Clinical management of osteoporotic vertebral fracture treated with percutaneous vertebroplasty

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Summary

Our study demonstrated percutaneous vertebroplasty (PVP) is an effective procedure to rapidly reduce back pain in patients affected by acute osteoporotic vertebral compression fractures (OVCFs) assessed by MRI. We confirmed in our sample, femoral bone density impacts more deeply than vertebral T-score and/or BMD on bone strength, as it is less affected by any interferences. We interestingly found the presence of previous osteoporotic fragility fractures and chronic glucocorticoids therapy should especially negatively influence bone health of our patients. On the other hand, even if both FRAX scores for major osteoporotic fractures and for femoral fractures seemed to globally define a population at major risk for fragility fractures, our analysis is retrospectively done. We choose and suggest a multidisciplinary medical management of these patients, considering OP is a multifactorial disease and OVCFs usually produce lots of different important consequences on general health.

KEY WORDS: vertebral fracture; osteoporosis; vertebroplasty; FRAX.

Introduction

Osteoporosis (OP) is the most common age-related progressive skeletal disease characterized by bone loss and consequent tendency to fractures (1, 2), generally found in postmenopausal women or in both sexes 65 years of age and older. On the other hand, a precocious and unusual reduction of bone mass and/or quality may be observed also in premenopausal women and men, due to other different conditions. In fact, secondary OP may be related to an underlying cause, like lifestyle factors, nutritional deficiencies, endocrinopathies, systemic affections (myeloma multiple, mastocytosis), or chronic drugs intake (immunosuppressive agents, glucocorticoids, etc.) (3-7). In both cases, bone loss results in increased susceptibility to fracture in different sites (mainly vertebrae, then femur, wrist) (8). Osteoporotic vertebral compression fractures (OVCFs) are the most common consequence of OP causing back pain and impairment in physical function and quality of life (QoL) (9, 10).

Percutaneous vertebroplasty (PVP) is a minimally invasive technique used to safely and effectively treat acute symptomatic OVCFs, injecting polymethylmethacrylate (PMMA) into the vertebral body to stabilize the fracture (11). PVP produces significant and immediate relief from pain and improvement of physical activity and QoL in patients with painful VCFs (12, 13). However, sometimes post-PVP new fractures may recur, and treatment must be repeated (14). Data show that 41-67% of new vertebral fractures occurs at level adjacent to the augmented vertebra (14-16). Subsequent compression vertebral fractures in patients affected by OP may not be a complication of the procedure itself but should be a part of natural course of OP (17, 18).

We report our experience about management of OVCFs after PVP, underlying role of medical multidisciplinary management after procedure. We also discuss possible impact of the main osteoporotic fracture risks considered in Fracture Risk Assessment Tool (FRAX) in causing fracture in these patients.

Patients and methods

We recruited a total of 73 patients of both sexes with at least one acute painful vertebral fracture for which they had been referred to our Unit. OVCFs were been detected by magnetic resonance imaging (MRI) scan of the spine. Patient history and MRI study, owing to its sensitivity for bone marrow edema, are both important to differentiate chronic from acute compression fracture and to establish the time of the fracture event. Patients with continuing pain due to compression fractures despite medical therapy and presenting bone marrow edema in MRI may be candidates to PVP. After informed consent, patients who agreed to undergo PVP, underwent complete anamnestic and clinical study comprehensive of family history, life risk factors, antropometric evaluation, blood sample and bone densitometry. We collected age, body mass index (BMI), smoking, use of chronic drugs, dietary calcium intake, number and level of the acute vertebral
fractures.
Baseline biochemical and hormonal evaluation were performed in all subjects to exclude abnormalities in calcium metabolism or secondary OP (e.g., for hyperparathyroidism, hyperthyroidism, or other systemic affections). In particular, we dosed plasma calcium, phosphorus, magnesium, serum parathyroid hormone (PTH), and serum 25-Hydroxy vitamin D (25(OH)D). Bone turnover markers such as bone alkaline phosphates (bALP), osteocalcin (OC) and beta cross laps (β-cross laps) were also assessed. Bone mineral density was assessed by double-energy X-ray absorptiometry (DXA) performed at vertebral and femoral sites according to WHO criteria (19).

The Fracture Risk Assessment Tool (FRAX) is generally used to identify individuals who should be candidates for BMD screening or pharmacological intervention. FRAX score for major osteoporotic fractures (fracture of hip, spine, wrist, humerus) risk ≥ 20% and for hip fracture ≥ 3% respectively reflect a significant 10-year probability to have a fragility fracture. In our study, this algorithm was used to retrospectively evaluate the 10-year absolute probability of hip or major osteoporotic fracture considering age, gender, race and clinical profile, with BMD value (grams/cm²), measured at femoral neck (19).

All PVPs were carried out by the same operator (AP). Vertebroplasty consists in percutaneous injection of bone cement called polymethylmethacrylate (PMMA) into the collapsed vertebrae under fluoroscopic imaging guidance (11). All procedures were performed on local anesthesia but didn’t require sedation. Before starting treatment, cefazolin 2 gr was administered intravenously as prophylaxis against any possible infection. All patients were fully monitored in the angio suite, where sterile preparation for surgery was performed. The operator infiltrated the skin and subcutaneous tissues overlying the pedicle of the target vertebrae with 1% lidocaine and generally reached and filled rim fracture through a monolateral access (transpedicular, parapedicular). The practitioner preferentially used 13G or 15G needle. After PVP, patients were monitored in the supine position for 1 to 2 hours before discharge. PVPs usually were well tolerated and produced rapid and persistent relief from back pain within few hours (20). The exclusion criteria for PVP were: systemic or local infections, suspected underlying malignant diseases, untreated coagulopathy, severe cardio-pulmonary condition, radicular or caudal compression syndrome and other active associated disorders (i.e. fibromyalgia or spondyloarthopathies) which may interfere with the correct assessment of pain and QoL after PVP.

Pain assessment was based on the Visual Analogue Scale (VAS) score, consisting in a scale from 0 to 10 in which 0 indicates no pain and 10 the maximum level of pain while 1-5 units are considered the minimal clinically relevant difference (21).

All patients were also asked about a previous diagnosis of OP and/or fragility fractures. We reported their therapy of OP before and after the treatment [a combination treatment including calcium and vitamin D supplementation with antiresorptive agents like bisphosphonates (BPs) – alendronate, risedronate, ibandronate – or denosumab (Dmb) – a human monoclonal IgG2 antibody inhibiting RANK signalling regulating osteoclastic activity and survival – (22, 23), anabolic agents like PTH analogs – available in the form of human recombinant PTH peptide 1-34 (Teriparatide) or as 1-84 rh-PTH, or strontium ranelate]. General postoperative management, including antiosteoporotic drugs, analgesics, and lifestyle education, was offered to all patients. In particular, analgesic therapy was considered a mainstay to strengthen the effect of PVP and was carefully managed by a specific team. Everyone was also invited to receive additional systematic back muscle exercises under specific physiotherapeutic indications (24). Systematic back muscle exercises were started at three to five days after PVP, when the pain level had been remarkably decreased by the procedure and walking ability had been regained. They were all informed that the systematic back muscle exercises had to be maintained throughout their lifetime. Training postures were checked at follow-up.

We registered new symptomatic VCFs and patients who need to repeat PVP. VAS score were also assessed before and after PVP. At the present, we report the results of about 1 month after PVP even if all patients were asked to return to control visits every 6 months thereafter, since follow-up is still ongoing. The pre-planned mean follow-up period will last a minimum of 12 months for each patient. The control visits were performed by the same physician.

Results
A total of 73 patients (61 females and 12 males) met the inclusion criteria and were treated with PVP and then included in the follow-up program which is still going on. Enrolled subjects were 77.3 ± 8.2 years old and had a mean BMI 25.4 ± 3.4 (Table 1). At baseline, mean spine T-score was -2.13 ± 1.69 and lumbar BMD was 0.865 ± 0.217 g/cm²; mean total hip T-score was -2.31 ± 0.957 with femoral total BMD 0.678 ± 0.139 g/cm²; femoral neck T-score was -2.65 ± 0.84 with corresponding BMD 0.583 ± 0.128 g/cm². A total of 130 vertebral fractures were treated with PVP and the majority of fractures were found on L1 and D12 vertebral bodies. The majority of patients were affected by post-menopausal OP, while in the smaller part, fractures were considered completely related to a secondary cause, or endocrinopathies (2 primary hyperparathyroidism).

A significant correlation was found between sex and BMD. In fact, mean female lumbar T-score was -2.3 ± 1.6 (BMD: 0.821 ± 0.184 g/cm²) versus mean male T-score -1.2 ± 1.8 (BMD: 1.082 ± 0.249) reported in men. Female total femoral T-score result -2.4 ± 0.9 (BMD: 0.649 ± 0.127) while it was -1.6 ± 0.5 (BMD: 0.823 ± 0.103) for male subjects. Femoral neck T-score was -2.8 ± 0.8 (BMD: 0.552 ± 0.103) in women and -1.9 ± 0.6 (BMD: 0.736 ± 0.137) in men. In our sample, age and BMI seem to especially impact on femoral bone density (age vs total femoral T-score p=0.022; age vs total femoral BMD p=0.011; age vs femoral neck T-score p=0.019; age vs femoral neck BMD p=0.006); BMI vs total femoral T-score p= 0.006; BMI vs total femoral BMD p= 0.005).

On the contrary, sex was demonstrated to affect bone density of both skeletal sites at major fracture risk: (sex vs lumbar BMD p=0.004; sex vs total femoral T-score p=0.038; sex vs total femoral BMD p=0.001; sex vs femoral neck T-score p= 0.009; sex vs femoral neck BMD p=0.001). Among all risk factors for bone fragility considered in our patients, previous use of glucocorticoids for treatment of other diseases was the most important in significantly influencing bone health, in particular, lumbar T-score (p=0.013), lumbar BMD (p=0.022), total femoral T-score (p=0.034). The pres-
ence of previous fragility fractures importantly affected total femoral T-score ($p=0.016$) and femoral neck T-score ($p=0.035$). In our sample, neither smoking or family history nor early menopause seem to effectively impact on bone density ($p= ns$).

None significant correlation were found between serum calcium, 25(OH)D and any markers of bone turnover levels and vertebral or femoral T-score/BMD. Neither thyroid function showed significant correlation with bone density. Previous therapy with BPs resulted to be correlated with femoral neck T-score ($p=0.018$).

We reported a strong correlation between the risk of major osteoporotic fractures assessed by FRAX and lumbar BMD ($p=0.042$), total femoral T-score ($p=0.003$), and total femoral BMD ($p=0.004$). Risk of femoral fracture evaluated by the same algorithm showed a significant correlation with lumbar BMD ($p=0.043$), total femoral T-score ($p=0.020$) and total femoral BMD ($p=0.029$).

VAS appeared to effectively reduce within few hours after PVP and, in preliminary data, maintained a significant reduction 6 months after the procedure ($p=0.02$).

### Discussion

Our paper describes clinical management of acute OVCFs treated with PVP reported in 73 patients 77,3 ± 8,2 years old. Post-menopausal women represent the majority of subjects enrolled in our study. Sex and mean age of our patients are in line with current epidemiological studies about bone fragility (25). Osteoporosis is a skeletal disease characterized by loss of bone density and/or quality which is usually much more common in the elderly (26). In fact, progressive bone loss is a physiological result of ageing. In particular, pre-menopausal and menopausal period (27, 28) owing to gradual reduction of estrogens and progesterone (P4), produce a higher rate of bone remodeling and a marked imbalance in Bone Multicellular Compartment (BMC) (29, 30). In the early stage of menopause, hyperactivity of osteoclasts, bone cells mostly involved in bone resorption, because of decreased level of estradiol (E2), causes rapid bone turnover with, at the same time, a significant reduction of bone formation rate, even due to lower P4 (29). On the other hand, the slow reduction of osteoblastic activity and survival, typical of the late post-menopause and ageing, gradually worsen bone health (31). In women, the risk of VCFs tends to increase after menopause owing to high involvement of trabecular bone into the remodeling process (32). However, VCFs are often underdiagnosed as they require hospitalization only in few cases; besides, a minimal reduction of vertebral body height does not ever produce significant back pain and sometimes may be totally asymptomatic or paucisymptomatic (33). Nevertheless, it is largely recognized the presence of previous radiographic and/or clinical VFs is strongly associated with higher probability of new fragility fractures in the same or in the other sites at major risk for osteoporotic fractures (34). OVCFs may also produce other important consequences on general health like impairment of cardiopulmonary performance, neurological sequelae, chronic back pain and permanent disability, highest mortality and morbidity (35, 36). Otherwise, recent data showed that only a small percentage of patients receives an adequate medical treatment, even after a clear diagnosis of OVCFs (37). Therefore, the need of increasing the awareness of the problem of OVCFs becomes crucial and our study would partially contribute to this purpose.

We interestingly found our patients are generally osteopenic as suggested by mean lumbar and total femoral T-score val-
ues. That evidence confirms results of National Osteoporosis Risk Assessment (NORA) study which surprisingly showed 82% of postmenopausal women with fractures had T-scores better than -2.5 (38). In NORA study, Siris et al. demonstrated even apparently less significant reduction of bone density like that observed in osteopenia, may lead to an increased risk of fragility fractures. We should explain these data considering decreased bone strength not only as the result of low bone density but also the possible consequence of loss of bone quality (39).

Our study showed a significant correlation between age and femoral bone density (age vs total femoral T-score \( p = 0.022 \); age vs total femoral BMD \( p = 0.011 \); age vs femoral neck T-score \( p = 0.019 \); age vs femoral neck BMD \( p = 0.006 \)) while lumbar spine T-score and/or BMD do not correlate with patients’ age. Femoral bone density is generally not affected by arthrosis, osteoarthritis or bone calcification which should make more difficult the interpretation of DXA at vertebral level. In that manner, femoral density usually more precisely reflect bone status of a patient as it is less influenced by these phenomena (40).

An important correlation was found between sex, on one hand and both lumbar and femoral bone density, on the other hand. Mean T-scores and BMD appeared lower in female subjects than in male ones, as osteoporosis/osteopenia are more clearly frequent in women (41, 42).

In our sample, BMI significantly correlates with total femoral T-score (\( p = 0.006 \)) and BMD (\( p = 0.005 \)). It is well known body composition is strongly linked to skeletal health (43, 44). Adipose tissue produces positive effects on bone through different mechanisms like the physiological peripheral conversion of androgens into estrogens, the effects of hyperinsulinemia in lowering Sex Hormone Binding Globulin (SHBG) and increasing Insulin Growth Factor type 1 (IGF-1) which both promote bone mass achievement (45-47).

We evaluated the impact of risk factors included in FRAX (48, 49), an algorithm worldwide used to assess risk of fragility fractures, on our sample. FRAX is an algorithm which combines anthropometric features, clinical risk factors and BMD value, usually detected at femoral neck, to estimate an individual’s 10-year osteoporotic fracture (both major osteoporotic fractures and hip fracture) probability. Additionally, FRAX scores were correlated with both vertebral and femoral T-score and/or BMD.

A history of previous osteoporotic fragility fractures strongly correlates with femoral bone density (femoral T-score \( p = 0.016 \); femoral neck T-score \( p = 0.035 \)), according to the well-known growing risk of subsequent fractures after the first fragility event (14, 50). Gehlback et al. demonstrated in their Global Longitudinal observational Study of Osteoporosis in Women (GLOW) (50), previous fractures of the hip, spine, or wrist are relevant independent predictors of future fractures. In particular, in that study the strongest predictors of incident spine and hip fractures resulted spine (hazard ratio [HR] = 7.3) and hip (HR = 3.5) fractures, confirming preceding data emerged from different articles (14).

Corticosteroid-induced osteoporosis is the most common form of secondary osteoporosis and the first cause of precocious bone loss in young people. In our patients, chronic glucocorticoid therapy seems to deeply influence vertebral T-score and BMD, as shown by the correlation between use of corticosteroids and lumbar T-score (\( p = 0.013 \)) and BMD (\( p = 0.022 \)) and total femoral T-score (\( p = 0.034 \)). Many studies prove glucocorticoids cause marked bone loss and relevant alterations of bone quality especially at higher doses and irrespective of methods of administration (51-54). However, bone loss magnitude is variable and there is no clearly identified predictor of the individual risk of fracture (53). A recent study interestingly revealed vertebral fracture incidence is higher among oral glucocorticoids users and may be more frequent than usually expected (52).

Among other fracture risk factors considered in FRAX tool, smoking, parental fractures, alcohol consumption or other possible causes of secondary OP (55, 56), like early menopause, do not seem to produce a major risk for osteoporotic fracture in our sample, if singly considered. Perhaps, all these factors can potentially impact on global risk of bone fragility when they act simultaneously. This observation may be explained by the fact that fracture event should be considered per sé a final multifactorial effect resulting from different factors which concurrently act in promoting bone fragility (19, 22).

In an interesting manner, in our study FRAX score for major osteoporotic fractures significantly correlate with lumbar BMD (\( p = 0.042 \)), total femoral T-score (\( p = 0.003 \)), and total femoral BMD (\( p = 0.004 \)). After all, major osteoporotic fractures include also vertebral fractures and bone density is one of the main determinant of skeletal resistance (52).

FRAX score calculated to estimate 10-year probability for femoral fracture risk shows a significant correlation with lumbar BMD (\( p = 0.043 \)), total femoral T-score (\( p = 0.020 \)) and total femoral BMD (\( p = 0.029 \)). This data confirms femoral bone density reflects more accurately than vertebral T-score and/or BMD bone strength, as it is less affected by various interferences (52). On the other hand, BMD is largely recognized as the main determinant of bone strength of cortical bone (57, 58).

FRAX tool seems to correspond to a subset of patients at major risk for fragility fractures even if our analysis was retrospectively done. Some studies supposed FRAX for major osteoporotic fractures (considered with and without femoral neck BMD) should predict vertebral fracture (59). However, the validity of the 10-yr probability of major osteoporotic fracture model (FRAX) for prediction of vertebral fracture has not been clearly elucidated in the general population. Donald et al. showed a combination of baseline radiographic vertebral fracture, femoral neck BMD, and age were effective predictor of future vertebral fracture (59).

Among other various possible risk factors of bone loss which are not included into FRAX (vitamin D deficiency, high bone turnover markers), none result to be individually related with bone density. This data may be explained pointing out bone mass achievement and maintenance depends on a mixture of different aspects which work together as always occurs in a multifactorial disease (60). On the other hand, the osteoporotic risk factors included in FRAX may be effectively the most important for bone homeostasis if considered all together.

In all patients enrolled, PVP produce an early significant pain relief in few hour after the procedure (\( p = 0.02 \)). This result is strongly demonstrated by the important reduction of VAS score indicating decreased back pain after the procedure. These data confirm beneficial effects of PVP in the management of acute OVCFs (61). In current follow-up of these patients, subsequent personalized analgesic and anti-osteoporotic medical treatment associated with a specific physical therapy appeared necessary to improve general health and quality of life. According to our preliminary evidence, this
multidisciplinary approach seems to be useful to obtain the best clinical, functional and psychological results in our patients.

Conclusion

Our study demonstrated PVP is an effective procedure to rapidly reduce back pain in patients affected by acute OVCFs assessed by MRI (61, 62). We confirmed in our sample, femoral bone density impacts more deeply than vertebral T-score and/or BMD on bone strength, as it is less affected by any interferences (52). We interestingly found the presence of previous osteoporotic fragility fractures and chronic glucocorticoids therapy should especially negatively influence bone health of our patients. On the other hand, even if both FRAX scores for major osteoporotic fractures and for femoral fractures seemed to globally define a population at major risk for fragility fractures (63), our analysis is retrospectively done. We choose and suggest a multidisciplinary medical management of these patients, considering OP is a multifactorial disease and OVCFs usually produce lots of different important consequences on general health (64).

References


