Building a Multidisciplinary Care Pathway Supported by a Surgical Approach to Local Bone Formation

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ABSTRACT

Osteoporosis is the most common disease of bone mineral metabolism. In Spain, it affects approximately 3 million people, of whom 80% are females and 20% are males. Despite the advances that have been made in this field, we continue to witness alarming levels of fragility hip fractures. In 2010, the cost of osteoporosis in the European Union was estimated to be 37,000 million euros, which included the costs for the treatment of incident fractures (66%), pharmacological prevention (5%), and long-term fracture care (29%).

A multidisciplinary care pathway supported by a surgical approach to local bone formation is needed. Recently, the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) included in their treatment guidelines a local osteo-enhancement procedure (LOEP) as a treatment option.

In the Ossure™ LOEP technique (AgNovos Healthcare USA, LLC, Rockville, MD), a calcium-based triphasic osteoconductive implant material (AGN1), which has been shown to increase bone mineral density (BMD) and proximal femoral strength, is introduced percutaneously in the femoral neck and intertrochanteric region. Basically, the procedure consists of three percutaneous steps: prepare, clean, and fill the cavity with AGN1. It can be carried out with sedation and local anaesthesia or spinal anaesthesia.

This report presents a clinical case and discusses how to select patients who could potentially benefit from this technique.

INTRODUCTION

Osteoporosis is the most common disease of bone mineral metabolism. In Spain, it affects approximately 3 million people, of whom 80% are females and 20% are males.[1] In 2010, the cost of osteoporosis in the European Union was estimated to be 37,000 million euros, including the costs for treatment of incident fractures (66%), pharmacological prevention (5%), and long-term fracture care (29%).[2]

Osteoporosis was first described by the French anatomist Joseph Guichard Duverney (1648-1730). In the 1940s, Fuller Albright described postmenopausal osteoporosis, and in the 1960s, estrogens began to be used to treat the condition. The 1980s saw the introduction of calcitonin and bisphosphonates, the latter of which have become the cornerstone of current osteoporosis treatment. During the 1990s, other therapeutic options appeared, such as selective estrogen receptor modulators, and in the 2000s, RANKL inhibitors and PTH analogues appeared, which greatly improved treatment options. In 2019, an anti-sclerostin monoclonal antibody was the latest addition to the armamentarium.

These effective osteoporosis treatments have been shown to reduce the risk of hip fractures by up to 40% and the risk of spine fractures by 30-70%.[3] However, despite all of these advances, fragility fractures are still a global health problem.

The risk of osteoporosis increases with age, and likewise the risk of falls increases, which causes the risk of fracture to skyrocket at older ages. According to the International Osteoporosis Foundation (IOF), a fragility fracture occurs every 3 seconds worldwide, and 1 of every 3 women, and 1 of every 5 men over 50 years of age will experience osteoporosis fractures in their remaining lifetimes.[4]

The incidence of hip fracture increases exponentially with age in both genders. In females younger than 35 years, the incidence is 2/100,000 person-years, whereas it is 3032/100,000 person-years in women older than 85 years. In men, the corresponding rates are 4 and 190 per 100,000 person-years. Most hip fractures occur in the elderly: 52% after the age of 80 years and 90% after the age of 50 years.[5] A recent real-world retrospective cohort study showed that hip fracture occurred in 1 of 4 patients with any initial fracture, most often after hip fracture, within an average of 1.5 years.[6] This supports a call to pursue early hip fracture-prevention efforts in post-fracture patients. When men suffer a fragility fracture, they are associated with more morbidities, a greater need for long-term care, more disabilities and greater mortality than women.[7]

Despite the advances in this field, we continue to witness alarming levels of fragility hip fractures, for several reasons:

1- Many patients are not detected because osteoporosis does not cause pain, which is why it is known as the "silent pandemic".
2- Even if the patient is detected, there is often a lack of adherence to the treatment.
3- When the patient is treated, there is a long period of time, the so-called "window period", until the bone recovers its resistance, which is normally between 2 and 5 years.
4- New osteoporotic fractures are often clustered in time.

We have proposed solutions for each of these problems.

1- Increase the detection rate of patients in primary care using bone densitometry tests and the FRAX index.
2- Improve adherence to an evolved treatment, from daily treatments to weekly, monthly or half-yearly treatments.
3- During the "window period", patients and caregivers must be introduced to treatments and training programs to strengthen muscles, promote exercise, improve balance, treat other pathologies that interfere with bone health, avoid deficiencies or food shortages and avoid falls with improvements in postural hygiene. Smoking cessation is mandatory.
4- Because new osteoporotic fractures are associated in a cluster of time, a multidisciplinary care pathway supported by a surgical approach to local bone formation is needed.

Recently, the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) included in their treatment guidelines a local osteo-enhancement procedure (LOEP) as a treatment option.[8,9]

To date, the contribution of surgery in the treatment of osteoporosis has been relegated to the treatment of fractures once they have occurred. This falls in the fields of traumatology and osteosynthesis, which is outside the scope of this article. As frequent examples of osteoporotic fractures, we must include all treatment techniques for femur fractures, vertebral fractures, and fractures of the wrist or proximal humerus. Femur fractures

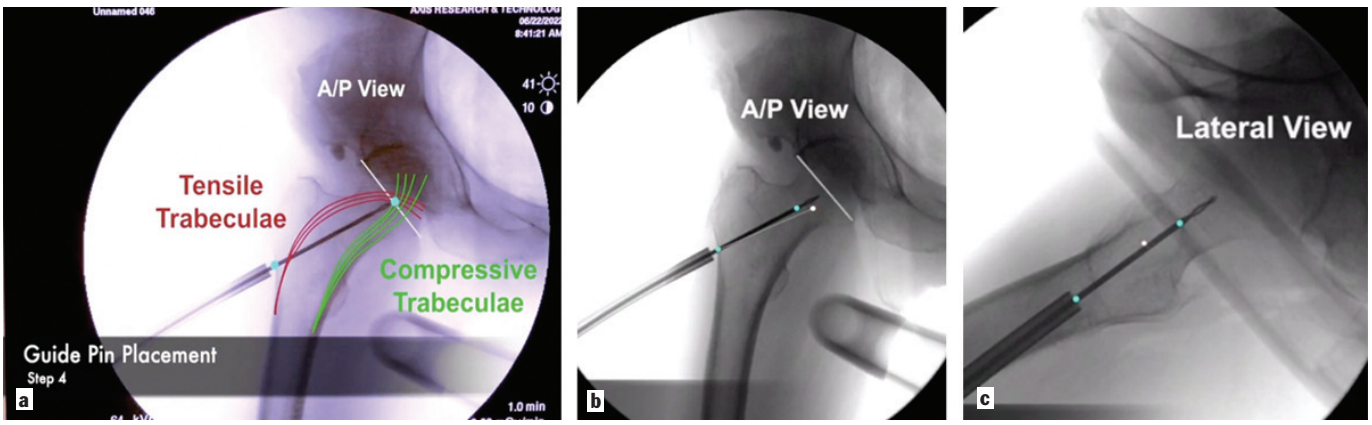

Figure 1. Insertion of a guide pin percutaneously to the base of the femoral head where the compressive and tensile trabeculae cross. AP and lateral view.

deserve special mention due to the arsenal of osteosyntheses and prostheses that allow the patient to sit and walk early and kyphoplasty, which allows pain to be reduced quickly and can sometimes prevent kyphosis of vertebral fractures.

Some efforts have been made to introduce osteogenic materials into fractured osteoporotic bones which would improve the strength of the bone while repairing a fracture. While kyphoplasty with a calcium compound [10,11] and the introduction of calcium material into wrist fractures [12] should be highlighted, neither is widely used.

There have been no previous reports on the use of reinforcement material based on calcium triphosphate for the prevention of osteoporotic femur fractures, although this is probably one of the major advances in prevention.

In a real-world retrospective cohort with 115,776 patients, Schemitsch et al. reported that subsequent hip fracture occurred in one of four patients with any initial fracture, most often after hip fracture, within an average of 1.5 years. These data support the need for early post-fracture interventions to help reduce the risk of imminent hip fracture.[6]

In a 2009 study of 4,140 osteoporotic fractures, van Geel et al. observed a distinct pattern of fragility fractures occurring in clusters. They suggested that once a patient experiences a fragility fracture, such as a vertebral fracture, there is an increased risk of subsequent fractures (relative risk = 2.1), including hip fractures, within 5 years. In Rochester, the cumulative risk of any fracture 10 years after a vertebral fracture was 70%.[13]

In 2016, Broy et al. highlighted that vertebral fractures are indicators of bone fragility and are associated with a cascade of recurrent fractures, which is known as the vertebral fracture cascade. The cascade includes bone and muscle loss due to immobility, changes in spinal mechanics, and the development of hyperkyphosis.[14]

In a meta-analysis, the presence of a vertebral fracture increased the relative risk of a future wrist fracture by 1.4, the risk of hip fracture by 2.3, and the risk of a subsequent vertebral fracture by 4.4.[15]

Finally, a 1999 study by Melton et al. in approximately 900 patients revealed that clinically recognized vertebral fractures are associated with an increased risk of subsequent fractures. The risk of any fracture was 2.8 times greater in individuals with vertebral fractures, and there was a notable correlation between vertebral fractures and hip fractures, with a 2.3-fold increased risk of hip fracture. These results demonstrate the size of the problem associated with hip fracture. Indeed, hip fracture is one of the world's greatest health problems.[16]

All of these findings indicate the need for a rapid response to osteoporotic fractures to help reduce the imminent risk of hip fracture, which carries high costs of personal, economic, social and humanitarian suffering.

MATERIALS AND METHODS

Ossure™ LOEP (local osteo-enhancement procedure; Agnovos Healthcare USA, LLC, Rockville, MD) is a minimally invasive procedure that includes a resorbable implant material intended to form new bone in voids in the skeletal system and is resorbed by the body and replaced with new bone. It is currently being used to treat osteoporosis in postmenopausal women. This technique introduces a calcium-based triphasic osteoconductive implant material (AGN1), which has been shown to increase BMD and femoral strength, percutaneously in the femoral neck and intertrochanteric region.[9]

AGN1 implant material consists of calcium sulphate, tricalcium phosphate and brushite ($CaHPO_4.2H_2O$), a calcium phosphate crystal. Brushite is a precursor and can be converted to hydroxyapatite.

This product has been shown to immediately increase the strength of the femur in cadavers.[17] In that study, treatment increased the failure load by an average of 19.2%, and in osteoporotic femurs, it increased the failure load by 23% and the work-to-failure by 30%.

Another study showed that AGN1 develops normal bone in a canine model.[18]

A human study by Howe et al. demonstrated that this treatment durably increased BMD in the femurs of osteoporotic postmenopausal women. That study included 12 women aged 56-89 years and showed that BMD at the neck of the treated femur increased by an average of 68% at 12 weeks, 59% at 24 weeks, and 58% at 5-7 years, compared to untreated control femurs. Additionally, the estimated femoral strength was increased by 41% at 12 weeks, 37% at 24 weeks, and 22% at 5-7 years.[9]

Additionally, in January 2022, AgNovos Healthcare (Rockville, MD) completed enrolment for its CONFIRM study, which was designed to generate additional data supporting the safety and efficacy of AGN1 LOEP in postmenopausal women with osteoporosis. This study includes 60 subjects and is the third and largest LOEP study to complete enrolment.[19]

This technique is meant to reinforce the femoral neck and intertrochanteric

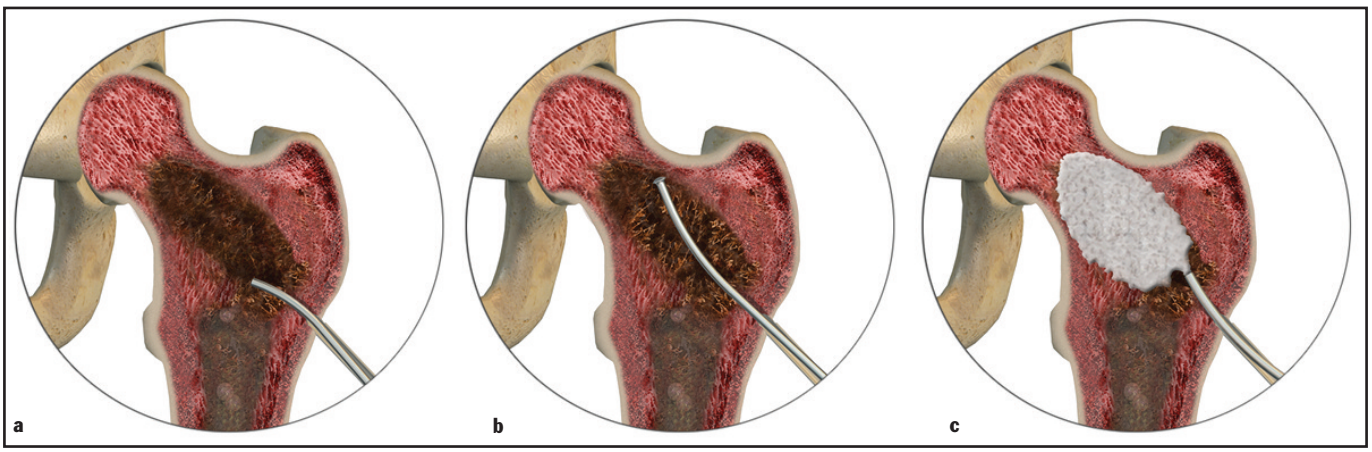

Figure 2. Preparation (a), Cleaning (b), and Filling (c) steps.

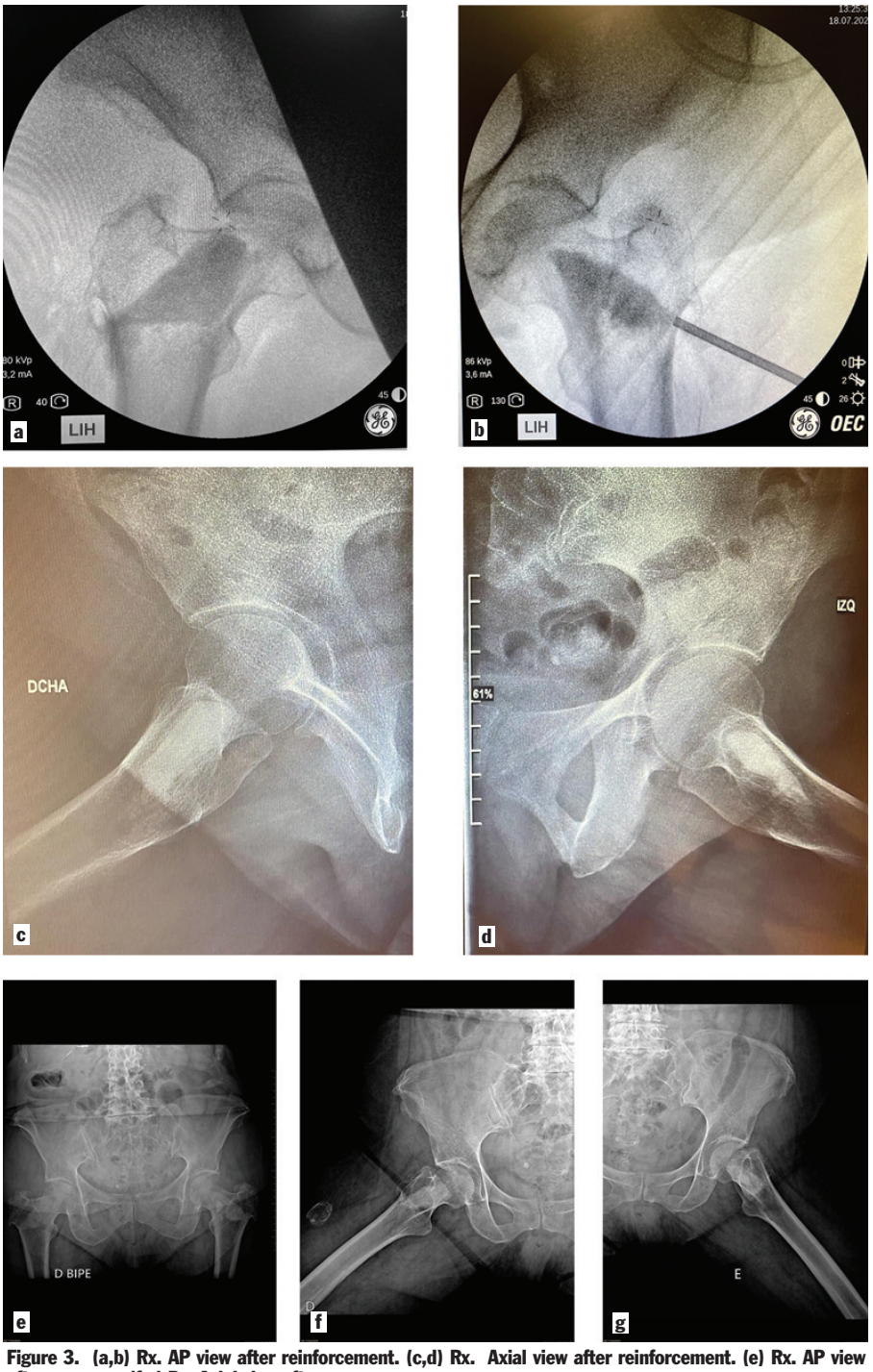

Figure 3. (a,b) Rx. AP view after reinforcement. (c,d) Rx. Axial view after reinforcement. (e) Rx. AP view after one year. (f,g) Rx. Axial view after one year.

region of the osteoporotic femur. Basically, the procedure consists of three percutaneous steps (prepare, clean and fill the cavity with AGN1) and can be carried out with sedation and local anaesthesia or spinal anaesthesia.

The procedure begins by inserting a guide pin percutaneously to the base of the femoral head where the compressive and tensile trabeculae cross (Fig. 1). A drill is then inserted and the following three steps are performed through the drilled hole (Fig. 2).

- PREPARATION consists of introducing a curette and cleaning the weakest area of the femur neck by breaking the scattered and fragile trabeculae that remain in the area.
- CLEANING consists of irrigating the area several times to evacuate debris.
- FILLING consists of filling the cavity with AGN1 to provide solidity to the most fragile area of the proximal femur where most porotic fractures occur.

One might think that passage of AGN1 into the bloodstream could lead to pulmonary vein thrombosis, as when PMMA is injected into vertebral fractures during the kyphoplasty procedure. Constant et al. demonstrated that the acute systemic and thromboembolic effects of a direct injection of a triphasic calcium-based implant material into the femoral vein appear to be comparable to or less than the effects of an injection of PMMA bone cement. Specifically, the severity and incidence of pulmonary histological changes with AGN1 may be weaker than those with PMMA; however, a larger study would be required to determine whether these differences are statistically significant. These preliminary safety data support further clinical evaluation of the implant material for vertebral augmentation. [20]

Clinical Case

A 79-year-old female patient suffering from osteoporosis had been treated by a rheumatologist for 15 years with teriparatide, risedronate, denosumab and once again risedronate. She had D12 kyphoplasty and old fractures at L1 and L4. Due to canal stenosis, she suffered from gait instability.

We performed bilateral reinforcement of the surgical neck of the osteoporotic femur using Ossure™ LOEP. The results are presented in Fig. 3.

DISCUSSION

According to the literature, the probability of a secondary femur fracture when there is an existing contralateral osteoporotic fracture is 10% in the first year and 20% at 5 years. The RESTORE study is currently underway to assess the positive effect of strengthening the contralateral femur with AGN1. It is a randomized, controlled, prospective, single-blinded, multi-national study with more than 2,000 patients in 10 countries on 3 continents. [21]

A second study with 150 patients (RECONFIRM) is also underway to evaluate the positive effect of femur strengthening. It is currently recruiting postmenopausal women with a femoral neck T-score of 2.5 or less. [22]

Because a high proportion of women who have a typical fragility fracture have BMD that is in the osteopenia range or even normal, [23] other risk factors that are grouped in the FRAX index [24] must be considered to detect and treat patients with osteopenia and to protect (using

AGN1) femurs that are most at risk of breaking; especially in older women.

The FRAX index is a clinical tool for assessing the risk of fractures in people with osteoporosis. It represents a person's 10-year risk of major osteoporotic fracture; i.e., their risk of fracturing their spine, hip, forearm, or shoulder over the next decade.The questionnaire includes age, gender, weight, height, previous fracture, parental hip fracture, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol intake, and femoral neck BMD.

A normal FRAX score indicates that the chance of getting a fracture in the next decade is less than 10%. If the FRAX score is 3% or more for hip fracture, or 20% or more for other major osteoporosis fractures, the patient may be at increased risk of fracture.

Finally, we identify suitable patients for an OSSURE™ LOEP procedure as follows:

- ◆In patients after a proximal femur fracture due to bone loss, we perform OSSURE™ LOEP on the contralateral femur to protect it.
- ◆In patients after any other porotic fracture (vertebrae, proximal humerus or distal radius), we perform dual x-ray absorptiometry (DEXA) and calculate the FRAX index. If the BMD is more than 2.5 SD below normal or if the FRAX index is above 3% per femur, we perform OSSURE™ LOEP bilaterally in the same surgical procedure.
- ◆In patients with osteoporosis (BMD more than 2.5 SD below normal) without fractures, we consider the FRAX index and pay special attention to patients under chronic treatment with corticosteroids, those with rheumatoid arthritis, and those who have balance problems of any nature (neurological, dementia, osteoarthritis, etc.).

As has been shown, treating osteoporotic femurs with AGN1 LOEP produces rapid and lasting increases in BMD and femoral strength.[9] The patients treated by our team notice better stability when walking. When the results of the RECONFIRM and RESTORE studies become available, it will be possible to quantify the prevention of fractures and to evaluate the contribution of this procedure to improving the quality of life of patients and caregivers, as well as the reduction in the cost of osteoporosis treatment. STI

AUTHORS' DISCLOSURES

The authors declare that there are no conflicts of interest.

RESULTS

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