Outcomes of Atypical Femur Fractures in Geriatric Patients Treated with Anabolic Osteoporotic Medications

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Abstract:

Research Question: In geriatric patients with osteoporosis experiencing an atypical femur fracture (associated with long-term use of anti-resorptive therapy), will standardized treatment including treatment with an intramedullary nail and a post-operative regimen of parathyroid hormone (PTH) analogs allow for fracture healing and improved bone density over time?

Background: Our retrospective study evaluated fracture healing and bone density after an atypical femur fracture in geriatric patients treated with a protocol of intramedullary nailing and a change of osteoporosis therapy to an anabolic osteoporosis medication (PTH analogs). Specifically, these medications included Forteo® (teriparatide) and Tymlos® (abaloparatide). The aim of our study is to use the large patient population suffering from osteoporosis who were followed up at a busy osteoporosis clinic, The Center for Osteoporosis and Bone Health (BHC) in Fort Worth and analyze outcomes of fracture healing and bone density to determine the efficacy of such medications. Currently, treatment with such medications for fracture healing is limited due to cost-effectiveness and lack of clear evidence. Conclusive evidence through a large study would provide further direction and treatment options for patients and physicians seeking nonsurgical and less invasive treatment options.

Materials and Methods: We retrospectively initially reviewed records of 133 patients with a femur fracture treated in the Texas Health Fort Worth (THFW) fracture database with an intramedullary nail from 2017 to 2021 and followed up at the BHC for osteoporosis. Records and radiographs were evaluated to determine atypical femur fractures (AFFs). Nine patients had AFFs and met criteria (mean age 77.1 years). Of the 9 patients studied, 9 were female. All

nine patients used oral bisphosphonate therapy before femur fracture, and all were prescribed a course of PTH analog therapy after surgical treatment with a femoral nail.

Results: The mean duration of follow up was 52 months. Patients were on anti-resorptive medications for an average duration of 9.4 years leading up to fracture (range, 3 to 18 years). Time to fracture-healing averaged 9 months (one patient [11%] underwent revision nailing prior to union) with all patients having a healed fracture during the course of PTH analog therapy for an average of 17.6 months (range, 8-24 months). The average T-scores improved over the course of treatment from an initial value of -0.986 to a repeat of -0.157. None had subsequent fractures.

Conclusion: In our study of 9 osteoporotic patients with AFFs, all fractures healed while on PTH analog therapy, T-scores improved, and no patients had subsequent fragility fractures on follow-up. This suggests that the implementation of a fracture-liaison service initiating PTH analog therapy plays an important role in fracture healing, combating delayed healing and non-union, improving bone density, and decreasing chance of subsequent fractures in osteoporotic patients.

<u>Research Question:</u>

In hospitalized geriatric patients (>60 years of age) experiencing osteoporotic atypical femur fractures, will treatment with parathyroid hormone (PTH) analogs allow for fracture healing and improved bone density over time? We predict that treatment with PTH analogs will

assist in healing and prevention of non-union while improving bone density and reducing the rate of subsequent fractures.

Introduction, significance, and rationale:

Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, or when the quality or structure of bone changes. This can lead to a decrease in bone strength that can increase the risk of fractures [1]. Based on 2005-2010 National Health and Nutrition Examination Survey (NHANES) data, an estimated 10.2 million adults 50 years and older in the United States have osteoporosis. This number is expected to increase by more than 30% between 2010 and 2030 [2]. It is estimated that by 2025 more than 3 million cases of osteoporotic fractures will occur annually, with an estimated cost of 25.3 billion dollars [3].

The management of fragility fractures is one of the major care gaps in osteoporosis in this country. Systematic literature reviews in the meta-analyses published between 2013 and 2018 found that fracture liaison services (FLS) were associated with increased treatment initiation and reduction of the rate of refracture [4]. The International Osteoporosis Foundation defines a FLS as “coordinator-based, secondary fracture prevention services implemented by health care systems for the treatment of osteoporotic patients”. They are designed to close the care gap for fracture patients, 80% of whom are not offered screening and treatment for osteoporosis. They are also used to enhance communication between health care providers by providing a care pathway for the treatment of fragility fracture patients. The FLS will ensure patients who present to an institution receive fracture risk assessment and treatment where

appropriate. It often comprises of a case worker, clinical nurse specialist, and a medically qualified practitioner (hospital doctor/primary care physician) [5]. Texas Health Resources Harris Methodist Fort Worth Hospital (THFW) implemented such a program in May of 2016.

THFW has partnered with The Center for Osteoporosis and Bone Health (BHC) in Fort Worth where the patients are referred for follow up. During their initial admission for osteoporotic fragility fractures, patients have a bone health consult. At the BHC there is a population of patients who have been treated with parathyroid hormone (PTH) analogs to aid in fracture healing. Parathyroid hormone is an 84 amino acid protein that is secreted by the parathyroid glands. It is released in response to low blood calcium levels. It binds to a G protein-coupled receptor on target cells in bone (osteoblasts) and stimulates them to resorb bone [6].

Traditionally, antiresorptive medications are first-line treatment for osteoporosis. These include bisphosphonates, denosumab, and selective estrogen receptor modulators. Of these, bisphosphonates are the most prescribed. In addition to pharmacologic therapy, adequate calcium and vitamin D supplementation in osteoporosis treatment is important. Other important interventions for bone health include regular weight bearing exercise, fall prevention, and risk factor modification such as avoidance of smoking and excessive alcohol intake [7]. Forteo® (teriparatide) and Tymlos® (abaloparatide) are FDA approved for the treatment of osteoporosis. Teriparatide (TPTD) is a truncated form of parathyroid hormone. Findings in studies with animals and human beings showed that intermittent exposure of bone to parathyroid hormone increased bone formation with smaller increases in bone resorption,

resulting in a net anabolic effect. It is FDA approved to reduce the risk of both vertebral and non-vertebral fractures [8]. Abaloparatide (APTD) is a synthetic peptide analog of the first 34 amino acids of the human parathyroid hormone-related peptide (PTHrP). Both abaloparatide and teriparatide interact with the parathyroid hormone receptor 1 (PTHR1) on osteoblasts to stimulate bone formation [9].

PTH analogs such as abaloparatide and teriparatide are being researched for their use as a nonsurgical solution in the treatment of patients who are experiencing femoral nonunion. Our research is based on the preliminary data of Collinge and Favela's article in 2016 where they reviewed basic science and animal studies that showed enhanced fracture healing with the use of teriparatide. They described that most osteoporosis drugs (e.g., bisphosphonates) increase bone density and resistance to fracture by inhibiting osteoclast activity. The lack of resorption may create a pathologic process where "old" bone is never recycled but retained as new bone is laid down. This may create paradoxical fragility of the treated bone which has been seen with prolonged use of bisphosphonates. Anabolic drugs like teriparatide work by increasing activity of both osteoblasts and osteoclasts. They suggested that the latter had a more "natural" effect on bone metabolism. Specific cases were presented supporting their points. They mentioned findings in other studies that intermittent doses preferentially stimulate osteoblast activity and result in a net increase of bone formation [10].

There have been case reports of the PTH analogues being used as a nonsurgical solution in the treatment of patients who are experiencing femoral nonunion. In 2012, Lee and colleagues reported of three cases in which patients who had suffered from femoral fractures due to traffic accidents were showing minimal or no signs of radiologic healing. In these cases,

teriparatide was used, and successful fracture union was reported with no adverse effects due to the use of the medication [11]. However, larger studies such as a 2016 randomized controlled trial of 161 patients treated with teriparatide did not find reduced frequencies of revision surgery or improved fracture healing at 12 months, compared to a placebo group [12].

Since those earlier reports and trials, there have been many more studies published. A 2017 retrospective review found teriparatide treatment in patients with atypical fracture may help in fracture healing, hip function, recovery, and pain relief. However, they did not find statistically significant bone union rates [13]. AFFs are stress or "insufficiency" fractures often complicated using bisphosphonates or other bone turnover inhibitors. While these drugs are beneficial for intact osteoporotic bone, they probably prevent a stress fracture from healing which thus progresses to a complete fracture[14]. A systematic review in May of 2020 found that teriparatide apart from reduces the risk of typical fragility fractures and that it may result in faster healing of surgically treated AFF [15]. Another systematic review in August of 2020 looked to answer the questions of whether teriparatide decreases fracture healing time and its alternative use for nonunion specifically of atypical femoral fractures. They reviewed 57 publications and concluded that teriparatide works to enhance fracture healing time and union of AFF [16]. There are case studies that support this too, however, prospective randomized controlled trials with larger patient populations are still lacking.

Therefore, based on the body of research, it is evident that further research is needed to determine the efficacy of PTH analog use in fracture healing. The aim of our study is to use the large patient population suffering from osteoporosis who were followed up at the BHC and analyze the outcomes to determine the efficacy of such medications. Currently, treatment with

such medications for fracture healing is limited due to cost-effectiveness and lack of clear evidence. Conclusive evidence through a large study would provide further direction and treatment options for patients and physicians seeking nonsurgical and less invasive treatment options.

Research Materials and Methods

Our study will be looking at the outcomes of geriatric patients (>60 years of age) with osteoporosis treated at a large community hospital and regional trauma center that has a robust bone health program. These patients are identified in hospital and evaluated and treated by the FLS while an inpatient if possible, or by outpatient referral to a free-standing focused bone health clinic. Many of these patients have been prescribed teriparatide or abaloparatide, which is just now evolving as a standard of care. This is a retrospective, descriptive study of geriatric patients treated for fractures at THFW Hospital by the FLS and followed as an outpatient by the BHC (928 Travis Ave #104, Fort Worth, TX 76104).

In our retrospective study, we selected subjects from the THFW trauma database from May 1, 2016, to December 31, 2021. Inclusion criteria for patients were persons >60 years of age admitted or in observation with a fracture of the axial skeleton. Patients with incomplete records, ≤60 years of age, with hand fractures only, or who were not seen by the FLS, or BHC admitted to THFW were excluded.

Data collected from these patients were obtained from hospital records or from the BHC and included:

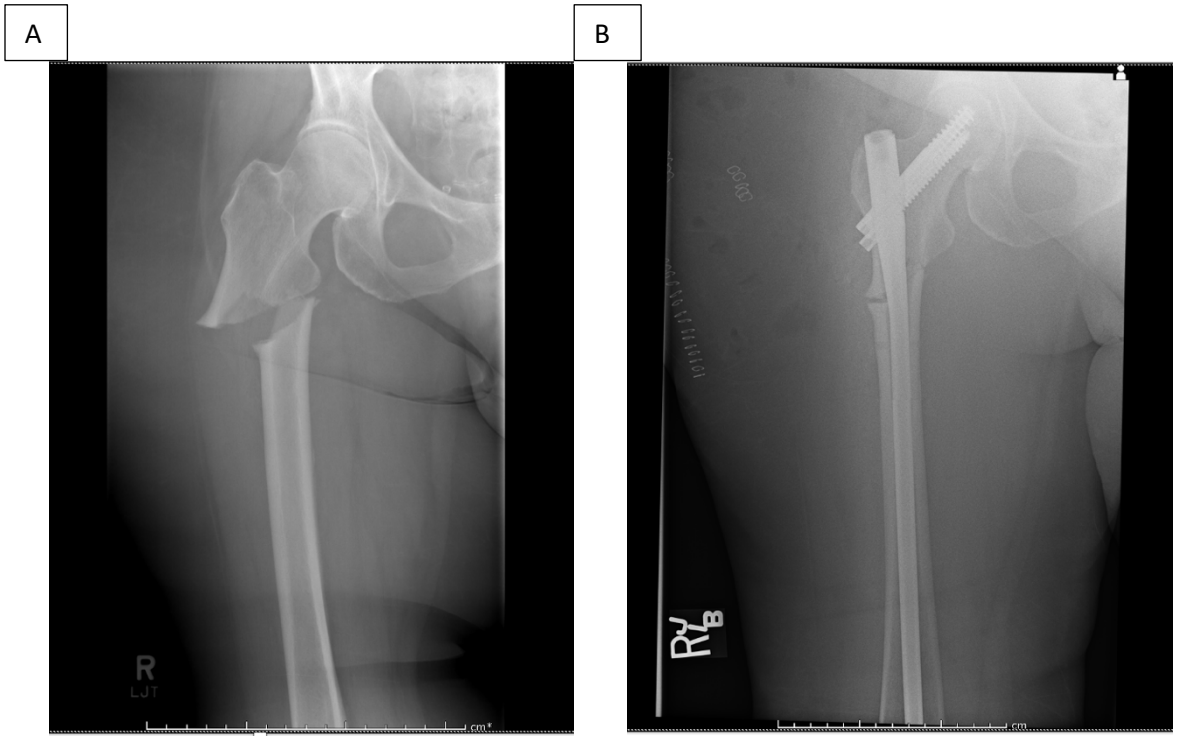
- Name
- ID
- Age
- Gender
- Admission date
- Orthopedic surgeon
- Diagnosis
- Weight and BMI
- Bisphosphonate use and duration
- Type of fracture and location
- Type of surgery
- Bone graft
- Whether the fracture is atypical or not
- Injury type
- Follow up and duration
- Healing information and date of healed
- Date of initial BHC visit
- Initial treatment and duration
- Post anabolic treatment
- DXA scores and interpretation
- T scores
- Level of service

- Previous history of osteoporosis
- Trabecular bone scores
- Initial and repeat vitamin D levels
- Vitamin D supplementation and duration
- Readmission from fractures
- Complications from medications
- Treatment failure

Waivers for consent were requested from patients and information from existing records were used.

Initially we had 2701 patients who were in the THFW trauma database and that was narrowed down to 133 total who had follow up at the BHC and were femur fractures. The 133 total femur fractures were then analyzed, and their x-rays read to determine which were atypical femur fractures. The key diagnostic features we looked for when determining if the fracture was atypical included: location in the subtrochanteric region and diaphysis; lack of trauma history and comminution; and a transverse or short oblique configuration [14]. All of these can be seen in a patient example (Fig 1).

Fig.1: Patient suffered a R subtrochanteric atypical femur fracture (A). Fixation with nail (B).



From there, we ended up with 19 atypical femur fractures with admission dates ranging from 2017 to 2021. Of those 19 fractures, 10 patients were excluded due to refusing medication, cost of medication, insurance denials, short duration of therapy, or no follow up. Two patients had bilateral femur fractures and were therefore included twice in the data, one for each fracture. Additional information regarding fracture healing for some patients was not available in the database and had to be obtained from other orthopedic surgeons offices. If the patients had been on bisphosphonates or anti-resorptive therapy beforehand, it was ceased after diagnosis and surgical intervention. During follow-up at the BHC, patient bone health was monitored with initial DXA scans and trabecular bone scores (TBS). These were compared with follow up routine imaging and compared to previous results to determine bone quality. During this time, vitamin D was routinely checked for patients too and they took over the counter

supplementation. Patients were started on either teriparatide at 20µg daily or Tymlos® abaloparatide at 80µg daily and followed up. Then after completion of therapy some were started on a post-anabolic treatment.

Outcome Measures

Postoperative assessment and radiographic outcomes

Patients were assessed postoperatively on whether they had any repeat fractures or further hospitalizations/revision surgeries. Additionally, their DXA and TBS scores were analyzed to see whether there was improvement or decline. The date of when the fracture was considered "healed" was based off the primary orthopedic surgeon's notes from x-rays during follow up visits. This was noted in addition to any additional information such as other surgeries, complications with healing, etc.

Statistical analysis

Since this was not a comparative study, no t-test was necessary. As a retrospective cohort study, means and ranges were calculated from the obtained data.

Results

A total of 9 AFFs were included in the study. Their demographic and pre-operative information is presented in **Table 1**. This includes an average age of 77.1 years (range 70-84), and all the subjects were women (100%). Average BMI was 28.20 kg/m^2 and all were diagnosed with osteoporotic fragility fractures on admission. All patients had a medical history of bisphosphonate use (100%), with the majority using alendronate (66.7%), then a combination

of alendronate/ibandronate/denosumab (22.2%), and least used was risendronate (11.1%). The average duration of bisphosphonate use prior to fracture was 9.36 years.All patients suffered from ground level falls, resulting in atypical femur fractures with 4 being subtrochanteric (44.4%) and 5 being shaft (55.6%) and all being surgically repaired with a nail.

We then collected data regarding patient treatment outcomes and follow up presented in **Table 2**. All patients followed up at the BHC for an average duration of 52 months (range 43-57) and all fractures had healed during their follow-up time, with a mean time-to healed being 9 months (range 5-20). All patients included started initial anabolic treatment with 4 receiving abaloparatide 80 mcg daily (44.4%) and 5 receiving teriparatide 20 mcg daily (55.6%). The average duration of treatment was 17.64 months (range 8-24). All patients received post-anabolic treatment with medications including fosteum (2 patients, 22.2%), zoledronic acid (1 patient, 11.1%), and denosumab (6 patients, 66.7%). These patients had an initial average T score of -0.986 and repeat average score of -0.157 with all seeing an improvement in their T score and bone density. All patients also had trabecular bone scores with the average initial score being 1.321 and a repeat of 1.329, demonstrating a slight improvement. Of these patients, 71.4% had improvements in their trabecular bone scores, 14.2% had their scores remain stable, while 14.2% had slight declines in their score. Vitamin d levels were measured during hospitalization and routinely on follow up, average initial levels were 44.564 ng/mL (range 26.1-67), and average repeat levels were 74.973 (range 26.6-95) with an average duration of supplementation being 3.43 years. Of these patients, none reported subsequent fragility fractures during the follow up period at the BHC.

Table 1

Preoperative Patient Demographics

Variables	Values
Number of fracture patients (n)	9
Female (n, %)	9 (100.0)
Average age (yrs)	77.1 (70-84)
Average BMI (kg/m^2)	28.20
Medical history of bisphosphonate (n, %)	9 (100.0)
Alendronate only	6 (66.7)
Risendronate only	1 (11.1)
Combination (Alendronate/Ibandronate/Denosumab)	2 (22.2)
Duration of Bisphosphonate Therapy (yrs)	9.4 (3-18)
Injury type (%)	
Ground Level Fall	100.0
Fracture Type (%)	
Atypical Femur	100.0
Location (n, %)	
Subtrochanteric	4 (44.4)
Shaft	5 (55.6)
Surgery type (n, %)	
Nail	9 (100.0)

Table 2

Treatment Outcomes and Follow Up

Variables	Values
Percent Healed (%)	100.0
Average Time to Healed (mos)	9 (5-20)
Percent Follow Up at BHC	100.0
Average Follow Up Duration (mos)	52 (43-57)
Initial Anabolic Treatment? (Y/N, %)	Yes (100.0)
Initial Anabolic Medication (n, %)	
Abaloparatide 80 mcg daily	4 (44.4)
Teriparatide 20 mcg daily	5 (55.6)
Average Duration of Treatment (mos)	17.64 (8-24)
Post Anabolic Treatment (%)	100.0
Post Anabolic Medications (n, %)	
Fosteum	2 (22.2)
Zoledronic Acid	1 (11.1)
Denosumab	6 (66.7)
Average T Scores	
Initial	-0.986
Repeat	-0.157
Improve/Declined (%)	Improved (100.0)
Average Trabecular Bone Scores	
Initial	1.321
Repeat	1.329
Improved/Stable/Declined (%)	
Improved	71.4

Stable	14.2
Declined	14.2
Vitamin D Supplementation (Y/N, %)	Yes (100.0)
Average Vitamin D levels (ng/mL)	
Initial	44.564 (26.1-67)
Repeat	74.973 (26.6-95)
Duration of Supplementation (yrs)	3.43
Subsequent Fractures (Y/N, %)	No (100.0)

Discussion and Innovation

Per the American Academy of Orthopedic Surgeons, postoperative management of atypical femur fractures associated with bisphosphonate therapy requires coordinated care with an endocrinologist or metabolic bone specialist. They recommend discontinuation of bisphosphonate therapy at diagnosis, vitamin D level checks and supplementation, calcium supplementation, and initiation of teriparatide immediately postoperatively to increase bone turnover [17]. The fracture liaison service partnered with THFW did exactly that when they were consulted on patients during admission. As our results emphasize, factors such as good longitudinal follow up, early initiation of anabolic treatment with teriparatide or abaloparatide and continuation, vitamin D supplementation, and post anabolic treatment all contributed to improvement in all the patient's bone mineral density through improvement in each patient's repeat T scores, 100% rate of fracture healing, and no subsequent fragility fractures.

Our study has several limitations. First is the study design which was retrospective cohort study of fracture patients who got a bone health consult and were seen by the fracture

liaison service. We did not have a control group to compare to, such as patients who did not receive anabolic treatment, therefore having such a comparator would have made the study stronger. A prospective randomized controlled trial would be ideal; however, atypical femur fractures are uncommon. Additionally, our sample size of 9 fractures is small, however, many of the studies have similar sample sizes, with the largest being 58 patients with follow up for > 1 year [18]. Initially we had narrowed our database down to 19 atypical femoral fractures to review. However, a few factors led to exclusion of 10 cases. These included patients not showing for follow-up, moving out of state or to other cities, refusing anabolic medications due to high insurance copays, and one refusing due to a known medication contraindication to treatment from a history of ionizing radiation [19].

Since the FDA approval of teriparatide in 2002, there have been many additional studies in PTH analogues and their additional uses and benefits. Since FDA approval, in November 2020 the FDA approved changes to the label for teriparatide, removing the 2-year lifetime treatment limitation. With these labeling changes however, it is still unclear how long to continue teriparatide beyond 2 years. There are recommendations to continue treatment if P1NP levels remain appropriately elevated. P1NP stands for bone formation marker pro-collagen type 1 N-terminal propeptide and it is a marker for new bone formation. Additionally, it can be continued longer than the 2-year initial limit if the patient has not had any new vertebral compression fractures [20].

Based on the meta-analysis of 57 publications related to teriparatide and abaloparatide, there were questions related to teriparatide decreasing fracture healing time, use as an alternative for nonunion, and its role in aiding the union of AFF's. Both short-term daily and

intermittent teriparatide administration have been found to speed up fracture healing recover time in osteoporotic patients, but an optimal and standard dose or duration is unknown. Data analyzed in this study showed the use of teriparatide can improve healing of nonunion. In terms of teriparatide use with atypical femur fractures, they concluded that strong evidence is lacking and recommended further RCTs for further evaluation. [16]. It is evident from the body of data that more research is needed regarding duration of therapy and dosing. This is where our study can shed light in this topic as our partnership with the BHC has provided us with a large patient pool treated with teriparatide and abaloparatide to answer many of these questions in further investigations.

Future Directions

With a patient database of almost 3000 patients and one that is rapidly growing since THFW has a large population of fracture patients each year, we have many future directions to focus on. Specifically, through the partnership with the BHC, there are patients who present from other hospitals and providers as well. A multicenter study would help in having a larger sample size of atypical femur fractures. Since the FLS began, there is about 7 years of data available and further following that longitudinally can present additional studies looking at the long-term effects of PTH analogs in osteoporotic patients.

With the large database of fractures, future studies can also look at other vertebral and nonvertebral fractures. Additionally, our study did not investigate glucocorticoid-induced osteoporosis and the effects of PTH analogs in that patient population could be another interesting study as well. During the study, we ran into many patients who stopped anabolic

treatment due to out-of-pocket costs. A further study could be a cost-effectiveness analysis where the cost of running a FLS (staffing, office space, DXA scanners and imaging, and treatment costs) is compared against the annual direct medical cost of osteoporosis related fractures. A 2018 systematic review in *Osteoporosis International* ran a simulation model based on costs in the United States and found that for every 10,000 hip fracture patients aged 65 and older, a nurse practitioner led FLS prevented 153 fractures and saved an overall amount of $66,879 USD [21]. A further study could be a cost-effective analysis where we get more detail about the average expenses patients had on the medications and how those costs add up in the long-term as compared to conventional treatment.

Finally, we have an extensive database of patients treated with teriparatide and abaloparatide. A future study comparing the two medications would yield useful information for clinicians and patients alike when it comes to fracture healing. A 2015 double-blind placebo-controlled trial examined the effects of abaloparatide on bone mineral density in postmenopausal women with osteoporosis. It concluded that abaloparatide induced robust increases in BMD at the total hip and that was greater than placebo and teriparatide, in addition to the hip and femoral neck. In their study they used 20, 40, and 80µg daily doses of abaloparatide compared to the marketed 20µg daily dose of teriparatide. They found that at the hip, 40µg and 80µg of abaloparatide increases BMD more than the currently marketed 20µg dose of teriparatide [22]. However, no human trials have looked at abaloparatide vs. teriparatide's effects on fracture healing. A 2018 study looked at mouse models in which fracture healing was assessed with the suggested (4:1) dose effect between abaloparatide and teriparatide found in the 2015 study previously mentioned. They found the potency per µg of

abaloparatide to be 2.5 times that of teriparatide and that changing drug from teriparatide to abaloparatide, regardless of dose, increased bone density but not to an amount that was statistically significant [23].

Conclusion

In our study of 9 osteoporotic patients with AFFs, 100% of fractures healed while on PTH analog therapy and no patients had subsequent fragility fractures on follow-up. This suggests that the implementation of a fracture-liaison service initiating PTH analog therapy plays an important role in fracture healing, combating delayed healing and non-union, improving bone density, and decreasing chance of subsequent fractures in osteoporotic patients.

Compliance

The project was approved by the IRB at THFW. Since it was a retrospective study and existing medical records were used, subjects were not asked to consent to participation. There is no more than minimal risk to the subjects, the main potential one being the release of PHI to unauthorized individuals. The retrospective chart review did not involve any direct patient contact and was strictly data and outcome analysis. Subjects were not directly identified when discussing data and data was email using encryption on password protected computers. Verbal discussion of patient health information occurred only in private settings. Potential benefits of the study include a basis for intervention to prevent further fractures.

Procedures were used to maintain confidentiality and those included:

1. Study data stored on computer/emailed using encryption on password protected computers.
2. Primary investigator/study staff/co-investigators will have access to the data
3. Data is encrypted
4. All identifying information will be maintained for 10 years
5. Study data will be stored on computer/emailed using encryption and any computer with patient health information will be password protected. Verbal conversations concerning patient health information will only occur in private settings.
6. We will not be obtaining a HIPAA authorization from the subjects since the study is a retrospective cohort study.

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