"Local femoral osteo-enhancement": an innovative approach to reduce the risk of osteoporotic fractures

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ABSTRACT

Fragility fractures of the femoral neck are among the leading causes of morbidity and mortality in osteoporosis in the elderly, carrying a high risk of contralateral fractures and placing a significant socio-economic burden on national health systems. Although pharmacological treatments are essential for improving bone mineral density (BMD, g/cm²), they require several months to significantly reduce fracture risk and are limited by low patient adherence. In this context, techniques such as the local osteo-enhancement procedure (LOEP) are emerging as promising strategies for the prevention of osteoporotic fractures, offering a more rapid therapeutic onset. LOEP with AGN1, a resorbable tri-phasic biomaterial based on calcium sulfate, brushite, and beta-TCP, represents an innovative alternative due to its ability to enhance the mechanical strength of bone and stimulate physiological bone regeneration. The material showed complete resorption within 24 weeks, leading to an average BMD (g/cm²) up to 68%. Unlike traditional techniques, LOEP with AGN1 does not interfere with potential subsequent surgical procedures and does not induce thermal necrosis, making it a promising therapeutic option for the prevention of fragility fractures of the proximal femur.

KEYWORDS

Osteoporosis, osteo-enhancement, local osteo-enhancement procedure, hip fractures, fracture prevention.

Introduction

Osteoporosis is a "silent" systemic disease characterized by reduction in bone mineral density (BMD, g/cm²) and deterioration of the bone tissue microarchitecture, increasing bone fragility and the risk of fractures, particularly of the vertebrae, femur, and humerus [1]. A multicenter study in Italy found the prevalence of osteoporosis in postmenopausal women to be 36.6% according to BMD (g/cm²) criteria, and 57% according to the National Bone Health Alliance criteria [2]. Femoral neck fractures are among the most severe consequences of osteoporosis, and significantly impact patients' quality of life and mortality [1]. Current anti-osteoporotic pharmacological therapies, although essential for improving BMD, require a number of months to significantly reduce fracture risk [2,3] and are limited by low patient adherence [2]. As a result, there has been growing interest in osteo-enhancement procedures, which are techniques aimed at mechanically reinforcing the femoral neck using biocompatible materials [3]. Current osteo-enhancement strategies include the use of bone cements (such as polymethylmethacrylate, PMMA), polymers, metallic devices, and ceramic materials [4,5]. However, many of these techniques have significant limitations, including the risk of thermal necrosis, challenges in potential future surgical revisions after the enhancement procedure, and limited long-term bone bio-integration [6,7]. In this context, procedures such as the local osteo-enhancement procedure (LOEP) are emerging as promising strategies for the prevention of osteoporotic fractures, offering a more rapid therapeutic onset [8,9]. Among the various procedures, injection into the proximal femur of a resorbable tri-phasic biomaterial called AGN1—composed of calcium sulfate, brushite, and beta-tricalcium phosphate (β-TCP), and gradually resorbed and replaced by new bone tissue within 24 weeks—significantly increases both BMD and the mechanical strength of the femur [8,10,11]. Compared with other bone enhancement techniques, such as the use of PMMA or metallic implants, AGN1 offers considerable advantages [8,9]. Being a minimally invasive approach, it reduces the risk of surgical complications and promotes rapid functional recovery [8,9]. Moreover, AGN1 does not generate heat during injection, thus avoiding the risk of thermal tissue necrosis associated with other materials used in similar procedures [6,9]. Clinical studies have shown that the LOEP procedure with AGN1 can reduce hip fracture risk by up to 70% within 12 months post-intervention, thanks to a rapid and significant increase in BMD [8,10]. This effect has been documented in a cohort of postmenopausal women with osteoporosis, who showed an average BMD (g/cm²) increase of 68% within six months, which was maintained for up to seven years of follow-up [10,11]. These results suggest that treatment with AGN1 represents an innovative and promising solution for the

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prevention of femoral neck fractures in osteoporosis, offering an effective alternative to traditional pharmacological therapies and other bone enhancement procedures [9,12,13].

In light of the growing clinical interest in femoral osteo-enhancement using resorbable biomaterials, this review—the first devoted entirely to this innovative procedure—analyzes its biological basis, indications, and clinical effectiveness, comparing it with other osteo-enhancement strategies. It aims to provide an up-to-date overview of osteo-enhancement techniques for the prevention of osteoporotic femoral fractures, with particular focus on LOEP with AGN1, evaluating its clinical efficacy, limitations, and potential integration with pharmacological therapies.

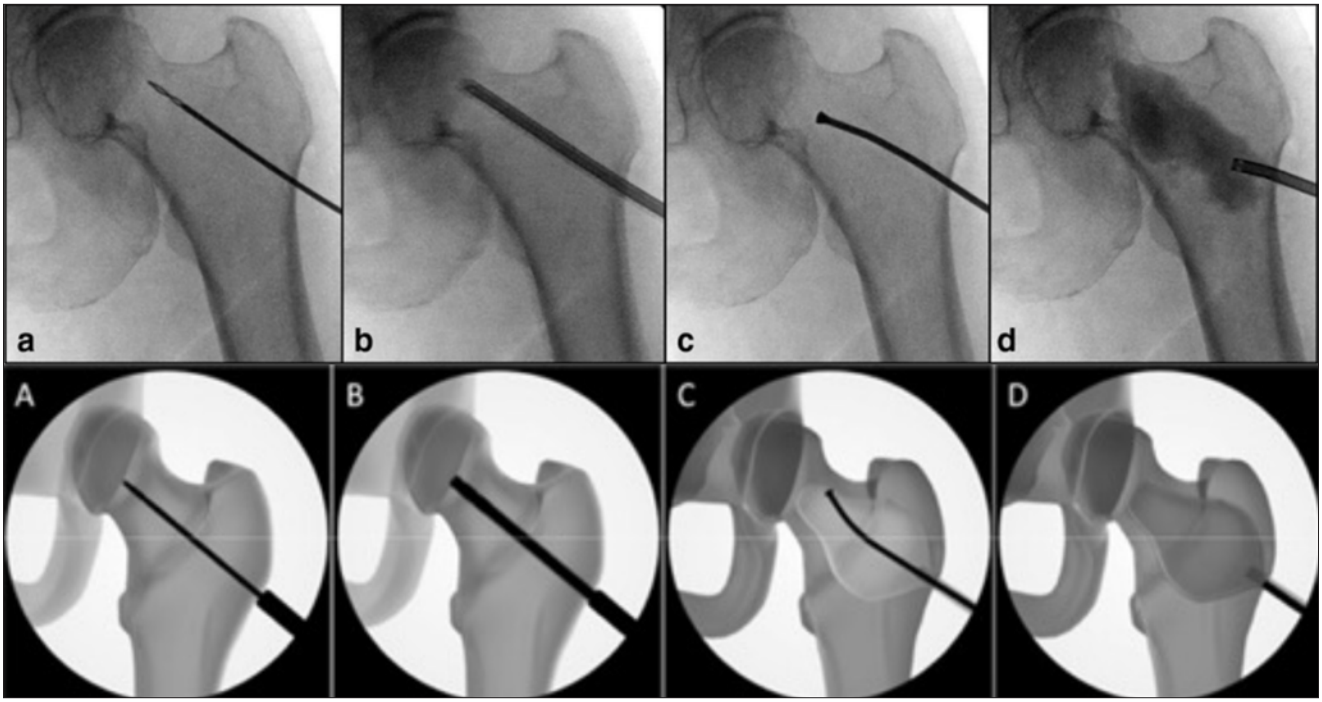
Surgical technique

After positioning the patient on the operating table in the supine position, fluoroscopic guidance is used to precisely identify the area of the proximal femur to be treated [8,14]. Following thorough disinfection, a small lateral skin incision of approximately 1.5–2 cm is made at the level of the thigh, corresponding to the area of interest [8]. Through this incision, a cannulated drill is introduced to create a cavity within the femoral neck, reaching the target site, specifically the Ward's triangle region [8,14]. Using dedicated instruments, meticulous debridement of the prepared bone site is performed to remove debris and necrotic material, followed by an accurate wash-out to thoroughly cleanse and prepare the area for the AGN1 implant [8,14]. At this stage, the biomaterial—composed of a tri-phasic mixture of calcium sulfate, brushite, and β-TCP—is carefully prepared within a few minutes [8,10]. A 20-cc dose of AGN1 is slowly injected through the preformed channel, completely filling the prepared cavity in the femoral neck [8,14]. After injection, fluoroscopic imaging is used to verify the correct distribution and localization of the material (Figure 1) [8,14]. Once injected, the material undergoes a progressive hardening process, gradually acquiring biomechanical and structural properties very similar to those of natural bone, allowing improved integration and mechanical stability of the treated area [8,15]. Patients are clinically monitored in the immediate postoperative period. Thanks to the minimally invasive nature of the procedure and the rapid solidification of the implanted material, patients are generally able to resume normal daily and ambulatory activities within a few days [8,15]. They are typically permitted to bear weight on the treated limb immediately postoperatively, depending on individual tolerance [8]. In frail patients or those with pre-existing functional impairments, a short course of targeted motor rehabilitation may be indicated to restore functional autonomy [8]. Clinical studies have confirmed the absence of biomechanical complications and the high safety profile of early weight-bearing following the procedure [8,10,15].

Osteo-enhancement procedures

Current pharmacological treatments for osteoporosis, including bisphosphonates, take 9 to 18 months to produce a significant reduction in hip fracture risk [2,3], a delay attributable to the time needed for these drugs to exert their anti-resorptive effect on bone tissue [2,3]. Consequently, there has been a growing need to develop new therapeutic strategies capable of providing more immediate risk reduction [3,4,6]. An ideal surgical enhancement procedure should ensure immediate, significant, and reliable mechanical reinforcement of the osteoporotic femur, be

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 then removed with irrigation and suction, and the implant material was injected into the proximal femur (D).



minimally invasive, and carry a low risk of adverse effects [3,4,6]. Additionally, such a procedure should be clinically feasible and ethically and economically acceptable [3,4,6]. Currently, the options described in the literature for osteo-enhancement of the osteoporotic femur can be classified into four main categories:

1. **Enhancement with ceramics**: The use of ceramic materials, such as hydroxyapatite and calcium phosphates, aims to mimic the mineral composition of natural bone, promoting bioactivity and osteoconductivity [4,16].
2. **Enhancement with metals**: The use of metallic scaffolds, such as titanium-based structures, provides robust structural support and promotes osseointegration thanks to the biocompatible properties of the metal [5].
3. **Enhancement with cement**: This technique involves the injection of bone cement, such as PMMA, into trabecular bone to increase its mechanical strength [6,7]. However, cement use may lead to complications such as avascular necrosis and material migration, and thus requires careful risk-benefit evaluation [6,17,18].
4. **Enhancement with polymers**: The use of biodegradable polymers aims to provide temporary bone support while promoting bone regeneration [19-21]. These materials can be loaded with osteoinductive drugs or growth factors to enhance osseointegration [19-21].

1. Ceramic enhancement

In recent years, ceramic biomaterials have attracted growing interest in osteo-enhancement strategies due to their unique biological properties, including high biocompatibility, bioactivity, and osteoconductivity [4]. From a compositional standpoint, the ceramic materials used in orthopedics are mainly divided into two categories: calcium phosphate-based and calcium sulfate-based ceramics [4]. Calcium phosphate ceramics are widely used because of their excellent osteoconductivity and biocompatibility; however, they degrade relatively slowly [4]. In contrast, calcium sulfate ceramics offer accelerated resorption but have limited mechanical strength and may trigger mild inflammatory responses during degradation [4]. To overcome these limitations, an innovative biomaterial called AGN1 has been developed specifically for reinforcement of the proximal femur [8,10].

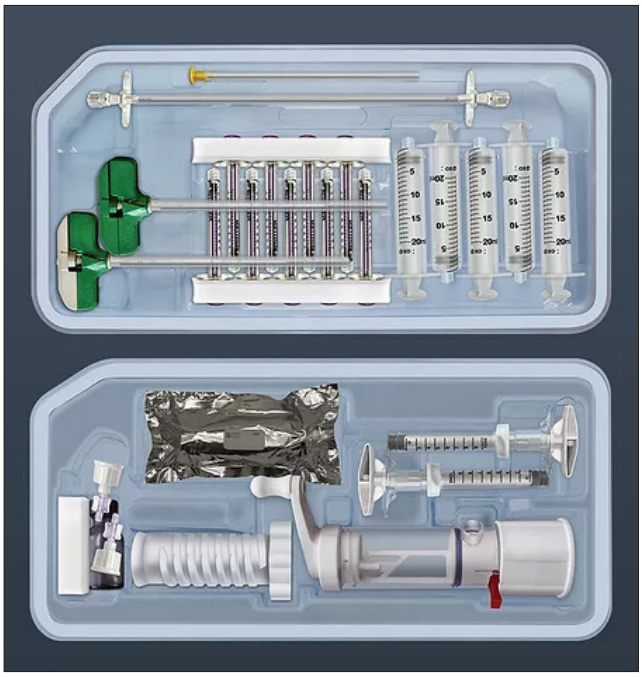
Ceramic enhancement with AGN1

AGN1 is a resorbable tri-phasic compound composed of a mixture of calcium sulfate, brushite, and β-TCP granules (Figure 2) [8,10]. Each of these components exhibits a specific resorption profile:

- Calcium sulfate: rapidly resorbed through direct dissolution within a few weeks post-implantation [8,10].
- Brushite: gradually converts into hydroxyapatite and is resorbed over several weeks to a few months [8,10].
- β-TCP: the most resistant phase, resorbed via osteoclastic activity and completely replaced by new bone tissue within approximately 3–6 months [8,10].

Solidification occurs through the hydration of calcium sulfate hemihydrate, which converts into calcium sulfate dihydrate ($CaSO_4$) via a low-temperature exothermic reaction, thereby preventing thermal injury to surrounding tissues [6,7]. AGN1 provides immediate biomechanical benefits upon implantation,

Figure 2 AGN1 enhancement procedure kit.



enhancing the structural stability of the proximal femur from the early postoperative stages [8,10]. Due to its controlled setting properties and uniform distribution, the material ensures immediate mechanical support, reducing the risk of micromovements and promoting early functional recovery [8,10]. Resorption occurs mainly through dissolution, generating a porous structure that facilitates vascular infiltration and new bone formation [11,12]. The β-TCP granules play a key role as an osteoconductive scaffold, supporting cell adhesion and osteoblastic proliferation, thus aiding osseointegration [11,12]. Several studies have assessed the efficacy of AGN1 in treating bone defects, demonstrating that this biomaterial not only provides adequate structural support, but also promotes bone regeneration via a mechanism of progressive degradation and replacement with new tissue (Figure 3) [9-11]. A further distinctive advantage of AGN1 is its compatibility with future surgical procedures. In the event of a fracture following the osteo-enhancement intervention with AGN1, it is possible to perform internal fixation using a femoral intramedullary nail, total hip arthroplasty, or osteosynthesis with cannulated screws without complications [11,12]. This marks a significant advance over other osteo-enhancement materials, which may hinder or preclude the insertion of osteosynthesis or prosthetic devices due to material incompatibility or mechanical interference [11,12]. Moreover, systemic side effects are extremely rare and less frequent than with conventional enhancement techniques [9]. Similarly, complications from the LOEP procedure with AGN1 are rare and generally mild. Only transient pain and localized swelling have been reported, occasionally accompanied by mild inflammatory responses or small hematomas, all of which are self-limiting [11,12]. No significant systemic complications, nor any cases of embolism, toxicity, or infection related to the biomaterial, have been observed [11,12]. AGN1 does not cause thermal necrosis, nor does it interfere with future surgical procedures [11,12]. Serious adverse events have not been reported in the current scientific literature (Figure 4) [9].

Figure 3 [Case 1 (A-B-C), Case 2 (D-E-F)] Sequential pre-operative (A,D), immediate post-operative (B,E), and 5 months post-AGN1 procedure (C,F) left hip X-rays in two 80-year-old women with osteoporosis, whose Ward's triangle (BMD, g/cm²) T-scores improved from -2.5 to 5.4 (A,B,C) and from -3.8 to 2.4 (D,E,F), respectively.

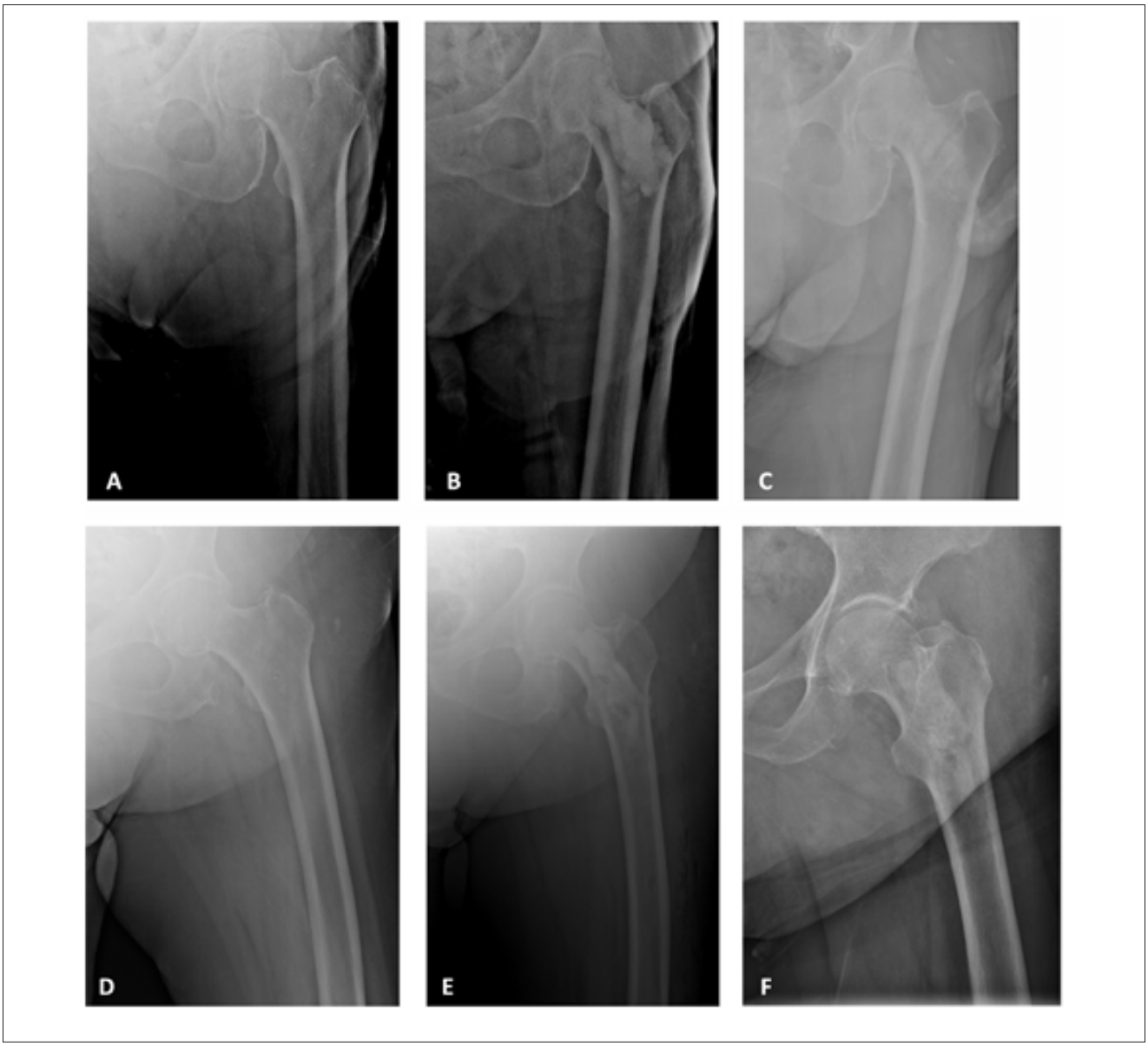
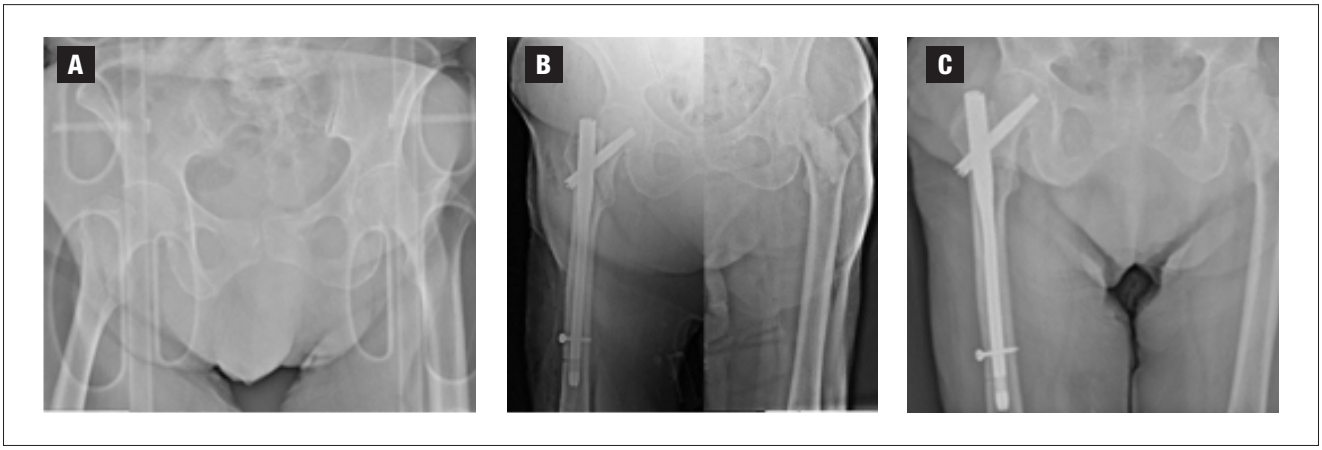


Figure 4 Sequential pre-operative (A), immediate post-operative (B), and 12 months post-AGN1 procedure (C) in an 80-year-old woman with osteoporosis, whose femoral BMD T-score improved from -3.8 to 2.1 over one year.



Indications and contraindications of LOEP with AGN1

Indications:

- Patients with severe osteoporosis, particularly postmenopausal women with a T-score ≤ -2.5 and a high risk of proximal femur fracture assessed through tools such as DEXA or DEFRA.
- Individuals with marked demineralization of the proximal femur who are unresponsive to systemic pharmacological therapy or present contraindications to it.
- Patients requiring structural bone reinforcement prior to elective surgical or rehabilitation treatment.

Contraindications:

- Presence of active local or systemic infections.
- Uncontrolled hematologic disorders.
- Active-phase osteonecrosis.
- Severe comorbidities increasing anesthetic risk.

2. Metallic enhancement

The use of metallic devices as a strategy for structural reinforcement of the proximal femur to reduce fracture risk has been explored in patients with osteoporosis [5]. A significant example is the Prevention Nail System (PNS, Medacta International), as described in the study by Giannini *et al.* [5]. This device consists of a self-tapping cephalic screw made of titanium alloy with a hydroxyapatite coating, designed to promote osseointegration [5]. In subtrochanteric or pertrochanteric fractures, it can be combined with a stainless-steel plate, serving a biomechanical function similar to that of the Dynamic Hip Screw system [5]. After surgical treatment, patients underwent rigorous clinical and radiographic follow-up, including serial standard radiographs and CT scans at 3 and 12 months [5]. Imaging revealed no radiological signs of device mobilization or peri-implant radiolucency [5]. Quantitative assessment through imaging showed no significant changes in peri-implant bone morphology during follow-up [5].

Despite excellent radiologic osseointegration (100%), interim analysis demonstrated that the PNS did not significantly reduce the incidence of medial femoral fractures compared with the control group [5]. Several factors may have contributed to this lack of efficacy: the presence of the intramedullary implant might have altered the physiological distribution of mechanical loads, causing stress shielding phenomena and consequent local bone resorption rather than structural reinforcement [5]. The static osseointegration of the hydroxyapatite coating alone may not have been sufficient to stimulate the level of functional remodeling needed to reduce fracture risk [5]. The high incidence of contralateral fractures suggests that bone fragility is multifactorial and systemic in nature, and therefore not addressable solely through a local mechanical solution [5]. Additionally, other studies have reported that some materials used (e.g., PMMA) can induce local complications, such as thermal necrosis at the bone-cement interface, due to the high polymerization temperatures of the cement [6,7]. This procedure is strongly contraindicated in cases of documented intolerance to the implantable biomaterials, local pathological conditions (infections, neoplasms, severe anatomical alterations) of the proximal femur, or conditions that can prevent effective osseointegration with the biomaterial [6].

3. PMMA enhancement

Polymethylmethacrylate (PMMA) is the most widely used bone cement in orthopedic surgery. It is a non-resorbable, inert polymer that provides immediate mechanical reinforcement by hardening at body temperature after mixing the powder with a liquid monomer [6,7]. The cement penetrates into the trabecular cavities of bone, creating a tight mechanical interlock with the trabecular architecture [6,7]. However, its use in the proximal femur is limited by some critical drawbacks: the exothermic polymerization reaction can induce local thermal necrosis of bone tissue [6,7], as well as a high risk of embolic complications related to the diffusion of PMMA into the venous system during injection [7,17,18]. Several studies have demonstrated that the polymerization temperature of PMMA can reach up to 70–120°C, significantly exceeding the threshold for bone cell necrosis, thereby causing osteonecrosis in the surrounding tissue [7]. Furthermore, once hardened, PMMA is not resorbed by the body and does not allow new bone tissue formation, which limits its biological integration [6,7]. Clinical evidence has reported cases of pulmonary embolism secondary to the migration of PMMA particles during augmentation procedures [10,17]. Although rare, these events highlight the risks of systemic complications associated with the use of PMMA in osteoporotic patients [10,17]. These findings underscore the need for alternative materials that combine mechanical reinforcement with biological resorption and bone regeneration, such as calcium-based biomaterials [8,10,15].

4. Polymeric enhancement

Polymeric biomaterials represent a promising alternative to traditional methods for bone reinforcement, particularly in the context of osteoporotic fractures [19-21]. These materials are designed to provide temporary structural support while gradually degrading and being replaced by newly formed bone tissue [19-21]. Among the most studied are polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers (PLGA), which degrade by hydrolysis of their ester bonds, producing biocompatible byproducts easily metabolized by the body [19-21]. These polymers can be combined with osteoinductive molecules, such as growth factors or bisphosphonates, to enhance bone regeneration and mechanical stability [19-21]. In addition to their degradability, polymeric biomaterials offer significant advantages, including the possibility of being processed into porous scaffolds, fibers, or injectable pastes, thereby adapting to various clinical requirements [19-21]. Their porosity facilitates vascular invasion and cellular colonization, essential processes for osseointegration [19-21]. However, the mechanical strength of polymers alone is generally lower than that of ceramics or cements, limiting their use in load-bearing areas such as the proximal femur [19-21]. For this reason, composite biomaterials combining polymers with ceramic or metallic phases have been developed, aiming to optimize both the mechanical and biological properties of the implant (Table I) [19-21].

Economic impact and costs of LOEP

Cost evaluation is a crucial element in the adoption of new techniques for the prevention of fragility fractures, especial-

Table I Outcomes, efficacy, and complications of various bone enhancement procedures.

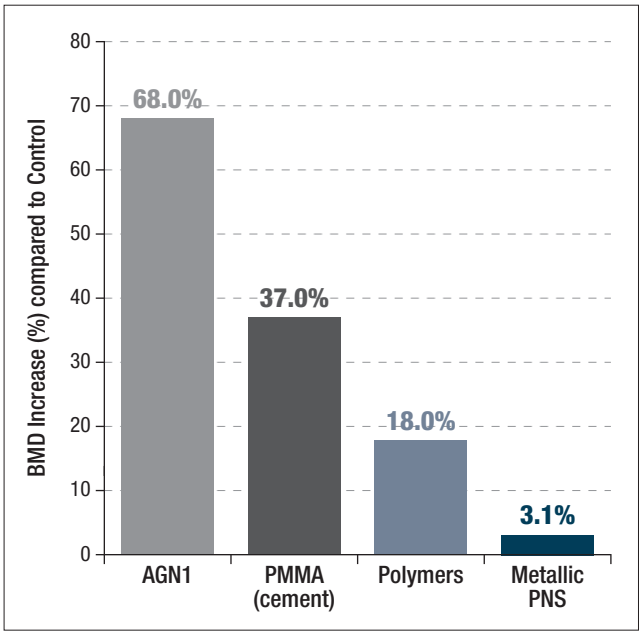
	CLINICAL OUTCOMES/ INCREASE IN BMD (g/cm²)	EFFICACY IN FRACTURE RISK REDUCTION	MAIN COMPLICATIONS
AGN1	↑ BMD by 68% within 6 months; maintained for up to 7 years (Figure 5)	Hip fracture risk reductions of up to 70% in cohorts of women with osteoporosis; limited data due to the innovative nature of the procedure	Minimal complication incidence, no thermal necrosis, no interference with future fixation procedures
Metallic augmentation	Improved local mechanical stability, no significant increase in BMD documented	Preventive efficacy on non-fractured femur not demonstrated on a large scale	Stress shielding
Ceramic augmentation	↑ local BMD, good bone osseointegration	Limited data on prophylactic efficacy, especially in advanced osteoporosis; useful as a scaffold, but clinical evidence remains scarce	Post-implantation fracture risk
Polymeric augmentation	Temporary support, no direct increase in BMD (g/cm²)	No strong evidence of fracture risk reduction in primary prevention; studies are in preclinical phase or early case reports	Limited data

ly in the context of an aging population and rising incidence of osteoporosis [1-3]. Femoral neck fractures place a substantial economic burden on national healthcare systems: according to recent analyses, the direct costs associated with treating a hip fracture can exceed €20,000–25,000 per episode in European countries, considering surgery, hospitalization, rehabilitation, and long-term complications [1,2]. Although LOEP with AGN1 involves an additional upfront cost compared with pharmacological therapy alone, it is positioned as a strategy for secondary cost savings thanks to its ability to significantly reduce fracture risk [8,10,11]. A prospective study published in *Osteoporosis International* showed that implementing LOEP in cohorts of women with osteoporosis resulted in an estimated 70% reduction in femoral fractures within 12 months, leading to a decrease in costs associated with the management of acute and chronic complications [8,10,11]. C

ost-effectiveness analysis, applied to both European and North American models, suggests that the procedure is economically sustainable, particularly in high-risk individuals or those with a history of contralateral fractures [1-3]. Comparison with other enhancement techniques reveals additional advantages of LOEP with AGN1: although PMMA-based procedures have similar operating costs, they often involve higher expenses related to complications (thermal necrosis, infections, surgical revisions) [6,7,16], while metallic implants incur greater costs due to the materials, postoperative management, and potential need for subsequent removal [5,23]. Furthermore, the early return to functional autonomy enabled by LOEP reduces indirect costs related to loss of productivity, home care, and long-term hospitalization [8,10]. Real-world evidence studies suggest that the procedure may reduce social costs by up to 30–40% compared with only treating fracture-related complications, particularly when applied as a primary prevention strategy in high-risk patients [8,10].

In conclusion, although LOEP with AGN1 requires an initial investment, it qualifies as a cost-effective procedure in the context of fragility fracture prevention, with potential economic benefits for both healthcare systems and patients, especially in cases of high risk and poor response or adherence to pharmacological therapy [8,10,11,23].

Figure 5 BMD percentage increase: comparison of femoral enhancement techniques. The graph compares femoral enhancement techniques, highlighting the superior increase in bone mineral density (68%) achieved with AGN1.



Conclusions

The increasing prevalence of osteoporosis and consequent rise in fragility fractures—particularly at the femoral neck—requires the introduction of innovative structural enhancement strategies to ensure effective prevention [1,2]. Among the various available techniques, LOEP performed with the resorbable tri-phasic biomaterial AGN1 is a particularly promising technique that has proven to offer not only immediate biomechanical improvement of the treated femur but also rapid postoperative functional recovery due to its minimally invasive nature [8-10] and the absence of the thermal complications typically associated with PMMA [6,7]. Available clinical data show that use of AGN1—composed of calcium sulfate, brushite, and β-TCP—leads to a significant average increase of 68%

in femoral neck BMD, with these results maintained for up to seven years of follow-up [8,10]. Compared with metallic or cement-based enhancement techniques, LOEP with AGN1 offers important biomechanical and biological advantages [8,9]. For example, although the PNS and metallic augmentation provide immediate mechanical stability, they have not demonstrated effective reduction in femoral fractures and are associated with risks such as stress shielding and altered load distribution [5]. Similarly, osteo-enhancement with PMMA offers significant structural benefits, but the high polymerization temperatures (60–70°C) can cause thermal necrosis of surrounding tissues [6,7,16]. Polymeric devices improve the biomechanical properties of the osteoporotic femur, but have limitations related to peri-implant thermal damage and can give rise to complications during potential revision surgeries [19-21]. In light of this evidence, LOEP with AGN1 currently represents an optimal solution for the preventive reinforcement of the proximal femur, offering an ideal balance between mechanical enhancement, biological safety, and clinical sustainability [8-10]. Future clinical studies may further confirm the efficacy of this technique and promote its large-scale application in the prevention of osteoporotic fractures [1,8,10]. However, based on currently available results, further research is needed to consolidate and optimize the procedure [8,10]. Large randomized clinical trials with extended follow-up will be essential to assess the true impact of LOEP on fracture reduction in various patient populations. Particular attention should also be paid to possible integration of this procedure with anti-osteoporotic pharmacological treatments, in order to explore potential synergies and combined approaches that may maximize fracture prevention and improve treatment adherence [3]. From a technical perspective, future refinements may focus on optimizing the volume of biomaterial implanted, personalizing treatment based on individual anatomical characteristics, and expanding the application of LOEP to other skeletal sites at high risk of fracture [10,13]. Finally, it will be important to evaluate the long-term interactions of AGN1 with possible future surgical procedures (such as fixation or arthroplasty), as well as its potential effects on the quality of the remaining bone [10,12]. The implementation of these research pathways may help define the true role of LOEP in fragility fracture prevention and promote its increasingly widespread and appropriate clinical use.

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