

Osteo-enhancement procedures in hip fracture prevention: definition and local interventions

Davide Guido, Francesco Raspanti, Niccolò Gabbiani, Matteo Innocenti, Roberto Civinini

University of Florence, Orthopaedic Clinic CTO – Florence, Italy

ABSTRACT

Fragility hip fractures are associated with increased morbidity and mortality in elderly patients and place a large medical and economic burden on affected individuals, families, and healthcare systems.

Furthermore, in patients with a recent hip fracture, the risk of a second contralateral hip fracture is doubled at 1 year, and increases to 9–20% after 5 years. Mortality can be up to three times higher following a contralateral hip fracture.

Currently available pharmaceutical treatments to improve bone mineral density in fragility fracture of the proximal femur can take up to 18 months to significantly reduce the risk of fracture, and have patient compliance issues.

Thus, given the limitations of existing methods, there is a significant need for new approaches to reduce hip fractures through so-called surgical osteo-enhancement.

“Osteo-enhancement” might be defined as any procedure in which a new material is surgically introduced with the aim of strengthening the proximal femur, increasing the resistance of the femoral neck to compression and distraction forces acting on it, and thereby preventing fall-related fractures.

In the past decade, several groups have presented various prophylactic augmentation approaches for the osteoporotic proximal femur and evaluated them by means of experimental biomechanical testing; however, none of them met the ideal requirements for *in vivo* application. Ideally, a surgical procedure should be minimally invasive and safe. The intervention must not increase the immediate risk of hip fracture, must provide long-term fracture risk reduction, and, if a subsequent fracture does occur, the intervention should not interfere with a standard approach for fracture repair.

More recently, to address local osteoporotic bone loss, a resorbable implant material named AGN1 was introduced as a new device for strengthening the proximal femur. The implant material sets in situ and is designed to be resorbed and replaced with new bone to improve femoral strength and reduce hip fracture risk in osteoporotic patients.

KEYWORDS

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

Introduction

Osteoporosis is a skeletal disorder characterized by an increased risk of fractures due to reduced bone strength^[1,2]. The strength of bone is a reflection of its density and quality; the decrease of bone mass and the micro-architectural deterioration that occur in osteoporosis cause bone fragility leading to low-energy fractures^[3–5]. Fragility fractures are among the major causes of morbidity and mortality worldwide. In Italy, there are 80,000 new femoral neck fractures due to osteoporosis every year, with a high prevalence in women (72%)^[6].

Moreover, fragility fractures of the hip are associated with significant morbidity and mortality, and place a considerable burden on affected individuals, families, and healthcare systems; at one year from fracture, about 80% of patients are unable to independently carry out at least one daily activity. Survival, especially in women, is significantly reduced, with 20% of patients dying within 1 year of a hip fracture^[7].

Hip fractures are associated with a 2.5-fold increase in the risk of a new fracture^[8]: 12% will sustain a second contralateral hip fracture within 2 years and this percentage increases to 20% at 5 years; mortality also increases, and can be up to three

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Contact

Francesco Raspanti; francescoraspanti91@gmail.com
University of Florence, Orthopaedic Clinic CTO – Florence, Italy
Mobile phone: +39 393 1486700

times higher following a contralateral hip fracture^[9,10].

Therefore, it is mandatory to adopt appropriate strategies to prevent a second fracture in these patients. Secondary prevention focuses on pharmacological and non-pharmacological therapies.

Currently available pharmaceutical treatments to improve bone mineral density (BMD) in fragility fractures of the proximal femur can take up to 18 months to significantly reduce the risk of fracture. Moreover, the pharmacological treatment is often started too late and shows low patient compliance: up to 50% of cases discontinue therapy prematurely^[11]. Parri *et al.*^[12], in a retrospective study, described a programme for hip fracture prevention in the over 65s called the “T.A.R.Ge.T. project” (the acronym standing for appropriate treatment of geriat-

ric re-fractures in Tuscany): from 2006 to 2010 they calculated the percentage of patients pharmacologically treated after a first fracture. They then calculated the percentage of patients pharmacologically treated after re-fracture who had not been treated before. The result was significant: first fractures were treated in 34% of cases on average, while the rate of treatment in the re-fracture group was about 43%.

This 9% difference clearly highlights how awareness of the problem increases when it is already present. Thus, given the limitations of existing methods, there is a significant need for new approaches to reduce hip fractures: we refer to so-called surgical osteo-enhancement.

By “osteo-enhancement” we mean any procedure in which a new material is surgically introduced with the aim of strengthening the proximal femur, increasing the resistance of the neck to the compression and distraction forces acting on it, and thereby preventing fall-related fractures.

Osteo-enhancement techniques

Current medical treatments have not been shown to reduce the risk of fractures during the early stages of therapy, since they take 9 to 18 months to significantly reduce the risk of hip fracture [13]. The efficacy of non-pharmacological techniques, such as external hip protectors (padding), has not been proven either, and they are rarely used. The associated discomfort and relevant comorbidities (e.g., incontinence) limit patient compliance with these devices, and this, in turn, leads to inconsistency in the efficacy data [14]. Consequently, the idea has recently emerged of a medical or surgical treatment that is able to reduce the risk in the short term.

A surgical procedure should provide immediate, significant, and reliable mechanical strengthening of the osteoporotic femur, and should be minimally invasive and with a low risk of

side effects. Moreover, it must be clinically feasible and both ethically and financially acceptable.

We can divide the various possibilities currently present in the literature for the preventive reinforcement of the osteoporotic femur into four categories: cement augmentations, polymer augmentations, metallic augmentations, and ceramic augmentations (Table I).

Cement augmentations

In a procedure analogous to vertebroplasty or kyphoplasty in spine surgery, percutaneous injection of poly-methyl-methacrylate (PMMA) cement into fractured or osteoporotic vertebral bodies, i.e., cement augmentation of the proximal femur (“femoroplasty”) could reinforce osteoporotic bones. Heini *et al.* [15], in 2004, described an experimental technique of this name which consisted of injection of PMMA into the osteoporotic femoral neck. The author used 20 pairs of osteoporotic femurs, each pair as a case-control, to assess the surgical reinforcement. Low-viscosity cement was inserted in a 4.5 mm hole on the lateral cortex at the base of the greater trochanter. In the study group, femurs showed a more than 82% increased breaking load compared with the controls, and a 188% increase in absorbed energy. Sutter *et al.* [16] found 37% and 154% increases in fracture load and energy, respectively, in 10 pairs of osteoporotic human cadaveric femora injected with 40–50 mL of PMMA. However, these authors maintained that there are concerns over the application of this technique *in vivo* due to the high volume of PMMA necessary, which generates enormous heat during polymerization (up to 60° *in vivo*) leading to necrosis of the femoral head. Moreover, in the event of a subsequent fracture, revision surgery would be challenging.

To avoid the side effects related to heat production, Beckmann *et al.* [17] used a bioactive composite cement that generated less heat, with similar results. In this study, the temperature peak of the composite cement used was about 11°C, which is

Table I Local osteo-enhancement procedure. Review of the literature from 2004 to 2021. (PMMA: poly-methyl-methacrylate; CBC: composite bone cement; RCT: randomized controlled trial; PCS: prospective cohort study).

REFERENCE	YEAR	TYPE OF STUDY	NO. OF PATIENTS	AUGMENTATION	FOLLOW-UP
Heini <i>et al.</i>	2004	<i>In vitro</i>	20	PMMA	-
Beckmann <i>et al.</i>	2007	<i>In vitro</i>	9+13	CBC	-
Sutter <i>et al.</i>	2010	<i>In vitro</i>	10	PMMA	-
Szpalski <i>et al.</i>	2015	<i>In vitro</i>	7	Polymer	-
Cornelis <i>et al.</i>	2017	PCS	14	Polymer	1-5 y
Varga <i>et al.</i>	2017	<i>In vitro</i>	15	PMMA	-
Hill <i>et al.</i>	2017	<i>In vitro</i>	30+30	AGN1	-
Giannini <i>et al.</i>	2018	RCT	72	Metallic	12 m
Stroncek <i>et al.</i>	2019	<i>In vitro</i>	45	AGN1	-
Howe <i>et al.</i>	2020	PCS	12	AGN1	5-7 y
Farvardin <i>et al.</i>	2021	<i>In vitro</i>	6	PMMA	-

acceptable, but still high compared with the near-isothermic curing composite cements based on calcium phosphates [18]. Furthermore, in contrast to PMMA, composite cements, as well as calcium phosphate cements, are presumed to be bioactive, meaning that they are osteoconductive and can be resorbed gradually over time and replaced by host bone [18,19].

Varga *et al.* [20] proposed new injection strategies, based on the principles of bone remodeling, for use in femoroplasty, and concluded that “compression bridge” injections aligned with the femoral neck axis showed the greatest biomechanical efficiency. Thanks to a new planning paradigm and an in-house navigation system, Farvardin *et al.* [21] were able to demonstrate that a planned injection of PMMA into the proximal femur can significantly improve its fracture-related biomechanical properties. However, temperature recordings of bone surfaces suggest that the risk of thermal necrosis remains a concern.

Polymer augmentations

Szpalski *et al.* [22], in 2015, described another approach for contralateral hip fracture prevention: the placement of a polymer augmentation device (Y-STRUT[®], Hyprevention[®], Pessac, France) consisting of two interlocking PEEK (polyether ether ketone) rods. These rods are made of colorless organic thermoplastic polymer and have multiple perforations for extrusion of the bone cement. This allows connection of the two components of the implant, increasing the contact surface with the surrounding bone; moreover, if bioactive PMMA cement is used, it can promote osseointegration of the construction. The results of this study showed that insertion of the implant significantly increased both fracture load (+18%) and energy to fracture (+32%) of the implanted femurs. Consequently, there was a potential decrease in the risk of femoral neck fracture (−28%) and trochanteric fracture (−52%). In 2017, Cornelis *et al.* [23] reported encouraging preliminary results, in terms of feasibility, safety, and tolerability, from the first-in-human studies of the Y-STRUT[®] device. However, albeit lower than with PMMA alone, the risk of thermal necrosis and the greater difficulty in the event of revision surgery remain.

Metallic augmentations

As regards metallic augmentations, Giannini *et al.* [24], in 2018, described a new method for surgical prevention of femoral neck fractures in elderly patients based on the prevention nail system (PNS) device (Medacta International, Castel San Pietro, Switzerland). This device consists of a self-tapping cephalic screw; it is made from titanium alloy with a hydroxyapatite-coated thread and has a Young’s modulus of 14.1 1011N/m². In trochanteric or sub-trochanteric fracture cases, a specifically developed stainless-steel plate can be used in conjunction with the PNS, thus obtaining a fixation device similar to the dynamic hip screw. After surgery, patients underwent clinical and radiographic follow up (FU) with X-ray at each check-up and CT scan at 3 months and one year to assess both the bone response (hypertrophy or atrophy) and the presence of osseointegration of the PNS.

Imaging of the reinforced hips showed no radiolucencies or PNS loosening. No differences were found at the various FU time-points in terms of atrophy or hypertrophy around the

hydroxyapatite-coated thread. The incidence of contralateral proximal femoral fracture was 0.92 (95% confidence interval [CI], 0.875–0.965) in the PNS group and 0.77 (95% CI, 0.671–0.873) in the control group. An interim analysis showed non-effectiveness of the device in preventing femoral neck fracture, thus the enrolment was suspended.

Ceramic augmentations

In recent years, ceramic-based materials have been attracting attention in the context of osteo-enhancement techniques, since they show excellent biological behaviors (e.g., biocompatibility, bioactivity and osteoconductivity). In addition, they are easy to use in the clinical setting, since they are usually commercially available in a liquid and solid phase which, when mixed, form a paste that can be injected, moulded, and shaped to fill the bone defect.

Two types of ceramic are available, which differ in their composition: the first group includes calcium phosphate ceramics, the second calcium sulphate ceramics. Calcium phosphate ceramics are biocompatible and osteoconductive, but their degradation rate is generally very slow. On the other hand, calcium sulphate ceramics are rapidly resorbed but they have poor mechanical properties, evoking only minimal inflammatory reactions during resorption.

In order to overcome these problems, a new biomaterial, AGN1, was introduced as a new device to strengthen the proximal femur. AGN1 is a tri-phasic resorbable material consisting of calcium sulphate, brushite and beta-TCP granules. It sets through the hydration of calcium sulphate hemihydrate to calcium sulphate dihydrate (CaSO₄), during an exothermic reaction that does not exceed 35°C.

The simple resorption by dissolution of CaSO₄ leaves an open-pore structure that allows infiltration and vascular growth, which in turn allows new bone ingrowth on beta-TCS that works as a scaffold for new bone formation. Hill *et al.* [25], in their preclinical study based on the treatment of defects in the canine proximal humerus, demonstrated the efficacy of the treatment independently of other medical treatments (e.g., alendronate). In a cadaveric study, Stroncek *et al.* [26], after testing the triphasic calcium-based implant, reported that failure load was increased by 20.5% on average. In the subset of osteoporotic femurs, treatment increased failure load by 26% and work to failure by 45%. Howe *et al.* [27], in 2019, described the first-in-human study of an AGN1 local osteo-enhancement procedure (LOEP). In this prospective cohort study, 12 postmenopausal osteoporotic women aged 56 to 89 years were enrolled with an average follow up of 6 years. It was shown that treated femoral neck areal BMD increased by 68 ± 22%, 59 ± 24%, and 58 ± 27% over control at 12 and 24 weeks and 5–7 years. Moreover, X-ray and CT scans demonstrated that AGN1 resorption and replacement with bone was nearly complete by 24 weeks and no serious adverse events were recorded in any case.

Surgical technique: The patient is positioned on a radiolucent fracture table. 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 cannulated drill over the guide pin was used to create

a 5.3 mm portal through the cortex, which was then extended from the lateral subtrochanteric region through the femoral neck. The enhancement site was gently debrided using a blunt probe brusher and the site was irrigated with sterile saline and then aspirated to remove fat and other loose non-structural elements. AGN1 was then manually injected into the proximal femur and hardened in about 20 minutes. Following recovery from anesthesia, subjects were fully weight bearing within 4 h of the procedure.

Conclusion

Fragility fractures are among the leading causes of morbidity and mortality worldwide and, from an economic point of view, represent an enormous challenge to our health care system. Although medical treatment is effective in reducing the rate of these fractures, it is essential to find a procedure that guarantees both immediate and lasting effectiveness over time: a LOEP with AGN1 represents, as demonstrated by Howe's first-in-human study^[27], an important step forward in the management of this pathology. Contrary to other types of osteo-enhancement, AGN1 maintains its effectiveness by restoring the bone stock in a more physiological way, while theoretically reducing possible adverse reactions (e.g., thermal necrosis, greater difficulty in the event of reoperation) observed with other procedures. The efficacy along with the safety for the patient are the basis for creating new clinical and comparative studies in larger case series and with longer follow ups, to demonstrate the real effectiveness and superiority of some procedures over others.

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