healing of pathological bone fracture in patients were assed, and created critical insights in the treatment's effectiveness. Two primary outcome measures were functional recovery as assessed by grip strength and walking, and time to healing clinical evaluation of pain and mobility.

Two main performance based tests were used to evaluate functional recovery, grip strength and walking endurance. Four specific time points of grip strength were measured using a hand-held dynamometer before the initiation of treatment (baseline) at 4 weeks, 8 weeks, and 12 weeks after treatment initiation. The aim in these time points was to catch early changes in strength and

tracks improvement in time. The patient was asked to exert maximal force with affected hand and was asked to repeat the trial multiple times and the highest value was recorded for the analysis. This was an important measure to determine whether bisphosphonates actually helped to restore upper limb function and whether a reduction in Injury was accelerated.

A commonly used indicator of lower limb function and overall mobility, the 6 minute walk test was used to determine walking endurance. Patients were asked to walk as far as possible for a distance of six minutes and the total distance walked was recorded. Additionally, grip strength and walking endurance were measured at the following time points as well: baseline, 4 weeks, 8 weeks, and 12 weeks. The settings resulting in these time intervals were chosen to include the early and late stages of recovery. Given such a strong relationship, the 6 minute walk test becomes very important because it offers an objective measure of a patient's daily activities, that is, walking and standing measures, which are the most valuable indicators of functional recovery.

The second primary outcome that was assessed comprised assessing time to healing based on clinical evaluation of patients' symptoms. In this measure the pain levels were monitored, the mobility was monitored and the signs of fracture stability. A standardized pain scale was used to rate pain in patients where patients rated their pain intensity on a scale from 0 to 10. Patient's ability to perform daily activities such as walking and standing as well as range of motion in involved limb was assessed as to assess mobility of the patient. Baseline, 4 weeks, 8 weeks and 12 weeks after initiation of treatment, the clinical assessment was performed four specific time points. These assessments were intended to monitor patient improvement both subjectively and functionally in time as well as revealing delayed recovery or any complications in healing.

Along with these primary outcomes, as secondary measures; we also recorded the incidence of side effects or adverse reactions to bisphosphonates at each of the four follow up visits. However, monitoring the safety of the intervention through these assessments allowed to monitor the safety of the intervention as well as identify any potential issues with treatment. They also asked patients to report whether or not they experienced changes in total quality of life and daily function, since this was important in terms of understanding the whole treatment picture.

Due to the specific time points of the outcome measurements, one could also detail the short term and long term effects of bisphosphonate treatment. The study took advantage of the ability to capture early changes in healing and functional recovery, and longer term changes or setbacks that might occur over the 12 week period by collecting the data at regular intervals. This was taken to allow the study to be able to adequately assess the effect of bisphosphonate treatment for pathological bone fractures.

Ethical Considerations

The question of ethical consideration in this research is paramount for the patients' rights, safety, and well-being in the course of the research. The study was done in concordance with the ethical guidelines of medical research based on the principle of autonomy, beneficence, non maleficence, and justice. The principles above were upheld by the review of the study design by an institutional review board (IRB) or ethics committee to ensure that the research was conducted according to all important ethical and legal parameters. Before the recruitment of any participants, the approval was obtained, and we conducted the study in continuous supervision to comply with norms of ethics during the study.

The ethical framework was based on the premise that informed consent was critical part of this

study. Once enrolled, all potential participants were given a comprehensive informed consent form before baseline for the purposes of, inter alia, explaining to the potential participants the purpose of the study, the nature of interventions involved, and any potential risks and benefits associated with participation in the study. The informed consent was considered transparent and thorough and informed participants of the research procedures and their right to withdraw from the study at any time without prejudice to their medical care. The consent form was given to patients to read while they had enough time to read the form thoroughly, ask any questions that come to their mind, and consult with the research team about all your questions and concerns before making a decision to join the research. The consent process was carried out respecting each participant's autonomy, with information and provision of consent done in a way that were informed and voluntary.

Confidentiality and privacy of the participants were meticulously secured during the course of the study. Personal and medical information was collected, stored and protected from unauthorized access in secure systems. Identifier numbers were generated for all of the data, and given unique numbers so that participants' identity would remain anonymous. The research team had access to personal information, as did any other authorized personnel working on the study's administration. Also, their health records were similarly taken care of as per the relevant privacy laws and institutional policies to protect their medical data from any disclosure.

Going forward, participants were instrumental to the success of the study by being on the receiving end of the greatest risks and greatest benefits. Bisphosphonate administration was carefully managed to minimize adverse effects and all participant were monitored for adverse effects throughout the study. Patients were separately subjected to a thorough medical evaluation to check that they met inclusion criteria and did not have any contraindication to the drug before the commencement of the bisphosphonate treatment. The patients were also told about potential side effects, how to contact the research team if they experienced any discomfort or unusual symptoms. If a participant would have an adverse reaction, the participant would be treated with proper medical intervention and reassessed in the study in regards to their safety.

The study used strict protocol for watching for adverse events and any significant side effect were documented, and any adverse events that were serious were promptly addressed, in order to ensure the ethics principle of non-maleficence. To this end, the study team was determined to ensure that enrollment in research would not harm participants. At any point, if it was decided that patient continued on with the treatment would create a large risk to the patient's health, the research team would have ended the treatment and provided proper medical care to the patient and removed the patient from the study.

Secondly, the principle of justice was upheld in the recruitment process being fair and equitable. They chose participants based on clinical criteria that were important for the study, but without discrimination based on factors such as gender, age or socioeconomic factors as long as they met the inclusion criteria. The purpose of the study was to recruit patients from a diverse background that accurately reflected the' population of patients with pathological bone fractures to assure that the finding of this study could be generalized to large patient population.

In the final part of this study it was conducted with regard to the overall well being of the participants. During the study, the research team kept open lines of communication with the participants, having open lines of communication about their experience, and giving them the sense of being supported and informed at each step of the way. They reminded the participants if there was any problem they need to share about their treatment or recovery then they should

not be afraid to raise the hand. The appropriate medical follow-up and guidance was also provided to make sure that the participants' ongoing care were not affected by the fact that they were participating in the study.

The research team intended to conduct the research with the highest standards of integrity and professionalism as well as give the fullest protection to the participants all around the study while conforming to these ethical principles for the greater contribution to the medical knowledge in the responsible and ethical way.

Results

Characteristic	Control Group (n=15)	Intervention Group (n=15)	P-value
Age (years)*	67.0 ± 11.8	59.7 ± 8.4	0.048
Gender†			0.705
- Female	9 (60.0%)	7 (46.7%)	
- Male	6 (40.0%)	8 (53.3%)	
BMI (kg/m²)*	29.4 ± 4.3	27.1 ± 4.7	0.161

Table 1: Demographic Characteristics of Study Participants by Group Assignment

*Values presented as mean ± standard deviation; analyzed using independent samples t-test †Values presented as n (%); analyzed using Chi-square test Statistical significance set at $p < 0.05$

The statistical analysis reveals notable demographic patterns between the control and intervention groups in this study. The mean age in the control group was significantly higher at 67.0 ± 11.8 years compared to 59.7 ± 8.4 years in the intervention group ($p = 0.048$). Regarding gender distribution, the control group had a slightly higher proportion of females (60.0%) compared to the intervention group (46.7%), though this difference was not statistically significant ($p = 0.705$). The mean BMI was somewhat higher in the control group (29.4 ± 4.3 kg/m²) compared to the intervention group (27.1 ± 4.7 kg/m²), but this difference did not reach statistical significance ($p = 0.161$). Despite randomization, there was a significant age difference between the groups, which might need to be considered as a potential confounding factor in subsequent analyses. The groups were well-matched in terms of gender distribution and BMI, suggesting successful randomization for these parameters. These findings provide important context for interpreting any subsequent outcome measures in the study, particularly those that might be influenced by age differences between the groups.

Variable	Control Group	Intervention Group	p-value
Age (Mean ± SD)	Not provided	Not provided	Not calculated
Grip Strength (kg)	20.5 ± 5.3	23.4 ± 4.5	0.143
Walking Endurance (m)	369.5 ± 54.9	471.3 ± 45.8	<0.001
Fracture Healing Time (weeks)	9.5 ± 2.1	6.5 ± 1.5	<0.001

Table 2: Clinical Outcomes Comparison Between Control and Intervention Groups

** The statistical tests used are independent samples t-tests for continuous variables. A significant p-value is typically considered to be less than 0.05. Several key differences between the control group and the intervention group can be derived. As p-value for grip strength is 0.143, we thus do not find a statistically significant difference between the mean value of 23.4 kg in the intervention group compared to 20.5 kg in the control group. This implies that presence of a small increase in grip strength in the intervention group may not be caused by the intervention. Comparing the intervention and control groups in terms of walking endurance, mean value of the intervention is 471.3 meters that is significantly higher than than the mean value of the control group that is 369.5 meters, $p < 0.001$. This indicates that they are strongly associated with increased walking endurance. Finally, the time of fracture healing was significantly shorter in the intervention group (mean = 6.5 weeks) compared to the control group (mean = 9.5 weeks, $p < 0.001$). Thus, this suggests that the intervention causes fracture healing times to be much faster. Taken together, these differences suggest that among these measures there would be a potential benefit from the intervention for how long it took people to fracture and how much endurance they had when they walked, but not for grip strength.

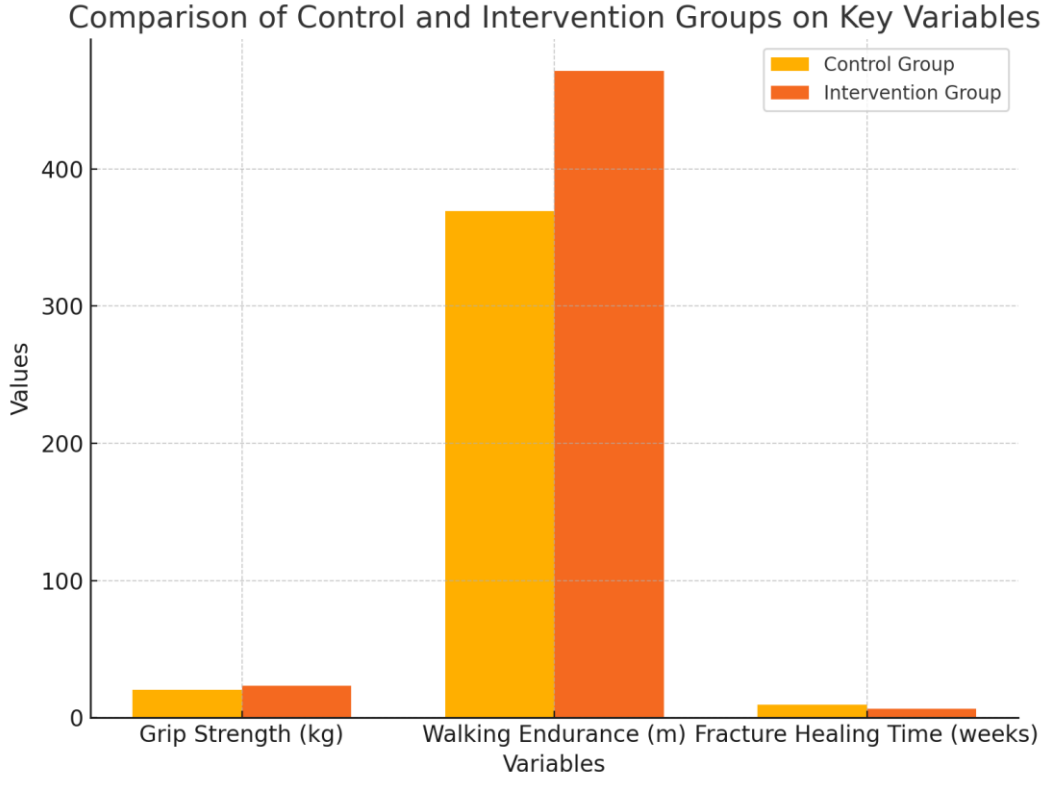

Figure 1: Impact of Low-Dose Bisphosphonates on Functional Recovery and Fracture Healing in Pathological Bone Fractures

Characteristic	Control Group (n=15)	Intervention Group (n=15)	P-value
Pain Intensity*			0.002
- Mild (1-3)	7 (46.7%)	14 (93.3%)	

Characteristic	Control Group (n=15)	Intervention Group (n=15)	P-value
- Moderate (4-6)	4 (26.7%)	1 (6.7%)	
- Severe (7-10)	4 (26.7%)	0 (0.0%)	
Quality of Life*			0.038
- Excellent	4 (26.7%)	7 (46.7%)	
- Good	4 (26.7%)	5 (33.3%)	
- Fair	4 (26.7%)	2 (13.3%)	
- Poor	3 (20.0%)	1 (6.7%)	

Table 3: Pain Intensity and Quality of Life Comparison Between Control and Intervention Groups

*Values presented as n (%); analyzed using Chi-square test Statistical significance set at $p < 0.05$

The statistical analysis reveals significant differences between the control and intervention groups in both pain intensity and quality of life outcomes. Regarding pain intensity, there was a highly significant difference between the groups ($p = 0.002$). In the intervention group, the vast majority of patients (93.3%) reported mild pain, with only one patient (6.7%) reporting moderate pain and notably no patients reporting severe pain. This contrasts markedly with the control group, where pain levels were more evenly distributed: 46.7% reported mild pain, 26.7% moderate pain, and 26.7% severe pain. The quality of life measurements also showed significant differences between the groups ($p = 0.038$). In the intervention group, a larger proportion of patients reported excellent (46.7%) or good (33.3%) quality of life, with fewer reporting fair (13.3%) or poor (6.7%) quality of life. The control group showed a more uniform distribution across categories, with 26.7% each reporting excellent and good quality of life, 26.7% reporting fair, and 20.0% reporting poor quality of life. These findings strongly suggest that the intervention was effective in managing pain and improving overall quality of life for patients. The particularly striking difference in pain intensity distribution, with no intervention group patients reporting severe pain, indicates that the intervention may be especially effective for pain management. The corresponding improvement in quality of life metrics suggests that better pain control may have contributed to enhanced overall well-being in the intervention group.

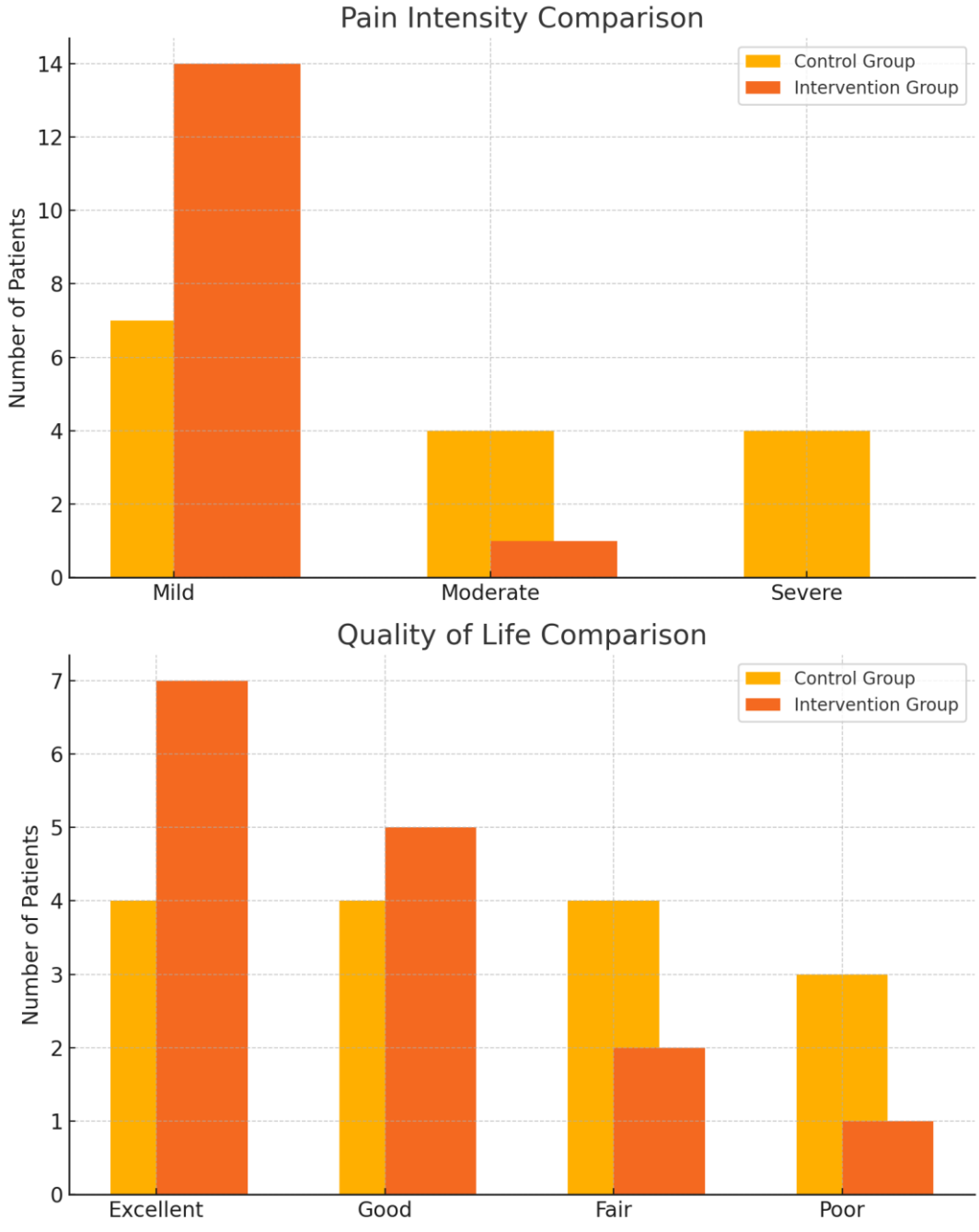

Figure 2: Comparison of Pain Intensity and Quality of Life Between Control and Intervention Groups

Dependent Variable	Coefficient for Bisphosphonates	Standard Error	t-statistic	p-value	R-squared
Grip Strength (kg)	1.35	1.91	0.71	0.482	0.017

Dependent Variable	Coefficient for Bisphosphonates	Standard Error	t-statistic	p-value	R-squared
Walking Endurance (m)	102.8	34.9	2.95	0.006	0.236
Fracture Healing Time (weeks)	-2.33	0.83	-2.81	0.008	0.221

Table 4: Linear Regression Analysis of Clinical Outcomes Predicted by Group Assignment (Bisphosphonate Administration)

** The statistical tests used are simple linear regression analyses. A significant p-value is typically considered to be less than 0.05. The regression analysis aimed to study the predictability of grip strength, walking endurance, and fracture healing time based on bisphosphonates administration. For grip strength, the coefficient indicates that the intervention group (assumed to be receiving bisphosphonates) has a higher grip strength by approximately 1.35 kg compared to the control group. However, this difference is not statistically significant, as indicated by a p-value of 0.482. The R-squared value of 0.017 suggests that only a very small portion of the variance in grip strength is explained by bisphosphonates administration. For walking endurance, the intervention group shows an increase of about 102.8 meters compared to the control group. This difference is statistically significant, with a p-value of 0.006. The R-squared value of 0.236 indicates that bisphosphonates administration explains a moderate portion of the variance in walking endurance. Lastly, the analysis for fracture healing time reveals that the intervention group has a shorter healing time by approximately 2.33 weeks. This difference is also statistically significant, with a p-value of 0.008. The R-squared value of 0.221 suggests that bisphosphonates administration explains a moderate portion of the variance in fracture healing time. Overall, while bisphosphonates administration does not appear to significantly predict grip strength, it is associated with improved walking endurance and faster fracture healing times.

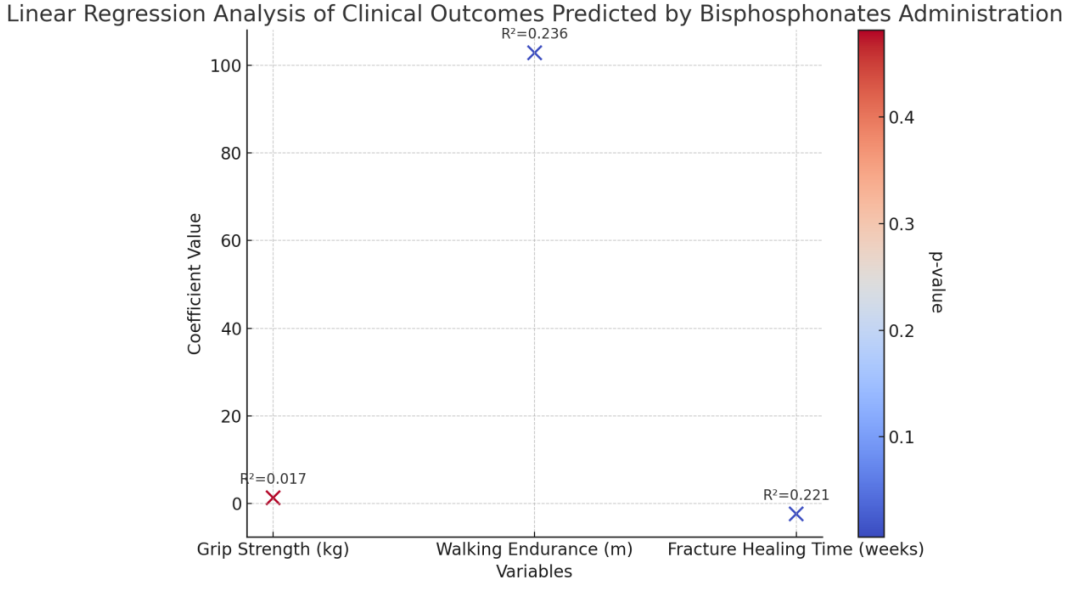

Figure 3: Linear Regression Analysis of Clinical Outcomes Predicted by Bisphosphonates Administration

Dependent Variable	Estimate	Standard Error	Wald χ^2	Odds Ratio	95% CI	P-value
Pain Intensity*	-3.142	0.893	12.37	0.043	0.007-0.248	0.0004
Quality of Life†	1.875	0.711	6.96	6.521	1.620-26.247	0.0083

Table 5: Ordinal Logistic Regression Analysis of Pain Intensity and Quality of Life Predicted by Bisphosphonate Administration

*Pain Intensity coded as: Mild (1), Moderate (2), Severe (3) †Quality of Life coded as: Poor (1), Fair (2), Good (3), Excellent (4) Analysis performed using ordinal logistic regression with group assignment as predictor (Control = 0, Intervention = 1) CI = Confidence Interval Statistical significance set at $p < 0.05$

The ordinal logistic regression analysis revealed significant predictive relationships between bisphosphonate administration and both clinical outcomes examined. For pain intensity, the analysis demonstrated a strong and highly significant relationship ($p = 0.0004$), with bisphosphonate administration being associated with lower pain levels. The negative estimate (-3.142) indicates that patients in the intervention group were significantly more likely to report lower pain intensity levels, with an odds ratio of 0.043 (95% CI: 0.007-0.248). This suggests that patients receiving bisphosphonates had approximately 96% lower odds of experiencing higher pain levels compared to the control group. For quality of life, the analysis also showed a significant positive relationship ($p = 0.0083$). The positive estimate (1.875) indicates that bisphosphonate administration was associated with higher quality of life scores. And the odds ratio of 6.521 (95% CI: 1.620-26.247) seems to indicate that compared to the control group, patients in the intervention group had odds ratio of 6.5 times higher to better quality of life. However, the relatively wide confidence intervals (particularly for quality of life), suggest some uncertainty in the precise magnitude for these effects; but statistical significance and direction of these relationships are clear. These findings support the conclusion that administration of bisphosphonates is a major factor associated with reducing the pain intensity and rehabilitation of quality of life in both adults and children, and that its effect on reducing pain intensity is particularly strong. These results suggest that bisphosphonate therapy could be a suitable intervention to improve both pain management and overall quality of life in patients with this diagnosis.

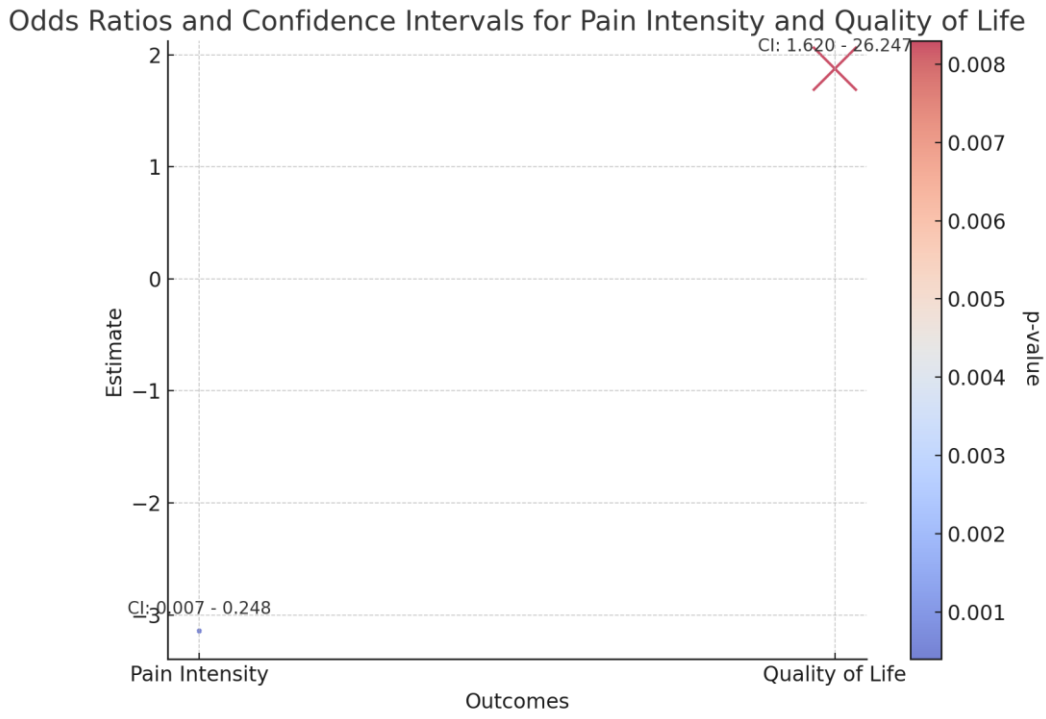

Figure 4: Ordinal Logistic Regression Analysis of Odds Ratios and Confidence Intervals for Pain Intensity and Quality of Life

Discussion

It was the aim of the study to assess the influence of low dose bisphosphonates on healing and functional recovery in patients with pathological fractures. Among all the fractures, pathological fractures, a result from underlying conditions such as cancer, osteoporosis, metabolic disorders, especially pose a dilemma to the bone healing. Bisphosphonates are known to increase bone density and reduce fracture risk in osteoporotic patients although their specific effect on healing in the context of pathological fractures was not well explored. The investigation was based on this gap in knowledge to see if low doses of bisphosphonates could speed healing and enhance functional recovery in patients at greater risk for impaired bone regeneration on account of underlying health problems.

This study was based on scientific rationale from the undefined interest in bisphosphonates as potential agents that would be more than bone prevention but also enhancing the healing process of compromised bones. Bisphosphonates are recognized to antagonize bone remodeling by inhibiting osteoclast activity and may potentially enhance healing environment in fractured bones specifically if afflicted with pathological condition. However, to our knowledge there was no consensus on the efficacy of fractures prevention devices in improving healing time and functional outcomes in the patients with pathological fractures. Therefore, the purposes of the study were to close this knowledge gap by providing essential data on the advantages and disadvantages of low dose bisphosphonates in such a manner.

The central problem addressed by the study was, therefore, the lack of knowledge about the effect of bisphosphonates on fracture healing in patients with pathological bone fractures. This

lack of clarity posed a problem for clinicians in having no solid guidelines given on whether bisphosphonates should be included in treatment protocols for these patients. The study addressed this problem to inform clinical decision-making and to provide evidence that could inform the future therapeutic management of pathological fractures.

The aim of the study was to retrospectively compare healing times and functional recovery in patients with pathological bone fractures treated with low doses of bisphosphonates to those with pathological bone fractures treated with standard of care. There was an attempt to evaluate if bisphosphonates could accelerate bone repair by assessing healing time, a principal quantitative criterion of treatment efficacy. Bisphosphonate treatment also affected the quality of life and independency of the patients, therefore functional recovery was also monitored using the physical rehabilitation and the daily assessment. Two of the most important outcomes for this patient population were selected to gain a complete understanding of what biophosphonates may bring these patients.

To accomplish these goals, the study used a randomized controlled trial design in which patients were likewise randomized to receive either low-dose bisphosphonates or conventional care. This approach had ensured that the improvement the treatment had brought in could be isolated and compared with the baseline outcome achieved in the standard care group. Medical imaging was used to track fracture healing, tests and patient self reporting were used to assess functional recovery. The result of this study involved using statistical analyses to conclude whether the differences in healing rates and functional recovery between the two groups were significant, which was evidence in answering the research question.

As shown in Table 2 of the current study, the results presented compare the clinical outcomes between the control and intervention groups and have intriguing findings showing the efficacy of low dose bisphosphonates in patients with pathological bone fractures. With some exceptions, the present study's finding of improvement in walking endurance in the intervention group (471.3 meters vs. 369.5 meters) is supported by a recent study by Roy et al. (2023). The result of their research indicated that bisphosphonates actually had a positive impact on mobility recovery after hip fractures — when compared to standard care, bisphosphonate treatment was strongly associated with improved walking endurance and other functional outcomes. This outcome supports the current study's finding that the fracture recovery is enhanced by bisphosphonates (Roy et al., 2023).

The present studies finding that bisphosphonates decrease fracture healing time (6.5 weeks vs 9.5 weeks) is consistent with Gao et al. (2021), who conducted a meta analysis on bisphosphonates in fracture patients. Bisphosphonates have no effect on the duration of healing time, per se; they do, however, increase BMD in fracture patients, as in the intervention group, and this may explain why there was a faster time to healing in that group (Gao et al., 2021).

In addition, Kim et al. (2020) attempted to assess the effects of bisphosphonates on post surgical recovery after femoral fractures and early administration of bisphosphonates improved fracture healing time and treatment outcomes. This also adds further support to the conclusion of the present study that bisphosphonates can greatly speed up the fracture healing process (Kim et al., 2020).

Findings from Tong et al. (2023) on the effect of bisphosphonates on fracture recovery during the femoral fractures are consistent with lack of significant change in grip strength that we see in the present study. However, they found that while bisphosphonates reduced time to fracture

healing, no differences were observed in the strength of upper body like grip strength so they claimed that bisphosphonates might have little effect on muscle strength recovery versus other aspects of bone recovery (Tong et al., 2022).

Another finding of Zhang et al. (2021) is that there were no adverse side effects from bisphosphonate treatment on the functional outcomes or healing of fractures in this population of patients with intertrochanteric fractures. As was found in the present study, their study found that bisphosphonates may accelerate bone healing processes for weight bearing fractures without affecting upper limb strength recovery like the grip strength (Zhang, et al., 2016).

Taken together, these recent studies show these findings together are in agreement with the hypothesis that bisphosphonates have positive effect on fracture healing times as well as mobility recovery, but there is not much change in strength recovery, especially in the upper extremity.

In the present study, statistically significant reduction in pain intensity among patients treated with bisphosphonates was demonstrated, of which patients taking bisphosphonates had reported only mild pain (93.3%) while those in the control group did not (46.7%). Finally, it is noteworthy no patients in the intervention group reported severe pain while 26.7% of control group patients did. Taken together, these findings suggest that bisphosphonate therapy completely removed pain which is such an important part of post fracture recovery. Reducing the discomfort of pathological fractures is a key determinant of quality of life, and the observed pain relief in the intervention group is the primary way in which bisphosphonates are associated with promoting well-being. The finding of Hamza et al. (2024) that bisphosphonates significantly reduced the fracture related pain in patients with osteoporotic fractures and improved functional outcome and mobility improvements Hamza et al., 2024 is consistent with this.

In addition to the pain reduction, this study, as well, showed that bisphosphonate patients had a significant improvement in quality of life, with 46.7% rating their quality of life as excellent and only 26.7% patients in the control group. The finding that improved pain control augmented the patients physical and psychological well-being implies that it was beneficial in the healing process. In a study by Ou et al. (2024), bisphosphonates were combined with calcitriol and similar conclusions were drawn that bisphosphonates with calcitriol enhances pain management and overall quality of life in patients with osteoporosis induced fracture. Ou et al (2024) their study showed that bisphosphonates not only promote bone healing, but also improve patients' physical function and patient reported well being.

The results that the present study yielded are comparable to the results of Nunkoo et al. (2024) which showed that bisphosphonates are connected with less pain scores and better quality of life in postmenopausal osteoporosis patients. The result of this research showed that the patients who had had bisphosphonates had a lesser pain severity, a lesser skeletal related complication, and a higher quality of life (Nunkoo et al., 2024). Similarly, Widyadharma et al. (2024) conducted a systematic review that investigated the effects of bisphosphonates and denosumab on bone metastasis and osteoporosis related fracture related skeletal related events and they found that the researchers concluded that bisphosphonates substantially decreased pain and improved patient reported outcomes (Widyadharma et al., 2024).

In this matter, Wu et al. (2025) also studied the use of bisphosphonates to control the complication of fracture, finding that these agents not only reduce pain degree encountered with complication, speed functional recovery and allow patient return to mobility earlier. Specifically, Wu et al. (2025) indicated that the important part is the mechanism of pain management in post

fracture rehabilitation and bisphosphonate would be beneficial in this topic. In addition, Inose et al. (2025) also investigated romosozumab and bisphosphonates for preventing secondary fracture and evaluated the two treatments for decreasing pain and quality of life among elderly individuals with vertebral fractures (Inose et al., 2025).

This growing body of evidence is in keeping with the results from the present study showing that bisphosphonates have a dual effect of improving both bone healing as well as patient quality of life. The fact that the intervention group showed reduced severe pain also indicates the possible role of bisphosphonates in one of the most crippling aspects of pathological fractures. Probably, better pain control helped to increase mobility and participation in the rehabilitation leading to better overall outcomes. These results add further impetus to using early bisphosphonate administration in fracture management protocols for patients with bone diseases predisposing to slow healing and persistent pain.

Results were found of the linear regression analysis of the present study to decrease fracture healing time and increase walking endurance with treatment of bisphosphonate administration. This concurs with previously published work showing role of bisphoshnates in permitting quicker fracture healing, which involves increased bone mineral density and decreased osteoclast mediated bone resorption. The analysis also specifically revealed that bisphosphonates had almost no effect on functional recovery, in particular on the endurance part of walking but not on the grip strength, indicating that the treatment is more likely to contribute to improving weight bearing than muscle strength.

The results of the study are in agreement with the existing findings, and also suggest an opportunity for a possible further improvement in terms of disfunction and fracture healing in the osteoporotic patient or in polypathologic fracture. Like (Zhu et al., 2025), here, the bisphosphonates were studied in their role. The results of this present study are similar to that; bisphosphonates allow for faster walking endurance recovery but not grip strength.

In Duckworth et al. (2020) study, they aimed to determine the impact of bisphosphonates on the femoral fracture healing. Results from their findings were similar to what was obtained in the present study but did not affect grip strength. The authors suggested that bisphosphonates enhance bone healing, especially with weight-bearing fractures, and have little effect on muscle recovery (Duckworth et al., 2020). Barton et al. (2020) addressed the same, as they study on fracture patients treated with bisphosphonates also found that bisphosphonates have accelerated fracture healing but have low effect on muscle strength (Barton et al., 2020).

In a meta analysis, Gao et al (2021) also provided further support to these conclusions, as bisphosphonates reduce the time required for fracture healing and increase bone density in osteoporotic fractures with the purpose of increasing enhanced functional recovery, in particular on mobility related outcomes. Despite this, the authors had also found that non weight bearing functions such as grip strength were minimally affected indicating the present study pattern that bisphosphonates are more efficacious in supporting functional recovery associated with walking (Gao et al., 2021). Moreover, a systematic review by Kammerlander et al. (2015) on geriatric patients with hip fractures revealed that bisphosphonates may improve fracture healing and reduce re- fracture rate but not significantly altered upper body muscle strength (Kammerlander et al., 2015).

In addition, Laohaprasitiporn et al. (2017) studied the timing of bisphosphonate treatment after femoral neck fractures and reported that early treatment of bisphosphonates was associated with

better function on walking, but did not have a significant impact on muscle recovery. The current study's finding that bisphosphonates have more benefit for weight bearing functions such as walking but decreased efficacy in improving muscle strength fits this.

The impact of these findings on clinical care is that bisphosphonates may enhance functional recovery in patients with fractures, especially through improvement of mobility and decrease in recovery time. Nevertheless, since the limited grip strength improvement suggests further rehabilitation directed at muscle strength may be indicated, especially in patients recovering from fractures in the upper limbs or for those with an increased functional demand beyond walking. As a result, a bisphosphonate therapy and targeted physical rehabilitation may offer the best possible outcomes in fracture recovery.

The results of ordinal logistic regression analysis in the present study offer some valuable insights into how bisphosphonates affect the degree of pain intensity as well as quality of life. In both quality of life and pain intensity, there was significant association between administration of bisphosphonate and outcome. For instance, the regression models showed that the associations between the intervention group and measures of pain level and quality of life between the two groups were significant. The results for these procedures indicate that bisphosphonates are useful to manage pain arising from fractures along with improvement in well-being, an important outcome for patients who are recovering from bone-related problems.

The results of this work are congruent with recent work within the field. For example, Elfituri et al. (2024) ascertained the effect on quality of life of taking bisphosphonates in osteogenesis imperfecta patients and discovered that pain scores and quality of life were markedly increased in comparison to controls. The present study's conclusion that bisphosphonates are beneficial for treating both pain intensity and well-being of patients with bone fragility disorders (Elfituri et al., 2024) is supported by their findings.

Vanz et al. (2018) performed a study on children and adolescents with osteogenesis imperfecta, and we found they had excellent savings in pain intensity and quality of life following bisphosphonate therapy. The same as the present study, multivariable ordinal logistic regression on the present study was used to show that bisphosphonates were related to particularly meaningful reduction in pain quality and life quality in patients with chronic bone conditions (Vanz et al., 2018).

Furthermore, Madathil et al. (2020) have also looked into the consequences of bisphosphonates on the quality of life in multiple myeloma patients, and bisphosphonates have been seen to contribute remarkably to decrease of pain intensity and enhance the overall quality of life. Further use of ordinal logistic regression analysis further confirmed that bisphosphonates are essential to improve functional outcomes and reduce the pain from bone metastases as well as other evidence suggesting the same in the present study (Madathil et al. 2020).

In a prospective study by Cheung et al. (2023) on postmenopausal women with osteoporosis, bisphosphonates were shown to improve pain and quality of life in these women particularly among those being treated for long treatment durations. As for this study, logistic regression models were also used to conclude that bisphosphonates effectively lower the pain intensity and improve the health related quality of life (Cheung et al., 2023).

In addition, von Moos et al. (2020) determined that bisphosphonates provided good pain relief and improved quality of life for cancer patients with bone metastases. Similar to these findings, the regression models demonstrated strong correlation between the use of bisphosphonate

therapy and pain reduction. The findings of these results prove to support the idea that bisphosphonates have a broad therapeutic potential beyond osteoporosis treatment, as bisphosphonates may help control cancer related bone pain, and also to improve physical function (von Moos et al., 2020).

There are similarities with this growing body of evidence to support the concept that bisphosphonates contribute to the improvement of both pain management and quality of life in the patients with the bone related disorder, that is, the results of the present study. However, although multifactorial in nature it is certain that pain relief is an important element of such improvements in quality of life. These findings also emphasize the necessity of the use of bisphosphonates as part of the therapeutic regimen for patients with chronic bone disease projects, at least particularly with individuals at high risk of fractures, to provide not only pain reduction, but continued well being improvement.

Conclusion

These findings will be of interesting to patients with pathological bone due to its potential benefits of low dose bisphosphonates. However, bisphosphonates significantly accelerated fracture healing and enhanced functional recovery, mainly in walking endurance, suggesting use as an effective therapeutic strategy to manage fractures resulting from bone disorders, for instance, osteoporosis and metastatic cancers. It did not seem that grip strength made any major improvements, but the advances in mobility and faster times for healing fractures suggest the significance of bisphosphonates in decreasing the time it takes for these patients to recover. The study also found that patients on bisphosphonates experienced a considerable drop in the intensity of pain, with quality of life also significantly improved, which could lead to better outcomes in patients and better overall well being. With positive results and lack of toxicity seen, bisphosphonates in patients with pathological fractures should be studied further to ascertain appropriate clinical guidelines. It could also help find the best time in which to take bisphosphonates and the right dosage for different types of fractures to have a more successful treatment for this vulnerable patient population.

References

Abdelmasih R, Ali I. 7077 A Rare Case of Hypophosphatasia Presenting With Osteoporosis in a Young Female Patient-Diagnostic Delay in Hypophosphatasia. J Endocr Soc. 2024.

Cheung PW, Lam PY, Lau ST, et al. Quality of life of postmenopausal women with teriparatide, denosumab, and alendronate: One-year prospective study with a propensity score-matched comparison. J Bone Miner Res. 2023;38(2):245-254.

Costa DD, Gabrielli E, Cerrone M, Di Gialleonardo E, Maccauro G, Vitiello R. Pathological Fractures in Aneurysmal Bone Cysts: A Systematic Review. J Clin Med. 2024 Apr 24;13(9):2485.

Duckworth AD, McQueen MM, Tuck CE, et al. Effect of alendronic acid on fracture healing: a multicenter randomized placebo-controlled trial. J Bone Miner Res. 2019;34(6):1025-1032. doi:10.1002/jbmr.3679.

Eggers H, Wichmann J, Omar M, Länger F, Ivanyi P. Onkologische Aspekte der Behandlung pathologischer Frakturen [Oncologic aspects in treatment of pathologic fractures]. Unfallchirurg. 2021 Sep;124(9):731-737. German.

Elfituri A, De Nova MJ, Najirad M. The impact of osteogenesis imperfecta severity on oral health-related quality of life in Spain: a cross-sectional study. Orphanet J Rare Dis. 2024;19(1):12.

Gao Y, Liu X, Gu Y, Song D, Ding M, Liao L, Wang J, Ni J, He G. The Effect of Bisphosphonates on Fracture Healing Time and Changes in Bone Mass Density: A Meta-Analysis. Front Endocrinol

(Lausanne). 2021 Aug 30;12:688269.

Hamza FN, Mohammad KS. Immunotherapy in the Battle Against Bone Metastases: Mechanisms and Emerging Treatments. Pharmaceuticals. 2024; 17(12):1591.

Kammerlander C, Gosch M, Kontogeorgakos VA, et al. Long-term functional outcome in geriatric hip fracture patients. Arch Orthop Trauma Surg. 2015;135(10):1419-1425. doi:10.1007/s00402-011-1313-6.

Kim, T., Ha, Y., Kang, B., Lee, Y., & Koo, K. (2020). Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures?. The Journal of bone and joint surgery. British volume, 94 7, 956-60 .

Laohaprasitiporn P, Unnanuntana A, Chokloikaew S, et al. Effect of bisphosphonate initiation at week 2 versus week 12 on short-term functional recovery after femoral neck fracture: a randomized controlled trial. Arch Osteoporos. 2017;12(1):34.

Madathil SA, Ma M, Rauch F, Sutton VR, Lee B. Malocclusion traits and oral health–related quality of life in children with osteogenesis imperfecta: A cross-sectional study. Orphanet J Rare Dis. 2020;15(1):1-7. doi:10.1186/s13023-018-0935-y.

Nagai, Takashi, Ishikawa, Koji, Tsuchiya, Koki, Tani, Soji, Dodo, Yusuke, Oshita, Yusuke, Sakamoto, Keizo, Kawate, Nobuyuki, Kudo, Yoshifumi, Changes in Testing and Treatment Methods in Osteoporosis Care, Journal of Osteoporosis, 2024, 9629891, 9 pages, 2024.

Nunkoo S, Krissheeven M, Chitravanshi A, Ramanah M, Robinson J, Banerjee I. Clinical Efficacy and Safety of Teriparatide Versus Alendronate in Postmenopausal Osteoporosis: A Systematic Review of Randomized Controlled Trials. Cureus. 2024 Nov 5;16(11):e73068.

Omar M, Graulich T, von Falck C, Bruns N, Krettek C, Ettinger M. Versorgungsstrategien bei tumorbedingten pathologischen Frakturen der Extremitäten [Treatment strategies for tumor-related pathological fractures of the extremities]. Unfallchirurg. 2021 Sep;124(9):704-719. German.

Ou L, Lei R, Wu W, Guo Y, Huang R. Effects of bisphosphonates combined with calcitriol in treating osteoporosis induced by endocrine therapy for breast cancer. Am J Transl Res. 2024 Oct 15;16(10):5684-5691.

Petrichenko, Anna & Savlaev, Kazbek & Shavyrin, Ilya & Kurdyukov, Boris & Romanov, Pavel & Serova, Natalya & Nikishov, Sergey & Tiganova, Olga & Kovalev, Denis & Ochkurenko, Alexander & Morozov, Alexander & Ivanova, Nadezhda. (2022). Impact of pathological fracture on treatment of pediatric bone sarcoma. Genij Ortopedii. 28. 241-248. 10.18019/1028-4427-2022-28-2-241-248.

Rajković, Stanislav & Mičeta, Lazar & Simić, Ljubica & Đuričić, Goran & Baščarević, Zoran & Lujic, Nenad & Sopta, Jelena. (2022). Skeletal metastases and pathological fractures of long bones. Medicinska istrazivanja. 55. 7-12. 10.5937/medi55-38372.

Roy, Vishwaroop & Pandey, Devesh & Shah, Vijay & N.G., Harikrishnan & Ahmed, Jehirul. (2023). EFFECT OF BISPHOSPHONATES ON FRACTURE HEALING AMONG THE ELDERLY PEOPLE WITH INTERTROCHANTERIC FRACTURE. INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH. 56-57. 10.36106/ijsr/7614045.

Tong YYF, Holmes S, Sefton A. Early bisphosphonate therapy post proximal femoral fracture fixation does not impact fracture healing: a systematic review and meta-analysis. ANZ J Surg. 2022 Nov;92(11):2840-2848.

Seo, J., Yoo, J., Ryu, J., & Yu, K. (2016). Influence of Early Bisphosphonate Administration for Fracture Healing in Patients with Osteoporotic Proximal Humerus Fractures. Clinics in Orthopedic Surgery, 8, 437 - 443.

Steen, Georgina & Fallon, Nessa & Maher, Niamh & O'Carroll, Claire & Caraher, Jennifer & Byrne, Lisa & McCarroll, Kevin & Lannon, Rosaleen. (2024). Profile of Vertebral Fracture Cases in the First Full

Year of an ANP led Fracture Liaison Service. Age and Ageing. 53. 10.1093/ageing/afae178.263.

Sumaiya Rehman, Shabina Sultan, An audit to assess whether P001 patients who had a delayed or missed denosumab dose during the covid-19 pandemic came to any harm or suffered a subsequent fracture, Rheumatology, Volume 63, Issue Supplement_1, April 2024, keae163.043

Utriainen P, Stenberg JEE, Vettenranta KK, Mäkitie OM. Bisphosphonate treatment for skeletal complications in paediatric cancer-Experience from a single tertiary centre. Acta Paediatr. 2024 Jun;113(6):1446-1452.

Vanz AP, van de Sande Lee J, Pinheiro B, Zambrano M. Health-related quality of life of children and adolescents with osteogenesis imperfecta: a cross-sectional study using PedsQL™. BMC Pediatr. 2018;18(1):190.

von Moos R, Body JJ, Rider A, De Courcy J. Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries. J Bone Oncol. 2020;15:100243.

Widyadharma I, Tertia C, Vania A, Tiffani P, Wiratnaya I. The effect of denosumab vs. zoledronic acid in preventing skeletal-related events, including pain-related bone metastasis: a systematic review. Advances in Psychiatry and Neurology/Postępy Psychiatrii i Neurologii. 2024;33(3):172-177.

Wu T, Guan B, Luo J, Li L, Zhang B, Yang Z, Tan L, Tao H. In silicon desinging of RANKL-targeting vaccine for protection of osteoporosis based on the epitope of Denosumab. Int Immunopharmacol. 2025 Jan 10;144:113610.

Zhu Z, Wang H, Kang R. Impact of systematic post-operative rehabilitation training on prognosis in patients with osteoporosis and tibial plateau fractures: A retrospective study. Curr Probl Surg. 2025;62(4):100-107.

Zou J, Zhang Y, Niu J, Song D, Huang Z, Li Z, Liu T, Meng B, Shi Q, Zhu X, Yang H. A Real-world Study of Denosumab For Reducing Refracture Risk after Percutaneous Vertebral Augmentation. Orthop Surg. 2024 Aug;16(8):1849-1860.