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The effect of combined drug therapy in lateral fragility fractures of the femur: a prospective observational study

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Abstract. – OBJECTIVE: Due to a growing number of lateral fragility fractures, and their high economic and social impact, we evaluated the combined drug therapy effectiveness in lateral fragility femur fractures treated by intramedullary nailing surgery comparing the clinical and radiological results of two groups of patients.

PATIENTS AND METHODS: From May 2019 to March 2020, we carried out a prospective observational study comparing the results of patients with femoral lateral fractures treated by the same intramedullary nail (PFNA Synthes®) using Clodronic acid and Vitamin D (study group, 25 patients) compared to patients with the same fractures treated with Vitamin D alone (control group, 25 patients). The evaluations were based on bone biochemical markers (serum calcium level, serum phosphate level, parathyroid hormone, Vitamin D, serum C-terminal telopeptide), Visual Analogic Scale and HHS (Harris Hip Score) score, and femur densitometric views. In order to evaluate the femur neck mineral bone density (BMD), two areas have been identified on the Anterior-Posterior view: the Region of Interest (ROI)1 (under the head screw) and the ROI2 (above the femoral screw). The BMD has been calculated using femur densitometric views at T0 (1st day post-surgery) and at T1 (12 months later).

RESULTS: As far as the BMD average of ROI1 is concerned, we found a significant statistical increase at T1 in the study group (0.93±0.07 gr/cm²) *vs.* control group (0.88±0.08 gr/cm²), $p=0.04$. Both biochemical and densitometric values were statistically increased in the study group from T0 to T1 ($p<0.05$), while control group showed an improvement in the biochemical values only.

CONCLUSIONS: Thanks to a one year follow-up, we are able to demonstrate that the administration of an adequate drug therapy after surgery can lead to a better control of the bone remodeling and reabsorption process.

Key Words:
Fragility lateral femoral fractures, Bisphosphonates, Clodronic acid, Bone density, Roi.

Introduction

Fragility fractures of the proximal femur are continually increasing due to life expectancy rise and due to the functional needs of population. This type of trauma has a great impact on National Health Service (NHS) and therefore it has become the topic of several scientific articles and studies. In 2000s, women were involved in 2/3 of total cases. An increase of this kind of trauma of 89% in men and 69% in women has been estimated in 2025[1,2]. A 2019 paper underlines that in the last 17 years there has been an increase in the mortality rate of patients suffering from proximal femur fractures, especially men, because of hospitalization, co-morbidity[3] and other fractures[4]. The epidemiological relationship between fragility fractures and comorbidities has been underlined in the recent literature[5,6]. Also in this pandemic period, the incidence of femur fragility fractures and complications linked to these lesions have increased[7]. The main difference from the young population (<65 y.o.), where

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the synthesis used could also be removed[8], is the presence of osteoporosis, which gives negative results of osteosynthesis, reducing stability and the timescale of bone re-growth.

Usually, lateral femur fractures are treated with surgery. Several different drugs can be used to keep the bone metabolism in balance, and these drugs are usually used for osteoporotic disease, but they can be administered also after bone surgery and other situations. The most common drugs are Vitamin D and bisphosphonates. Bisphosphonates are a class of drugs that prevent the loss of bone density. They preferentially bind to calcium ions. The largest store of calcium in the human body is in bones, so bisphosphonates accumulate to a high concentration only in bones. Bisphosphonates, when in the bone tissue, attach and bind osteoclasts, where they disrupt intracellular enzymatic functions needed for bone resorption[9]. In April 2018, a review[10] about bisphosphonates and their role in osteoporotic people, especially in postmenopausal women was published. The review pointed out the relationship between the administration of long-term bisphosphonate and the increasing risk of atypical femur fractures (AFFs). Another important article underlined how bisphosphonates affect fracture healing: in animal models, bisphosphonate treatment is associated with a larger fracture callus, coincident with a delay in remodeling from primary woven bone to lamellar bone, but there is no delay in formation of the fracture callus. In humans, the use of bisphosphonate therapy after fracture does not appear to have a significant effect on fracture healing[11]. The effect of bisphosphonates and other drugs, such as Teriparatide and monoclonal antibody used in osteoporotic disease, is the topic of many scientific articles due to the importance of this kind of treatment and the incidence of osteoporosis in world population[12-14]. The aim of this work is to evaluate the effectiveness of using combined drug therapy in lateral fragility fractures of the femur, comparing the clinical and radiological results of two groups of patients. Both of them were treated by intramedullary nailing surgery, while Clodronic acid and Vitamin D were administered in the study group and Vitamin D in the control group. We were able to follow up the patients through densitometry exams of the femoral neck, as well as through functional question test and biochemical markers. In 1979, Gruen et al[15] described 7 areas ROI of femoral component in Dual Energy X-Ray Absorptiometry (DEXA) for the first time. In 2010, Cadossi et al[16], introduced the new periprosthetic area called ROI 8 and they discovered a direct connection between bone density and the position of the femoral component prosthesis using bone mineral densitometry. Furthermore, in 2014, Pesce et al[17] defined two areas (ROI1 and ROI2) for densitometry analysis, which are the first references in bibliography associated with femoral nail. We hypothesized a better clinical, biochemical and densitometric result in combined drug therapy patients. The aim of our paper is to confirm the efficacy of the densitometry exam in order to evaluate the early onset of bone healing in the group treated by Clodronic acid and Vitamin D.

Patients and Methods

Patients

This study was performed on a cohort of patients consecutively admitted to the Orthopedic and Traumatology Unit of Azienda Ospedaliero Universitaria Ospedali Riuniti, Foggia, Italy, from May 2019 to March 2020 with femoral lateral fractures treated by intramedullary nail. All enrolled patients gave their written informed consent to participate, according to the Declaration of Helsinki. The inclusion criteria were: (1) according to AO classification, all of the fractures were 31-A1, A2; (2) age between 60-85 years; (3) co-operative patients; (4) Body Mass Index (BMI) < 30 kg/m²; (5) patients treated by intramedullary nailing surgery (PFNA Synthes®); (6) Patients with osteoporosis disease if T-Score < -2.5.

The exclusion criteria were: (1) patients with heart, kidney, neurological diseases; (2) patients with metabolic and systemic diseases (rheumatoid arthritis, diabetes mellitus); (3) previous surgery or severe osteoarthritis of lower limbs; (4) specific drugs treatments, such as anticoagulants or psychiatric drugs. The interruption criteria were: (1) appearance of adverse reactions; (2) death of the patient; (3) institutionalization of the patient; (4) surgical revision and (5) failing of osteosynthesis in the follow-up period.

Study Design

The present study was performed following STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist for case series[18]. This was a prospective obser-

vational study approved by our Local Review Board (Prot. No. 143/C.E.) and registered at ClinicalTrials.gov (NCT05183308). From May 2019 to March 2020, we enrolled patients with femoral lateral fractures treated by intramedullary nail using Clodronic acid and Vitamin D (study group) compared to patients with the same fractures treated by Vitamin only (control group). The randomization criteria were applied using a predefined program (available at: http://www.randomization.com). We discharged the patients with different osteoporosis drug prescription. The Study group was treated with Clodronic acid 200 mg fl intramuscular (im) per day for a week after surgery and then 1 fl im per week for 12 months associated to Vitamin D 25,000 UI per 15 days for 12 months. The control group was treated only with Vitamin D at the same posology of the study group. Early Weight-bearing was allowed for both groups.

Intramedullary Nail

The PFNA nail Synthes® (Proximal Femoral Nail Antirotation), was used for every patient. It is an anatomic nail in Titanium available in 4 different sizes. In our study we used the same size (190 mm) for all groups. It has a medial-lateral angle on 6° that allows insertion at the tip of the great trochanter. The main characteristic is the spiral blade, which is responsible for preserving the cancellous bone, providing additional anchoring, which is especially important in osteoporotic bone. Moreover, the large surface and the increasing core diameter guarantee maximum compaction and optimal hold in bone. Compared with commonly-used screw system, it leads to a higher resistance and stability[19].

To evaluate the correct position of the head screw, using the fluoroscopy view, we measured the Tip Apex Distance (TAD), according to the Cleveland and Bosworth method[20]. The Authors found that The Tip Apex Distance had to range from 11 to 25 mm in order to decrease the risk of screw cut out[21]. For all patients the surgery was performed within 48 h after the injury. Under spinal anesthesia, we placed the patient on a traction bed, and we performed the reduction and the stabilization of the fracture with a nail in a dynamic configuration.

Outcome Measures

Biochemical and clinical evaluation of the patients were conducted. We recorded the bone biochemical markers (serum calcium level, serum phosphate level, PTH, Vitamin D, serum C-terminal telopeptide (CTX)) and clinical score VAS (Visual Analogic Scale) and HHS (Harris Hip Score). The C-terminal telopeptide is a telopeptide that can be used as a biomarker in the serum to measure the rate of bone turnover[22]. The test measures the presence and concentration of a crosslink peptide sequence of type I collagen, found in bones. This specific peptide sequence relates to bone turnover because it is the portion that is cleaved by osteoclasts during bone resorption, and its serum levels are therefore proportional to osteoclastic activity at the time the blood sample is drawn. Serum levels in healthy patients not taking bisphosphonates tends to hover above 300 pg/mL[23]. Research by Pesce et al[17] defined the two parts of the femoral neck: ROI1 (under the head screw) and ROI2 (above the femoral screw) on the Anterior-Posterior (AP) view. In our study we used the same areas in order to follow the changes of bone density using DEXA (Figure 1).

It can be useful in the study protocols to determine a patient's nonsurgical treatment response as well as evaluate a patient's risk of developing complications during healing following surgical intervention.

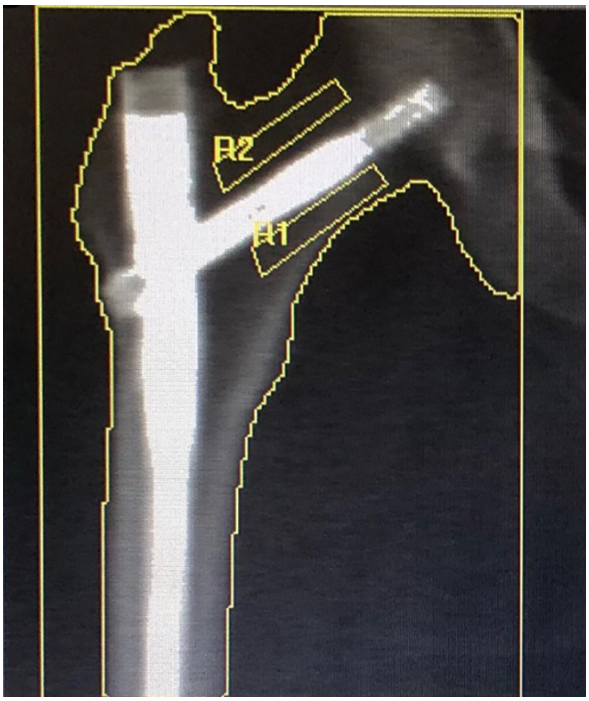

Figure 1. Division of the femoral neck in two parts (ROI1 under the head screw and ROI2 above the femoral screw) on the AP view.

Statistical Evaluation

We analyzed clinical, biochemical and densitometric values at T0 (1st day post-surgery) and at T1 (12 months later). For each patient, we completed a form reporting demographic data, date of surgery, densitometry value, VAS, HHS, and biochemical markers at the different time. These data were collected into a database using Microsoft Excel software and analyzed using Software SPSS 25.0 (IBM Corp., Armonk, NY, USA). Due to the non-homogeneous distribution of the values using Kolmogorov-Smirnov 's test ($p > 0.05$), except for ROI2 area in T1, we used non-parametric tests.

To compare the average value between the two groups at the same times, we used the Mann-Whitney U test for independent samples. To compare the average value within the same group at different times, we used the Wilcoxon's test for paired samples. For all tests, a *p*-value lower than 0.05 was considered to be statistically significant.

Results

We enrolled 50 patients (40 females and 10 males) with an age range between 60 and 85 years old. These patients were under our observation due to proximal femur fragility fractures who fitted the necessary criteria. The control group was composed by 25 patients (20 females and 5 males, average 75.9 ± 7.6 y.o.), while the study group was made up of 25 patients (20 females and 5 males, average 75.4 ± 8.4 y.o.). Both groups were made up by 20 females (80%) and 5 males (20%). The BMI of the study group was 23.8 ± 2.7 kg/m^2, while the BMI of the control group was 23.7 ± 1.7 kg/m^2. The femur injured in the study group was the right one in 48% of the cases (12 patients), while in 56% of the cases (14 patients) in the control group (Table I).

Table I. Epidemiological data of the study sample.

	Study group (n = 25)	Control group (n = 25)
Age	75.4 ± 8.4	75.9 ±7 .6
Gender (F)	20 (80%)	20 (80%)
BMI (kg/m^2)	23.8 ± 2.7	23.7 ± 1.7
Side of the trauma (Right)	12 (48%)	14 (56%)

Data are presented as mean ± standard deviation or number and percent unless stated otherwise.

At T0 (1st day post-surgery), we analyzed ROI 1, ROI 2, HHS, VAS, serum Vitamin D, serum calcium, serum phosphate, CTX both in the control group and in the study group. We compared the results using Mann-Whitney U test for independent samples (Table II).

At T0 the VAS was 5.16±1.67 in the study group and 6.28±1.61 in the control group (p=0.01) with statistical differences between the groups. There are no statistically significant differences for the other parameters between the groups.

At T1 (12 months after surgery), we analyzed same parameters both in the control group and in the study group. Statistical analysis was performed using Mann-Whitney U test for independent samples (Table III).

At T1, we revealed statistical differences between the study and the control group in ROI1 ($p < 0.05$). In fact, ROI1 bone density (under the head screw) in the study group was 0.93±0.07, while in the control group was 0.88±0.09 ($p < 0.05$). We were not able to evaluate CTX due to the difficulties in the test execution in the private laboratory. As far as other parameters, we did

Table II. Characteristics of sample at T0 (1st day after surgery).

	Study group	Control group	*p*-value
T0_HHS (score)	44.60 ± 9.83	47.56 ± 16.67	0.78
T0_VAS (score)	5.16 ± 1.67	6.28 ± 1.61	**0.01**
T0_PTH (pg/ml)	26.20 ± 7.27	23.58 ±6.01	0.09
T0_VITD (ng/ml)	22.54 ± 6.89	22.46 ± 7.09	0.82
T0_CALCIUM (mg/ml)	8.48 ± 0.50	8.55 ± 0.49	0.85
T0_PHOSPHATE (ng/ml)	2.67 ± 0.73	2.73 ± 0.65	0.73
T0_CTX (pg/ml)	0.34 ± 0.05	0.34 ± 0.02	0.80
T0_ROI2 (gr/cm^2)	0.71 ± 0.09	0.72 ± 0.09	0.58
T0_ROI1 (gr/cm^2)	0.88 ± 0.08	0.87 ± 0.07	0.64

Data are presented as mean ± standard deviation or number and percent unless stated otherwise.

Table III. Characteristics of sample at T1 (12 months after surgery).

	Study group	Control group	*p*-value
T1_HHS (score)	83.83 ± 7.62	84.55 ± 7.90	0.53
T1_VAS (score)	1.96 ± 1.02	2.12 ± 0.97	0.60
T1_PTH (pg/ml)	53.72 ± 16.80	50.62 ± 15.65	0.56
T1_VITD (ng/ml)	34.05 ± 9.70	31.92 ± 7.57	0.37
T1_CALCIUM (mg/ml)	9.50 ± 0.44	9.37 ± 0.42	0.33
T1_PHOSPHATE (ng/ml)	3.26 ± 0.36	3.28 ± 0.37	0.85
T1_ROI2 (gr/cm^2)	0.71 ± 0.09	0.72 ± 0.10	0.51
T1_ROI1 (gr/cm^2)	0.93± 0.07	0.88 ± 0.08	**0.04**

Data are presented as mean ± standard deviation or number and percent unless stated otherwise.

not find any significant statistical differences between the study group and the control group calculated at T1.

Using the Wilcoxon's test for paired samples, we analyzed the differences between T0 and T1 within each group (Table IV and V).

In the study group, if we examine the tendency from T0 to T1 (Table IV), a statistically significant improvements of all clinical scores, laboratory and ROI1 densitometric values emerged.

As far as HHS was concerned, it ranged from 44.60±9.84 at T0 to 86.84±7.63 at T1 ($p < 0.05$). For what concerned VAS, it ranged from 5.16±1.68 at T0 to 1.96±1.02 at T1 ($p < 0.05$). These values were associated to a better quality of life and a major autonomy of the patient. As far as laboratory values were concerned, a statistical improvement was registered. In fact, PTH value ranged from 26.20±7.27 at T0 to 53.72±16.80 at T1, Vitamin D from 22.54±6.89 at T0 to 34.05±9.70 at T1, Calcium value from 8.49±0.50 at T0 to 9.50±0.44 at T1 and Phosphate value from 2.68±0.74 at T0 to 3.26±0.36 at T1 ($p < 0.05$).

Therefore, comparing the tendency of bone density value from T0 to T1 in ROI1, we described a significant statistical improvement in

Table IV. Differences between T0 and T1 in the study group.

Study Group	T0	T1	*p*-value
HHS (score)	44.60 ± 9.84	86.84 ± 7.63	**< 0.05**
VAS (score)	5.16 ± 1.68	1.96 ± 1.02	**< 0.05**
PTH (pg/ml)	26.20 ± 7.27	53.72 ± 16.80	**< 0.05**
VITD (ng/ml)	22.54 ± 6.89	34.05 ± 9.70	**< 0.05**
CALCIUM (mg/ml)	8.49 ± 0.50	9.50 ± 0.44	**< 0.05**
PHOSPHATE (ng/ml)	2.68 ± 0.74	3.26 ± 0.36	**< 0.05**
ROI2 (gr/cm^2)	0.71 ± 0.09	0.71 ± 0.09	1.00
ROI1 (gr/cm^2)	0.88 ± 0.08	0.93 ± 0.07	**< 0.05**

Data are presented as mean ± standard deviation or number and percent unless stated otherwise.

Table V. Differences between T0 and T1 in the control group.

Study Group	T0	T1	*p*-value
HHS (score)	47.56 ± 16.67	84.55 ± 7.90	**< 0.05**
VAS (score)	6.28 ± 1.62	2.12 ± 0.97	**< 0.05**
PTH (pg/ml)	23.59 ± 6.01	50.62 ± 15.65	**< 0.05**
VITD (ng/ml)	22.46 ± 7.08	31.92 ± 7.57	**< 0.05**
CALCIUM (mg/ml)	8.55 ± 0.49	9.11 ± 0.41	**< 0.05**
PHOSPHATE (ng/ml)	2.73 ± 0.65	3.38 ± 0.42	**< 0.05**
ROI2 (gr/cm^2)	0.72 ± 0.10	0.72 ± 0.10	1.00
ROI1 (gr/cm^2)	0.87 ± 0.08	0.88 ± 0.08	0.52

Data are presented as mean ± standard deviation or number and percent unless stated otherwise.

the study group ranging from to 0.88±0.08 to 0.93±0.07 ($p < 0.05$); as far as ROI2 value was concerned, we did not report any significant statistical improvement ($p = 1.00$; Table IV).

In the control group (Table V), using the Wilcoxon's test for paired samples, analyzing the tendency of values from T0 to T1, a statistical improvement of clinical scores and laboratory values emerged. As far as HHS was concerned, it ranged from 47.56±16.67 to 84.55±7.90 ($p < 0.05$). As regarded the VAS score, we reported an improvement from 6.28±1.62 to 2.12±0.97 ($p < 0.05$). As far as laboratory values were concerned, a statistical improvement was also registered. In fact, PTH value ranged from 23.59±6.01 to 50.62±15.65 at T1, Vitamin D from 22.46±7.08 to 31.92±7.57at T1, Calcium value from 8.55±0.49 to 9.11±0.41 at T1 and Phosphate value from 2.73±0.65 to 3.38±0.42 at T1 ($p < 0.05$). Besides, comparing the tendency of ROI values from T0 to T1, we did not report any significant statistical difference neither in ROI1 (T0: 0.87±0.08; T1:0.88±0.08 p=0.52), nor in ROI2 (T0: 0.72±0.10; T1:0.72±0.10 p=1.00).

Studying the tendency of ROI1 values between the study group and the control group, we reported an increase from T0 to T1 (Figure 2).

If we evaluate the tendency of ROI2 from T0 to T1 between the study and the control group, we did not show any differences (Figure 3).

Discussion

Due to a growing number of lateral fragility fractures of the femur and their high social and economic costs, it is necessary to optimize the therapeutic strategy in order to improve the results and to reduce the complications of nailing in the fragility fractures[24,25]. In fact, the relationship between the risk of failure of osteosynthesis and bone stock is straight[26].

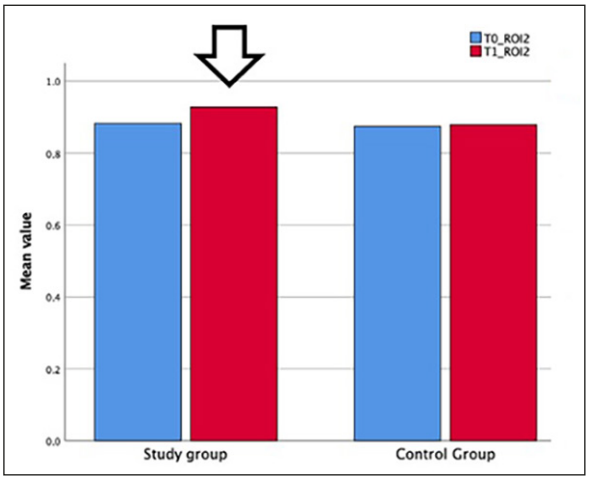

Figure 2. The tendency of ROI1 values of the two groups from T0 to T1.

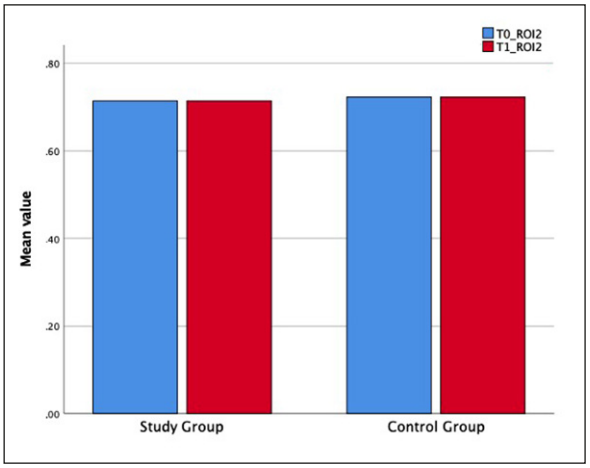

Figure 3. The tendency of ROI2 values of the two groups from T0 to T1.

Due to higher life expectancy in older patients and the higher risk of surgery failure, we focalized our attention on the relationship between the biological ad mechanical aspects in femur nailing. In our study, we observed the results of the Clodronic acid assumption and bone ingrowth near to cephalic screw, with aim to ensure a good stability of nail, to improve the bone quality and interface bone - implant reducing the risk of complications[27]. As regards osteoporotic bone, there is a higher risk of screw mobilization indeed. According to literature, Cavenago et al[28] in 2010 detected that the main complications of nails were caused by cephalic screw loosening (3.1%), diaphyseal fracture under the implant (5.3%) and nail rupture (1%). These authors identified relationship between the fracture, osteoporosis disease, the quality of reduction and the position of the cephalic screw. The bone trabecular density near the nail is able to guarantee a biological support for the nail and its reduction causes unstable bone implant interface.

Our study underlines the important role of the pharmacological treatment in order to reach a better result about bone healing. Many different drugs can be used, as for instance exogenous Calcium, Vitamin D, Bisphosphonates, Teriparatide and biological drugs such as monoclonal antibody. These drugs can have an important role

in the treatment of osteoporosis after surgery, in multiple myeloma[29], in breast cancer and in other diseases[30]. Most of them work as inhibitors of bone resorption and they lead to a secondary increment of the bone mass. With this work, our aim is to evaluate how combined therapy improve fracture healing in patients who already had an alteration of bone architecture due to the osteoporotic condition.

In our study the sample is homogeneous for age, gender and BMI, as reported in Table I. Furthermore, we did not observe any differences between the groups at T0, as reported in Table II, and this aspect confirms the value of statistic evaluation.

In April 2018, Dell and Greene[10] published a review about bisphosphonates and their role in osteoporotic people, especially in postmenopausal women. Author pointed out the relationship between the administration of long-term bisphosphonate and the increasing risk of atypical femur fractures (AFFs).

Kates and Ackert-Bicknell[11] described how bisphosphonates affect fracture healing. In animal models, bisphosphonate treatment is associated with a larger fracture callus, delay in remodeling from primary woven bone to lamellar bone, but there is no delay in formation of the fracture callus. In humans, the use of bisphosphonate therapy after fracture does not appear to have a significant effect on fracture healing.

The effect of bisphosphonates and other drugs (Teriparatide, monoclonal antibody) used in osteoporotic diseases is the topic of many scientific articles due to the importance of this kind of treatment and the incidence of osteoporosis in world population[12-14,31,32].

Thanks to our study, we have been able to underline the importance of the Clodronic acid administration in patients affected with femur fragility fractures treated using nailing. In fact, as reported in Table III at T1, we found a statistically significant increase in the BMD ROI1 area for the study group rather than control one. We could explain this through the bone remodeling due to the effectiveness of the administration of Clodronic Acid. Leighton et al[33] reported the results of murine study in which antiresorptive drugs after fracture were used to improve bone remodeling without a significant effect on periosteum healing. At the same time, the efficacy of Clodronic Acid in post-fracture edema in patients suffering from osteoporosis was an established therapy[34].

As for the study group we are able to reveal a statistical improvement of ROI1 bone density value from T0 to T1 (Table IV) underling the main role of the Clodronic acid administration per 1 year, whilst it was not significant in the control group (Table V).

Intramuscular administration of a therapeutic dose of Clodronic acid, followed by a maintenance dose, is effective in the management of symptomatic knee osteoarthritis, improving functional outcome and reducing pain and bone marrow edema[35]. As far as clinical and functional analysis was concerned, we did not report any statistical differences between the groups from T0 to T1. In view of the contradictory data respect to recent literature, we related these results to the subjectivity of VAS value and pre-existing hip osteoarthrosis, especially for the elderly.

Comparing the analysis of the data reported in Tables IV and V regarding the results for each group, an improvement of laboratory values within reference limits can be seen. We may underline that although both groups were treated with an equivalent dosage of Vitamin D, the average values at T0 and T1 were at limits of normal values. (Vitamin D sufficiency value 10-30 ng/ml).

This underlines the great importance of Vitamin D supplementation in elderly patients with femur fragility fracture who underwent femur nailing.

Pesce et al[17], in 2014, demonstrated the efficacy and reliability of the ROI areas evaluation to quantify the peri-implant loosening in patients treated by intramedullary nailing. Unfortunately, the evaluation of ROI areas is still little used in clinical practice.

As regards ROI2, we are not able to reveal a statistical improvement of bone density values from T0 to T1 between the groups (Table III) and within each group (Table IV-V). We asked ourselves a question: why did only ROI1 (under the head screw) present a statistically significant improvement in terms of bone mineral density increase between the groups? We could link to the anatomical and biomechanical characteristics of the proximal femur and to the identification of different trabecular systems divided into primary and secondary[32]. The trabecular organization is designed to resist the axial loads. In fact, there are several bibliographic references[36] that describe the distribution of axial loads on the femoral neck in experimental models (Figure 4). Cowin[37] reported a greater load on the calcar portion rather than the proximal femoral part, as well-known

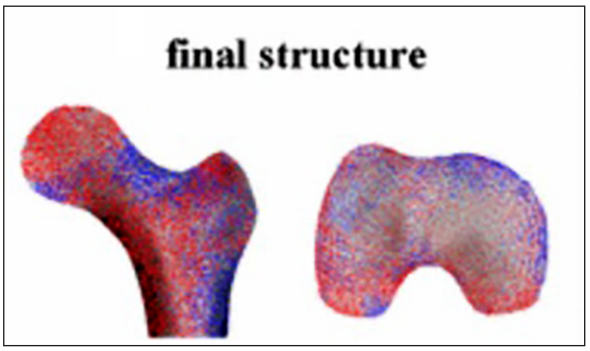

Figure 4. Geraldes et al[36] – The authors showed the distal part of the calcar is subjected to a greater axial load (*bright red*).

Wolff's law[37]. Therefore, reproducing the distribution of loads to the subdivision of the ROI areas in the study conducted, the major increase in the ROI1 area can be justified through the greater load in the distal calcar area and therefore, in accordance with Wolf's law.

Conclusions

The growing number of femur fragility fractures has determined a wide interest in the biological and mechanical augmentation. According to recent literature, the bone-implant interface play an important role in terms of primary results and risk of complications. Due to this interest, we conducted a prospective observational study on Clodronic acid that could influence the interface bone implant. In accordance with literature, we used a densitometric evaluation to follow the effects of Clodronic acid administration to bone density and ROI areas at 1 year after femur nailing.

In fact, studying our data, we have been able to report that the administration of an adequate antiresorptive drug therapy (Vitamin D in association with Clodronic acid) could increase the bone mineral density values. The improvement of ROI1 only is linked to the mechanical effect of the load distribution on calcar and biochemical effects of Clodronic acid. The data of these study support the efficacy of Clodronic acid in terms of biological reply on bone implant interface improving the bone mineral density in the ROI1 area. Thanks to one year of follow-up, we suggest considering the Clodronic acid as a possibility in order to increase the bone biological reply after the surgery. Further studies are needed in order to verify the biological reply in terms of incidence of complications and clinical results.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We would like to thank all participants who took part in this study.

Ethics approval

This was a prospective observational study approved by our Local Review Board (Prot. No. 143/C.E.) and registered at ClinicalTrials.gov (NCT05183308).

Informed Consent

All enrolled patients gave their written informed consent to participate, according to the Declaration of Helsinki.

Data Availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

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Authors' Contribution

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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