Addressing local bone loss in the proximal femurs of women at high risk of fracture

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ABSTRACT

Proximal femoral fractures in older women are a worldwide leading cause of morbidity and mortality and a public health problem. Although pharmacological therapies can improve bone mineral density (BMD) and reduce fracture risk, current efforts are focused on researching a procedure that guarantees both immediate and long-lasting effectiveness over time. The AGN1 local osteo-enhancement procedure is a recently developed bone augmentation procedure. This minimally-invasive surgical approach is used to prepare an enhancement site, the area where new bone is desired within a local bony region weakened by osteoporotic bone loss, and fill it with a triphasic, resorbable, calcium-based implant material. This procedure results in a notable, statistically significant and sustained long-term increase in proximal femur BMD and femoral strength, improving femoral neck resistance to compression and distraction forces acting on it and thereby preventing fall-related fractures.

KEYWORDS

Proximal femur fracture, osteoporosis, Fracture Liaison Service (FLS), Local Osteo-Enhancement Procedure (LOEP)

Introduction

Fragility fractures of the hip in the elderly are a public health problem because of both the increasing incidence of these lesions related to the aging of the population globally and the significant morbidity and mortality associated with them. Overall, more than 80,000 new femoral neck fractures due to osteoporosis are recorded annually in Italy, with a high prevalence in women (72%), generating a cost of over 800 million euros for hospital care alone. The incidence rate of these fractures increases exponentially from the age of 65 onwards, doubling approximately every five years of age and reaching values of over 4 out of 100 in women over 85. Furthermore, the mortality rate is estimated to be 5% to 10% at one month and 15% to 30% in the first-year post-fracture [1-3].

The impact of these data has enormously improved the standards of care of the elderly and has allowed the creation of a comprehensive pathway for patients, aimed at reducing the risk of fragility fracture recurrence. Globally adopted by over 50 Nations and known worldwide as the "Fracture Liaison Service" (FLS), this pathway is a multidisciplinary model of management and monitoring of patients with fragility fractures that recognizes the urgency of capturing in the "network" frail subjects who are possibly still at their first fracture ("Capture the Fracture"), with the aim of preventing further ones [4-12]. The FLS, led by a bone specialist who should coordinate activities between all the other medical figures involved, has the task of identifying and diagnosing patients with osteoporosis in order to reduce the "treatment gap", meaning the interval of time between a fragility fracture and the start of an appropriate osteoporotic therapy, as well as of evaluating, treating, and following up the patient with the aim of ensuring continued therapeutic compliance. The effectiveness and cost-effectiveness of the FLS, in systematically identifying men and women at risk of fragility fracture, have recently been established [13-19].

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ESCEO/IOF intervention thresholds

The recently published "European guidance for the diagnosis and management of postmenopausal osteoporosis in women", supported by the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the International Osteoporosis Foundation (IOF), has shaped an assessment strategy for the diagnosis and treatment of postmenopausal women at risk of fractures due to osteoporosis [1].

For decision-making purposes, intervention thresholds have been established on the basis of FRAX algorithm-derived probabilities of major osteoporotic fracture (of the spine, wrist or humerus) and hip fracture in postmenopausal women. The ten-year fracture risk assessment is arithmetically calculated by combining clinical risk factors (e.g., age, sex, body mass index, prior fragility fracture, family history of hip fracture, current tobacco smoking, any lifetime use of long-term oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, alcohol consumption) with bone mineral density (BMD)

measurement, and on this basis three risk categories (low, intermediate, high risk) have been outlined.

Although a BMD test might be appropriate, the guidelines recommend that women with a prior fragility fracture may be considered for intervention without the necessity for further risk assessment, since a prior fracture can be considered to carry a risk sufficient to warrant possible treatment. Furthermore, the intervention threshold in women without a prior fracture can be set at the age-specific fracture probability of women with a prior fragility fracture, and therefore rises with age.

A similar treatment scheme has been applied in Italy since 2015 when the Italian Medicines Agency (AIFA) developed "Nota 79" in order to regulate treatment reimbursement of osteoporosis medications, in consideration of fragility fracture risk stratification based on several factors like demographic and anthropometric data, femoral and/or lumbar spine BMD T-score, family and/or background history of previous femoral or vertebral fractures, pharmacological anamnestic data, and severe comorbidities [20].

In 2020 Kanis *et al*. proposed an algorithm for the management of patients at risk of osteoporotic fractures. Their first suggestion was to adjust the FRAX-based arithmetically calculated risk of fragility fractures by including simple anamnestic variables in the algorithm, and they finally outlined a new "very high risk" category in which the first-line treatment should be bone anabolic agents, possibly combined with local osteo-enhancement procedures [21].

Osteoporosis management

The first-line treatment in osteoporosis consists of pharmacological therapies that improve BMD and reduce fracture risk, and range from osteoinhibitors like bisphosphonates and denosumab to osteoinductors like teriparatide. The HORIZON Recurrent Fracture Trial studied the protective effect of zoledronic acid on femur fracture in those who had already suffered a hip fracture, and demonstrated a modest increase in femoral neck BMD (2.6% over 3 years), leading to a clinically meaningful and significant 30% decrease in the incidence of hip fracture. Similarly, the FREEDOM study showed denosumab to increase hip strength by 8.6% at 36 months, which corresponded to a hip fracture reduction of 40% compared with placebo [22-26].

However, while it is true that current pharmacological therapies can reduce hip fractures by up to 50%, these drugs have not been shown to reduce hip fracture risk during the early stages of therapy, taking from 9 to 18 months to significantly reduce the chance. Furthermore, the treatment is often started too late and less than 35% of patients continue with osteoporosis therapy at 1 year. In a patient with a recent hip fracture, the risk of a second contralateral one is significantly elevated in the months after the first event and remains elevated for years (9-20% risk after 5 years) [27]. It is important to specify that, according to the literature, well-defined areas of the proximal femur are at risk of rapid bone loss with aging, since they are relatively stress-shielded during walking and sitting. Focal osteoporosis in those areas may contribute to fracture, and targeted 3D measurements might enhance hip fracture prediction. Women with femoral neck fractures had large focal defects located within the superior neck, particularly at the head-neck junction, while women with trochanteric fractures lacked trabecular bone throughout the femur and also lacked cortical bone both in the lateral trochanter and superior femoral neck. Femoral neck and trochanteric hip fractures involve distinct patterns of focal osteoporosis [28-30].

Bone augmentation procedures

The 2019 ESCEO/IOF Guidelines include local osteo-enhancement procedures (LOEP) as a treatment option for postmenopausal osteoporosis [1,21,31].

Prior investigations on surgical approaches to strengthen the proximal femur included the use of polymethyl methacrylate (PMMA), PMMA-filled carbon sleeves, and prophylactic bioactive screws. However, these non-biological implants involve the permanent placement of inert materials that create a mismatch in elastic moduli with the surrounding bone, which may alter normal load-transmission pathways and result in stress risers to the point of risking additional fractures, apart from other biocompatibility issues, undermining the potential for consistent, safe, in vivo resorption and bone regeneration. Preclinical studies show 30-80% increases in proximal femur strength using PMMA, while others report no impact of PMMA on biomechanical properties of treated bone. The 29°C above baseline exothermic setting reaction, resulting from using PMMA to strengthen bone, increases the risk of thermal damage to surrounding tissues, i.e., osteonecrosis risk. Furthermore, the fact that PMMA shows non-degradability, residual monomer toxicity, and lack of bioactivity, leading to osteoporosis complications and bone re-fracturing, greatly impedes its translational use in bone defect treatment [32-35].

In case of autologous bone grafts, donor site morbidity, time to healing, and potential complications preclude their use in the frail osteoporotic population at risk of fractures [36].

Therefore, research in the field of bone augmentation procedures has focused on developing new resorbable osteoconductive materials characterized by bioactivity, washout properties, and controllable biodegradability, and intended for osteo-enhancement procedures in order to strengthen skeletal areas in osteoporotic people at the highest risk of fragility fracture.

The majority of these procedures have been tested only on murine animal models, including deproteinized bone added with VEGF gene transfer plasmid that provides bone regenerative effects through the enhancement of local angiogenesis, platelet-derived biomaterials endowed with bone healing properties thanks to the migratory ability of embryonic fibroblasts, autologous adipose-derived stem cell-seeded scaffolds that increase femoral strength and bone density in osteoporotic rats, and injectable nano-reinforced bone cement with controlled biodegradability and osteoconductive effect [37-40].

AGN1 osteo-enhancement

The latest product in commerce is a novel triphasic, calcium-based, resorbable osteoconductive material called AGN1,

designed by AgNovos to locally replace bone loss due to osteoporosis and provide immediate biomechanical benefit. The first in-human study of AGN1 LOEP was published in 2019, and demonstrated that this minimally invasive treatment durably increased BMD in femurs of postmenopausal osteoporotic women (femoral neck T-score < -2.5 by DXA scan). AGN1 resorption was coupled with new bone formation by 12 weeks and the new bone was maintained for 5-7 years, resulting in substantially increased femoral strength.

Treated femoral neck BMD underwent marked changes: an immediate dramatic increase due to calcium-based paste density (68 ± 22% at 12 weeks), followed by a period of rapid decrease as AGN1 resorbed (59 ± 24% at 24 weeks), and finally a gradually declining steady state that remained significantly greater than the control at the final time point (58 ± 27% at 5-7 years). Qualitative analysis of X-ray and CT scans demonstrated that AGN1 resorption and replacement with bone was nearly complete by 24 weeks and fully complete by 5-7 years (or else there was no residual AGN1 in the hip). Femoral strength was significantly higher in the treated femur compared with the control contralateral one at 12 weeks, 24 weeks, and 5-7 years (36% greater) following the LOEP procedure. No procedure or device-related serious adverse events have been recorded [41-43].

Italian experience and surgical procedure

At the "FLS Center", Department of Orthopedics and Traumatology, "San Giuseppe Moscati" Hospital in Aversa (Italy), the first experience with AGN1 LOEP was in June 2022 when two 80-year-old osteoporotic women, who had undergone fixation surgery for a right hip fracture three months earlier, had an AGN1 injection in their left proximal femurs. Both of them had undergone a pre-operative DXA scan, which demonstrated a left femoral neck T-score within osteoporotic range, and an X-ray exam in order to exclude left femoral head osteonecrosis or impending hip fracture.

AGN1 LOEP was performed with the patient positioned on a fracture table under anesthesia; a 1 cm skin incision was made to gain access to the proximal lateral femoral cortex just below the greater trochanter, and a 2.5 mm guide pin was inserted centrally to the apex of the femoral neck under fluoroscopic guidance. A 5.3 mm cannulated drill was advanced 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 and then aspirated to remove fat and other loose non-structural elements. The prepared AGN1 implant material was injected starting at the apex of the enhancement site using low pressure under fluoroscopic guidance to fill it. The average implant volume injected was 19 ± 2 cc (Figure 1).

Both the patients were clinically and radiographically monitored for the following 5 months while fully weight bearing; the cortical access portal was healed at 5 months, as shown by X-ray imaging, and no adverse events were recorded during the follow up. A DXA scan was repeated at 5 months after surgery, and showed a considerable increase in proximal femur BMD (this increased from 0.45 to 1.36 g/cm^2 in the first patient and from 0.28 to 1.01g/cm^2 in the second), with a corresponding improvement in the Ward triangle T-score (from -2.5 to 5.4 and from -3.8 to 2.4, respectively). Sequential pre-operative, immediate post-operative, and 5 months post-procedural X-rays were performed in order to verify the gradual remodeling of the injected calcium-based paste into bone and the progressive bone regeneration (Figure 2).

The findings of this case report suggest potential clinical utility of this new treatment in the worldwide fight against osteoporosis, and support what is already known in the scientific literature, namely that AGN1 LOEP results in notable, statistically significant and sustained long-term increases in proximal femur BMD and femoral strength, improving the femoral neck resistance to compression and distraction forces acting on it and thereby preventing fall-related fractures [31].

However, a comparative cost-benefit analysis should be conducted to state the superiority of this bone augmentation procedure over the others in reducing hip fracture risk.

Conclusions

The continuous medical fight against the "silent epidemic" of osteoporosis is moving towards the development of emerging treatments for local osteoporotic bone loss in patients at high risk of hip fracture.

Figure 1 A rendering of 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**) [42].

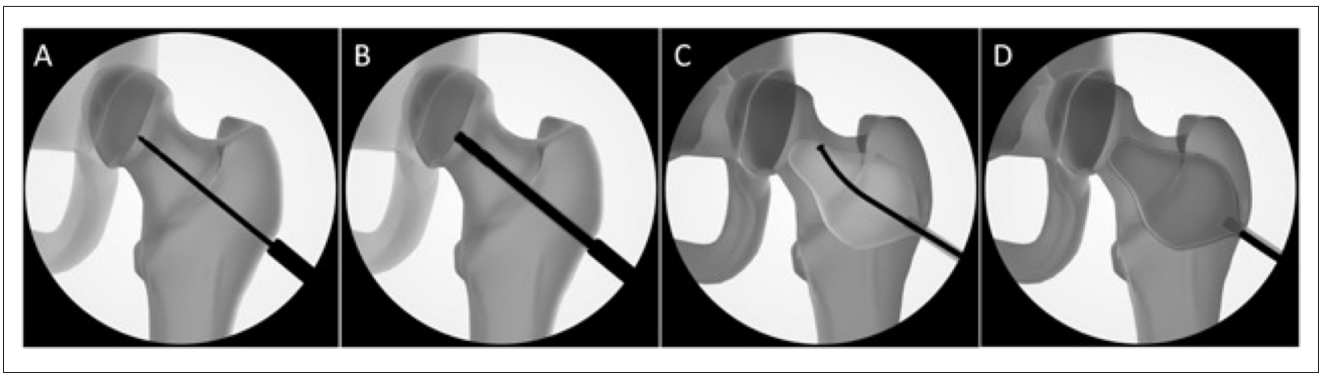
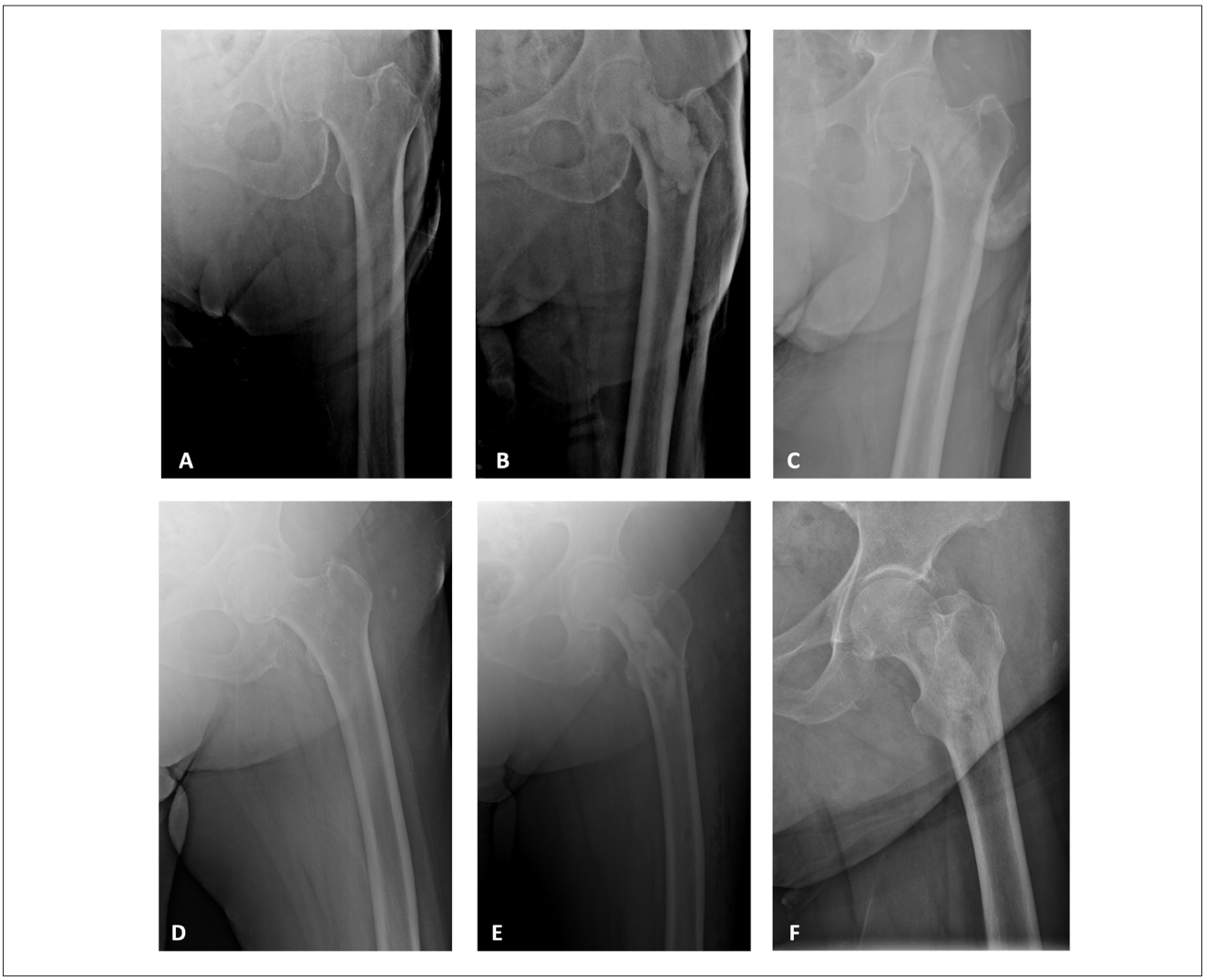


Figure 2 Sequential pre-operative (**A,D**), immediate post-operative (**B,E**), and 5 months post-AGN1 precedural (**C,F**) left hip X-rays in two 80-year-old osteoporotic women, whose Ward triangle BMD T-score improved from -2.5 to 5.4 (**A,B,C**) and from -3.8 to 2.4 (**D,E,F**), respectively.



AGN1 LOEP is a minimally-invasive surgical approach used to prepare an enhancement site, the area where new bone is desired within a local bony region weakened by osteoporotic bone loss, and to fill it with a triphasic, resorbable, calcium-based implant material. This approach involves a single treatment that provides immediate strengthening, followed by resorption of the implant material and replacement with new bone, leading to a reduction of fracture risk in the femurs of osteoporotic postmenopausal women and providing a strong rationale for further clinical investigations.

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