A combination of osteosynthesis in proximal femur fracture and contralateral femoral neck local osteo-enhancement procedure (LOEP) in severe osteoporotic bone loss

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ABSTRACT

Proximal femur fractures are among the main causes of mortality and morbidity worldwide in the elderly female population. Research efforts are currently focused on the development of a procedure that has immediate and long-term effectiveness, although pharmacological therapies are already capable of improving bone density and reducing the risk of fracture. A local bone enhancement procedure (LOEP) has been developed to facilitate bone augmentation. The procedure requires the preparation of an area of osteoporotic bone into which a triphasic, resorbable, calcium-based material is injected. Following the procedure, both the bone mineral density of the proximal femur and the bone resistance to compression and distraction forces acting on the femoral neck, which can cause fracture, are significantly improved.

Ten women suffering from severe osteoporosis and intertrochanteric fracture underwent preliminary investigations after application of a local bone-strengthening procedure involving the use of AGN1 and nailing of the contralateral proximal femur.

KEYWORDS

Proximal femur fracture, osteoporosis, local osteo-enhancement procedure (LOEP), proximal femoral nail (PFN).

Introduction

Due to the aging of the world's population and increasing morbidity and mortality rates, fragility hip fractures in the elderly have become a public health problem. 23 million men and women in the European Union are at high risk of osteoporosis fractures. This costs European healthcare systems more than 56 billion euros per year [1,2].

The incidence of fragility fractures increases exponentially from the age of 65 [3,4]. The impact of this situation has led to the development of a system aimed at reducing the probability of fragility fractures. Known as the "fracture liaison service" (FLS), it has been applied in 55 countries as a model for the management and monitoring of patients with fragility fractures, with the objective of identifying frail individuals and preventing further fractures [5-12].

The FLS identifies osteoporosis patients, reduces the time between a fracture and the most suitable therapy, and follows up the patient, ensuring therapeutic compliance. The FLS approach has been found to be beneficial both economically and in terms of identifying individuals at risk [13,16].

ESCEO/IOF intervention thresholds

The "European guidance for the diagnosis and management of osteoporosis in postmenopausal women", published with the help of the European Society for the Clinical and Economic Aspects of Osteoporosis (ESCEO) and the International Osteoporosis Foundation (IOF), considers the situation of women at risk of fragility fractures.

On the basis of the FRAX algorithm, capable of establishing the probability of serious osteoporosis-related fractures, intervention thresholds have been established. The combination of clinical risk factors (age, sex, BMI, previous osteoporosis fractures, smoking, family history, intake of corticosteroids, autoimmune arthritis, water consumption) with measurement of bone mineral density (BMD), to establish the risk of fracture after ten years, resulted in the identification of three risk categories (low, medium, high).

In 2020, Kanis et al. suggested an algorithm for the management of patients at risk of fracture using FRAX and including anamnestic variables. This allowed them to identify a new "very high risk" category for which the first-line treatment should be a bone-strengthening procedure [17].

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Osteoporosis management

Pharmacological therapies based on bone resorption inhibitors such as bisphosphonate and osteo-inducers such as teriparatide represent the first-line treatment for osteoporosis and are able to improve BMD and reduce the risk of fractures. The Horizon study evaluated the protective effects of zoledronic acid in people with previous hip fractures, demonstrating an increase in the BMD of the femoral neck (2.6% in 3 years), a clinically significant improvement, and a reduction in the incidence of hip fractures. The FREEDOM study demonstrated that taking denosumab resulted in a 40% reduction in the rate of hip fractures compared with placebo [18-22].

Pharmacological therapies reduce the incidence of proximal femur fracture by 50% but require on average 9 to 18 months for a clinically significant result to be achieved [23,24]. Furthermore, pharmacological treatment is started late, less than 35% of patients continue beyond a year, and the risk of a second fracture is significantly high in the months following the first, and remains high for many years [25-28].

Bone augmentation procedures

For the treatment of post-menopausal osteoporosis, the 2019 ESCEO/IOF guidelines include the local osteo-enhancement procedure (LOEP) [29]. Previous surgical methods for strengthening the femur involve the use of polymethyl methacrylate (PMMA). However, this material is inert and could determine an alteration in load transmission and an increase in stress, creating a risk of new injuries and compromising safe bone regeneration. Some studies have shown that use of PMMA leads to a 30% to 80% increase in the resistance of the femoral head; on the contrary, other studies have reported that PMMA has no effect on the biomechanical properties of bone. Furthermore, the application of PMMA involves an exothermic reaction at 29°C which could increase the risk of osteonecrosis. A possible worsening of osteoporosis and an increased risk of bone refracturing could occur due to the non-degradability and lack of bioactivity of PMMA [30-33]. The frail population subjected to the use of PMMA could be at risk of complications related to autologous bone harvesting, donor site morbidity, and wound healing times [34].

Research is currently focusing on the development of resorbable and bioactive materials. Most of the identified materials, including platelet-derived materials, autologous adipose stem cell-seeded scaffolds, and injectable nano-reinforced bone cement, have been tested in murine animal models [35-37].

AGN1 osteo-enhancement

A new triphasic calcium-based and resorbable material designed by AgNovos and called AGN1 was recently introduced on the market. Used to treat bone loss, it may provide an immediate biomechanical benefit. A study published in 2019 demonstrated that minimally invasive treatment with AGN1 can increase BMD in post-menopausal osteoporotic women (femoral neck T-score < -2.5 on DXA scan). New bone formation occurs in just 12 weeks after the resorption of AGN1, leading to an increase in femoral strength [38,39].

First Italian experience

In May 2022, ten osteoporotic women in their 80s underwent treatment with AGN1 LOEP following intertrochanteric femoral fracture. All were treated at the "FLS Center", Department of Orthopedics and Traumatology, "San Giuseppe Moscati" Hospital in Aversa (Italy). The treatment involved closed reduction and internal fixation with a proximal femoral nail (PFN) and, simultaneously, injection of AGN1 into the contralateral proximal femur. A preoperative DXA scan, to confirm that the unfractured femoral neck had a T-score < -2.5 standard deviations (Table I), and an X-ray to exclude osteonecrosis of the femoral head or a possible hip fracture, were performed [40-42].

Materials and methods

Inclusion criteria: women aged at least 65 years with intertrochanteric fractures (AO-OTA 31-A1) and a T-score at the contralateral femoral neck ≤ -2.5 standard deviations, as established by BMD testing [43,44].

Exclusion criteria: (i) pathological fractures (such as bone metastasis, primary bone tumor, and metabolic bone disease) or a history of oncological disease; (ii) history of previous fractures in the contralateral osteoporotic femur; (iii) severe arthritis or femoral head necrosis in the osteoporotic contralateral hip; (iv) intake of antiplatelet or anticoagulant drugs, which can preclude execution of the procedure under spinal anesthesia within 48 hours of hospitalization; (v) previous walking disabilities (e.g. neurological, musculoskeletal, or mental disorders); and (vi) a post-operative follow-up time of less than 1 year [45,46].

General data on the participants: A total of 10 women admitted to our hospital from May 2022 to October 2022 were selected for treatment of a femoral intertrochanteric fracture

Table 1 Patients' anthropometric measurements and DXA values.

PATIENTS	AGE	HEIGHT	WEIGHT	DXA VALUES (T-SCORE)
1	80	1.57 cm	55 kg	-2.5
2	82	1.63 cm	50 kg	-3.8
3	79	1.68 cm	60 kg	-2.7
4	84	1.54 cm	46 kg	-4.0
5	81	1.60 cm	60 kg	-3.2
6	86	1.65 cm	61 kg	-3.4
7	78	1.56 cm	46 kg	-3.8
8	82	1.56 cm	50 kg	-2.7
9	77	1.50 cm	45 kg	-2.8
10	88	1.55 cm	48 kg	-4.1

with PFN, and for treatment of contralateral femoral neck osteoporotic bone loss with AGN1 LOEP (Table I); their average age was 82 years. Before the operation, six patients had hypertension, four had diabetes, and three had general osteoarthritic disease. All the patients underwent a pre-operative cardiological evaluation in order to establish the presence of good cardiac function and eurythmy. All the patients underwent BMD testing in order to certify the presence of osteoporosis in the contralateral unfractured femur.

Surgical strategy and procedures: The double surgical procedure was performed within 48 hours following the patient's admission, in accordance with the literature [47-49].

After a spinal anesthesia, the patient was placed in a traction bed with the pelvis in a horizontal position. Under fluoroscopic control, traction reduction of the fracture was performed and an intramedullary PFN was placed to stabilize the extracapsular fracture line. Keeping the patient on the same fracture table, under the same anesthesia control, AGN1 LOEP at the contralateral femur was then performed by the same surgical team. A 1-cm skin incision was made to access the lateral femoral cortex just below the greater trochanter, and a 2.5-mm guide pin was inserted into the center of the femoral neck up to the apex under fluoroscopic guidance. A 5.3-mm cannulated drill was passed over the guide pin to the subcapital femoral epiphyseal scar to access the enhancement site. The augmentation site was gently debrided and irrigated with sterile saline, then suctioned to remove fat and other loose, non-structural components. The prepared AGN1 implant was injected starting from the top of the enhancement site using low pressure under fluoroscopic guidance to fill it. The mean volume injected was 19 ± 2 cc (Fig.1). An example of intraoperative sequence and 12 months follow-up is illustrated in Figure 2.

Figure 1 A rendering of the AGN1 injection procedure into the proximal femur. A 2.5-mm guide pin was inserted into the femoral neck (A), a 5.3-mm cannulated drill was inserted over the guide pin (B), the implant site was manually debrided to loosen fat and marrow (C), which was removed with irrigation and suction, and the implant material was injected into the proximal femur (D).

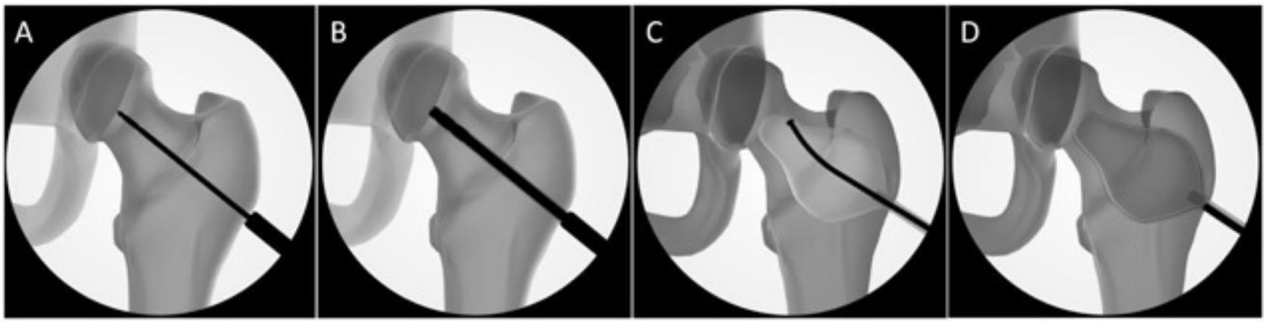
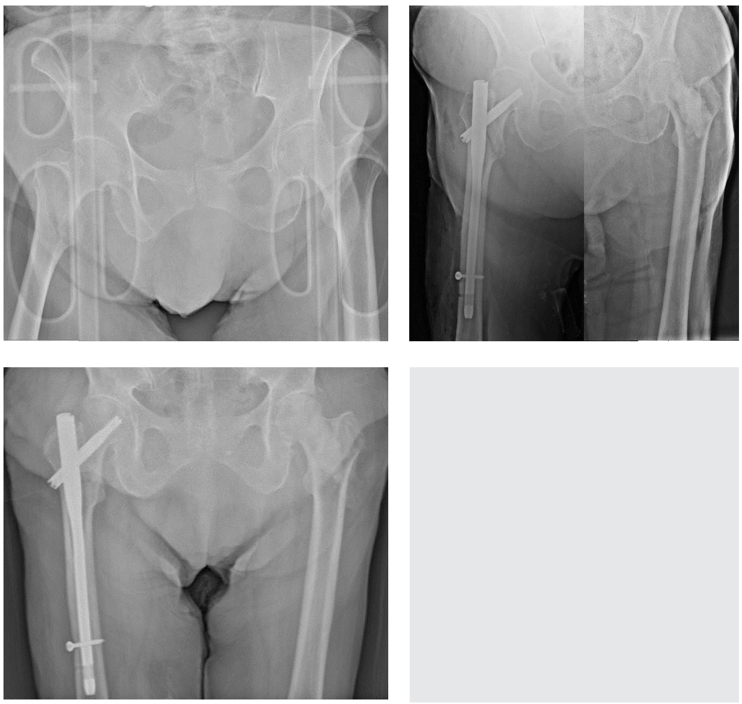


Figure 2 Sequential pre-operative (A), immediate post-operative (B), and 12 months post-AGN1 procedure (C) in an 80-year-old osteoporotic woman, whose femoral BMD T-score improved from -3.8 to 2.1 over a year (D).

A

B



C

D

Postoperative follow-up and data collection: After leaving the operating room, post-operative radiographic control was done on both hips. For the first two weeks, the patients were allowed to perform non-loaded activities like passive and active-assisted hip flexion and isotonic quadriceps contraction on both sides; then, progressive weight-bearing activity was started from the third week post-surgery. Within a year after surgery, we performed a regular outpatient review of each patient, and we reviewed both the healing of the fracture and the bone remodeling process of the enhanced femur through X-rays repeated at 1, 3, 6 and 12 months; we also checked the increase in strength of the AGN1-injected femur by repeating the DXA examination at 6 and 12 months after surgery.

The "Hip disability and Osteoarthritis Outcome Score" (HOOS) score was used, at 12 months of follow up, to evaluate postoperative recovery of hip joint function. To date, the HOOS system is the only functional hip scale officially validated in Italian. It evaluates five main aspects: pain, symptoms, activities of daily living, sports and recreational activities, quality of life [50,51]. A normalized score (100 indicating no symptoms and zero indicating extreme symptoms) was calculated for each subscale, as was the overall score which is the sum of the five domain scores, and ranges from 0 to 500. Higher scores indicate better hip function and quality of life.

Results

Hospitalization lasted on average 8 ± 1.5 days. Within the first 48 hours, four out of ten patients displayed anemia (hemoglobin level < 8 g/dl), which was corrected by hemotransfusion [52,53]. There were no severe complications (thromboembolism, infection, renal or cardiac dysfunction, pneumonia) or late complications (dislocation, peri-implant fracture, pseudarthrosis, necrosis of the femoral head), and no patient suffered fracture of the proximal extremity during the year of follow-up.

Fracture was already considered radiographically healed at 3 months after surgery. At 6 months post- surgery, the calcium-based injection was found to be completely resorbed and replaced by new bone; the remodeling process continued for 12 months until radiographic quality comparable to that of healthy bone was achieved.

Tests performed <6 months after surgery showed a significant increase in femoral neck BMD (from an average of 0.36 to 1.18 g/cm^2) and an improvement in Ward's triangle T-score (from an average of -3.2 to 3.9) (Table II). At 12 months DXA showed a femoral neck BMD of 1.07 g/cm^2 and an average T-score of 3.6. (Table II) All the patients did the HOOS survey. By providing standardized answers based on the 5-point Likert scale (none, mild, moderate, severe, extreme), they were able to express their opinions by assigning each item a score of between 0 (no problem) and 4 (extreme problems). At the end of the questionnaire, a standardized score was calculated using the following formula: 100 – [(patient's score of the subscale x 100)/(total score of the subscale)].

The results (Table III) show that the enhancement procedure did not cause any illness or disability and that the patients' overall quality of life was comparable to that before the hip fracture.

Table 2 Summary of DXA results.

AVERAGE AGE	AVERAGE BMD (G/cm^2)	CHANGE IN BMD (G/cm^2) VS. BASELINE	AVERAGE FEMORAL NECK BMD AT 12 MONTHS (G/cm^2)	AVERAGE T-SCORE BASELINE	CHANGE IN T-SCORE VS. BASELINE
82	0.360	1.18	1.07	-3,2	3,9

Table 3 Average HOOS subscale scores and total score.

HOOS SUBSCALES	AVERAGE SCORE AT 12 MONTHS
Symptoms	75 (60-90)
Pain	80 (60-92.5)
ADL	85 (65-92,5)
Sport/Rec	85 (68.75-93.75)
QoL	87.5 (81.25-100)
Total	412.5 (335-467.5)

Discussion

According to a study conducted by Howe et al., the application of AGN1 determines statistically significant and long-lasting improvements in both BMD and resistance to compression and distraction forces acting on the femoral neck, thus helping to prevent any fractures [29,38].

In a sample of 12 post-menopausal osteoporotic women, it was observed that application of this calcium material resulted in a significant increase in BMD after 12 weeks (68 ± 22%), followed by a rapid decrease in BMD at 24 weeks, linked to the resorption of AGN1 (59 ± 24%); finally, after 5-7 years, patients displayed gradual and better stabilization compared with previous controls (58 ± 27%).

The application of the LOEP procedure resulted in a significant increase in the strength of the treated femur compared with the contralateral femur as shown by the results of the follow ups performed at 12 weeks, 24 weeks, and 5-7 years (>36%).

Stroncek et al. conducted an *in vitro* study on 46 pairs of cadaveric femurs taken from osteoporotic post- menopausal women aged over 60 years. Randomly, one femur from each pair was treated with AGN1 and the other was placed in the control group.

X-ray examinations and mechanical tests were performed and the data obtained demonstrated the immediate improvement of the biomechanical and resistance properties in the treated femurs compared with the control ones:

- failure load was numerically higher in 88% in osteopenic and of 84% in osteoporotic treated femurs [53];
- higher work to failure in 69% of osteopenic and 80% of osteoporotic treated femurs [53].

In conclusion, both studies demonstrated that AGN1 LOEP is a surgical procedure capable of producing an immediate and long-term increase in the strength and resistance of treated femurs.

The results we obtained are comparable to those of the previously described studies, highlighting a significant increase in the protective effect against fragility fractures of the femur in osteoporotic women, with no disability occurrence, as shown by the HOOS results.

Nonetheless, a comparative cost-effectiveness analysis is needed in order to demonstrate the superiority of this procedure.

Conclusions

Medical research is focusing on the development of new procedures aimed at treating local osteoporosis-related bone loss in patients at high risk of fracture.

The data derived from the present study and from the scientific literature demonstrate that treatment with AGN1 LOEP, a minimally invasive surgical procedure involving the implantation of triphasic and resorbable calcium material in a bone area weakened by osteoporosis, leads to a reduction in the risk of fracture in the femurs of post-menopausal osteoporotic women, with immediate and long-lasting results. These findings provide the basis for further clinical investigations.

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