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Review article

Management of glucocorticoid-related osteoporotic vertebral fracture

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ABSTRACT

The vertebral column is the most common site of osteoporotic fractures in long-term users of glucocorticoids. Vertebral fracture leads to significant morbidities such as unrelenting pain, spinal deformities and reduced mobility, leading to diminished quality of life. Epidemiological data on the prevalence of glucocorticoid-induced vertebral fractures are limited. As vertebral fracture is a strong risk factor for further fragility fractures and mortality, it should be treated appropriately. This article reviews recent data on the prevalence of vertebral fractures in glucocorticoid users, fracture risk stratification, and evidence-based treatment options. The risk of osteoporotic fractures estimated by FRAX should be adjusted for glucocorticoid users. The first-line treatment of glucocorticoid-induced osteoporosis remains the bisphosphonates. Teriparatide and denosumab are alternative options. Percutaneous vertebroplasty and kyphoplasty may be considered for symptomatic control of acute vertebral fracture-related pain when conservative measures fail.

1. Introduction

The chronic use of glucocorticoids (GCs) is the main cause of nontraumatic vertebral fracture (VF) in patients with autoimmune inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). GCs alter the cellular composition of bone by interfering with the recruitment, proliferation and lifespan of osteoclasts and osteoblasts, which lead to impairment of bone formation, increase in bone resorption and deterioration of bone microarchitecture [1]. GCs also influence the survival of the long-lived osteocytes that mediate the homeostatic adaptation of bone to mechanical forces [2]. In long-term users of GCs, fractures occur more frequently in the vertebral column than the long bones. Despite the spine being the commonest site of osteoporotic fracture, it is often overlooked because clinical symptoms and precipitating factors such as a recent fall may not be apparent [3,4]. As a result, only 30%–40% of VFs finally come to medical attention [5]. As VF is linked to substantial morbidity and mortality [6,7], and predict future osteoporotic fractures [3,8], secondary prevention is of utmost importance. This article reviews the current evidence for the primary and secondary prevention of VF related to the chronic use of GCs.

2. Methods

A MEDLINE search for articles between years 1989 and 2019 were conducted using the key words “prevalence,” “fragility,” “fracture,” “osteoporosis,” “spinal,” “vertebral,” “glucocorticoids,” “randomized controlled trials,” “kyphoplasty,” “vertebroplasty,” “recommendations,” and “guidelines.” Articles returned were filtered and summarized under the following headings: (1) prevalence of VF in the general population; (2) prevalence of GC-induced VF; (3) assessment of VF; (3) risk factors of GC-induced osteoporosis; (4) randomized controlled trials (RCTs) on treatment of GC-induced VF, and (5) consensus recommendations from various professional bodies.

3. Prevalence of VF in the general population

There is still no gold standard for the radiological diagnosis and grading of VF [9]. Different approaches have been used for screening and assessment of VF in the general population, leading to a discrepancy of its reported prevalence in different epidemiological studies [10–14]. Three methods are commonly used for the identification of morphometric VF and deformities, namely qualitative visual assessment of VF (Qual) [15], semiquantitative (SQ)

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method developed by Genant and colleagues [16], and the algorithm-based approach for qualitative identification of VF assessment (ABQ) proposed by Ferrar et al. [17]. The main features of these methods for detecting VF are summarized in Table 1. There is poor agreement among these methods, with the more stringent ABQ yielding a lower prevalence of radiographic VF than the Qual or SQ methods [18].

In the general population, the incidence and prevalence of VF as screened by qualitative morphometric methods increases with age [10–12]. Results are consistent across different ethnic groups in countries of Asia, Europe, Latin America, Canada, and the United States [10–14,19–22]. The risk of VF is higher in men than women before the age of 55 years but the incidence of VF rises rapidly in women after the age of 60 years [10]. There is also interethnic difference in the prevalence of VF. For instance, the age-specific prevalence rate of VF is higher in the Caucasians but lower in Asians and the Latin Americans [10].

A few studies reported the prevalence of VF in the Chinese population [11–14]. In an epidemiology study from mainland China, the prevalence of VF was <20% in individuals aged 50–69 years in Beijing, Shanghai, and Chengdu, and 19%, 25.1%, and 25.4%, respectively, in those aged 70–79 years in these 3 places. In people aged >80 years, the prevalence of VF was above 36% [11]. Another study from Beijing [12] revealed the prevalence of VF, as defined by vertebral morphometry, increased from 5% in women with 50–59 years of age to 37% in women of age greater than 80 years [12]. In Hong Kong, the prevalence of VF (Genant's SQ scoring system ≥ grade 2 [17]) was 5.0% and 12.1%, respectively, among older men and women (mean age, 72 years) [13], while in Taiwan, the adjusted prevalence rate of VF (radiomorphometric method) for women >65 years was 20% [14].

4. Prevalence of GC-induced VF

There are only several observational studies on the prevalence of VF in users of GCs and its correlation with GC dosage. In a 20-year longitudinal study of 161 male adult patients [23], initial high-dose GC (≥20-mg/day prednisolone or equivalent) was associated with a significantly higher prevalence of symptomatic VF than those not using GCs. Another retrospective study evaluating the impact of systemic GC exposure on fracture risk among young patients with new-onset RA showed a dose-related increase in VF rate with daily and cumulative doses of GC, while discontinuation of GC was associated with a decreased risk in the next 12 months [24]. On the other hand, a meta-analysis published in 2002 reported strong correlation between use of GC, loss of bone mineral density (BMD) and the risk of VF [25].

Population-based studies [26–29] have demonstrated high prevalence (13.7%–50%) of morphometric VF in patients with SLE, of whom more than 30% had normal BMD. Increasing age, longer disease duration, previous GC use, and previous fractures were reported to be independent risk factors for VF in SLE patients [26–30]. In a recent study of 134 children with rheumatic disorders [31], correlations have also been found between increasing dose of GC and VF risk. Each 0.5-mg/kg increase in the mean daily dose of GC was associated with a 2-fold increase in VF risk. The incidence of VF was 4.4 per 100 person-years within the first 3 years following GC initiation. VF risk was highest in the first year of GC treatment and remained elevated during the first 3 years of GC initiation [31].

5. Management guidelines on GC-induced VF

Different national and regional recommendations for the management of glucocorticoid-induced osteoporosis (GIOP) have been published. A summary of the American College of Rheumatology (ACR), United Kingdom (UK) and the International Osteoporosis Foundation recommendations is shown in Table 2 [32–34].

6. Nonpharmacological treatment

Weight-bearing exercise, high calcium diet and removal of modifiable risk factors such as habitual smoking and drinking are important nonpharmacological measures of GIOP. A calcium intake (1000–1500 mg/day) and vitamin D intake (600–1000 IU/day) are recommended [32–34]. It is also important for physicians to use the lowest GC dose as possible once the underlying disease is under control.

7. Pharmacological treatment

The indication for pharmacological intervention of GC-related osteoporosis depends on the fracture risk estimation of individual patients as suggested by the ACR (Table 3). The use of FRAX algorithms as fracture risk stratification will be discussed below. Intervention threshold of different guidelines are shown in Table 2. All patients with prior osteoporotic fractures are regarded as high-risk group and pharmacologic treatment may be started even without a baseline FRAX score or DXA scan assessment.

8. Estimation of VF risk using the FRAX

The World Health Organization developed a fracture risk assessment algorithm (www.shef.ac.uk/FRAX) to provide the 10-year probabilities of hip and major osteoporotic fracture (clinical spine, hip, humerus, and forearm) based on a profile of clinical risk factors (e.g., GC use for ≥3 months at a dose of prednisolone of 5 mg daily or more, confirmed diagnosis of RA, age, sex, current smoking, drinking, personal and parental history of fragility fractures, etc.)

Table 1
Comparison of plain radiological methods to define vertebral fractures.

	Qualitative visual assessment [15]	Semiquantitative methods [16]	Algorithm-based qualitative method [17]
Osteoporotic vertebral fracture identification	Radiographs qualitatively read with the aid of a radiological atlas of normal variants	Visual estimation of apparent % reduction in vertebral height; fracture identified when vertebral height appears to be reduced by ≥ 20%–25%	Diagnosed based on the assumption fractures always involve fracture of the endplate within the vertebral ring; collapse occurs primarily at the center of the endplate (central depression) (concave, wedge, and crush fracture); vertebral fracture diagnosed by an algorithm to exclude normal variants and nonfracture deformities.
Severity and occurrence of new osteoporotic vertebral fracture	–	Apparent reduction in vertebral height: Grade 1 (mild): ≥20%–25% Grade 2 (moderate): >25 to <40% Grade 3 (severe): ≥40%	New fracture: change from normal to abnormal appearances Worsening of exiting fracture: new fracture at opposite endplate, change in type of fracture at the same endplate or further reduction in around 4 mm of the vertebral height at the same endplate

Table 2
Guidelines for the management of GIOP.

Guidelines	ACR [32]	UK [33]	IOF [34]
Pharmacological intervention threshold	GC-adjusted risk stratification by FRAX Moderate to high risk for men/women (non−child-bearing potential) < 40 and ≥ 40 years of age	GC-adjusted risk stratification by FRAX Previous fractures, age ≥70 years or prednisolone ≥7.5 mg/day or FRAX risk above intervention threshold in different localities	GC-adjusted risk stratification by FRAX Previous fractures, age ≥70 years or prednisolone ≥7.5 mg/day or FRAX risk above intervention threshold in different localities
Calcium and vitamin D	Calcium (1000−1200 mg/day); vitamin D (600−800 IU/day)	Calcium (700−1200 mg/day); vitamin D (≥800 IU or 20 μg)	Calcium (1200−1500 mg/day); vitamin D (800−1000 IU or 20 −25 μg)
Pharmacologic recommendations			
Medication recommendation	First-line: oral BSPs, followed by IV BSP > teriparatide > denosumab > raloxifene Second-line (new fracture after 18 months' treatment or ≥10% yearly loss of BMD): teriparatide or denosumab or IV BSP	First-line: oral BSPs Second-line: IV BSP or teriparatide	Oral BSPs, etidronate, IV BSP and teriparatide for most patients
Discontinuation of treatment	If GCs are discontinued and low risk of fracture on reassessment	Consider when GCs are discontinued	Consider when GCs are discontinued

GIOP, glucocorticoid-induced osteoporosis; ACR, American College of Rheumatology; UK, United Kingdom; IOF, International Osteoporosis Foundation; GC, glucocorticoid; BSP, bisphosphonate; IV, intravenous; BMD, bone mineral density.

Table 3
Fracture risk stratification in GC-treated patients [32].

Fracture risk	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤ -2.5 in men age ≥ 50 years and postmenopausal women FRAX[a] (GC-adjusted[b]) 10-year risk of major osteoporotic Fracture[c] ≥20% FRAX (GC-adjusted) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX (GC-adjusted) 10-year risk of major osteoporotic Fracture 10%−19% FRAX (GC-adjusted) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z-score < −3 or rapid bone loss (≥10% at the hip or spine over 1 year) and Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX (GC-adjusted) 10-year risk of major osteoporotic Fracture <10% FRAX (GC-adjusted) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

GC, glucocorticoid.
[a] https//www.shef.ac.uk/FRAX/tool.jsp.
[b] Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is ≥ 7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
[c] Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

and country-specific fracture rate and mortality [35]. GC use is an important covariate in the FRAX regression equation. However, the cumulative and initial dosage of GC is not considered in the FRAX risk estimation models. To address this limitation, arithmetic adjustment to the probabilities of having a hip or major osteoporotic fracture is suggested in patients with low, moderate and high exposure to GCs [35]. For patients using a daily prednisolone dose of 7.5 mg or more, a 15% increase in the major osteoporotic risk and 20% increase in hip fracture risk at 10 years should be added to the estimated figures [35].

9. Estimation of fracture risk using qualitative computed tomography

In addition to quantity of bone, GCs also have a deleterious effect on bone quality which increases the risk of fragility fractures per se [36]. As a result, the lumbar spine BMD may underestimate the VF risk in chronic GC users [36]. A cross-sectional study of bone quality assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) and microfinite element analysis (μFEA) in GC-treated SLE patients showed that bone microarchitecture was disrupted and bone strength was reduced in patients as compared to normal controls [37]. However, the relationship between the increase in bone fragility as detected by HR-pQCT and VF risk could not be evaluated as a result of the limited number of patients with a fracture history and the absence of data on asymptomatic VF. Whether HR-pQCT and μFEA can provide more accurate information for prediction of VF risk beyond areal BMD requires further study.

10. Pharmacologic treatment

Pharmacological agents approved for prevention and treatment of GIOP and associated VF include the bisphosphonates, parathyroid hormone (PTH) (teriparatide) and denosumab.

10.1. Bisphosphonates and VFs

Antiresorptive agents such as bisphosphonates are

recommended in both ACR and Royal College of Physicians guidelines as first-line treatment for GIOP [33,34]. Most available data favor the use of the oral bisphosphonates (e.g., alendronate or risedronate). Intravenous (IV) zoledronic acid (ZOL) is an acceptable alternative for those patients who cannot tolerate oral bisphosphonates. A study by Saag et al. [38] involving 477 GC-treated patients who were randomly assigned to alendronate (5 or 10 mg of alendronate daily) or placebo demonstrated that the use of alendronate was associated with fewer incident VF than those treated with placebo after 2 years (2.3% vs. 3.7%; relative risk, 0.6 [0.1–4.4]).

In an RCT investigating the use of risedronate therapy in preventing bone loss in 224 GC-treated patients [39], incident VF was found numerically less common in the 5-mg risedronate group than placebo users after 12 months (5.7% vs. 17.3%, P = 0.07). Another study randomly assigned 290 patients receiving long-term GC treatment (defined as prednisolone >7.5 mg/day for >6 months) to either risedronate (2.5 mg–5 mg/day) or placebo for 12 months [40]. The collective data for the risedronate 2.5 and 5 mg groups showed a statistically significant reduction in VF incidence by 70% (P = 0.04). The reduction of VF in the risedronate 5 mg group did not reach statistical significance (P = 0.13) [40]. A larger RCT of patients receiving moderate to high doses of oral GCs (≥7.5-mg/day prednisone) were conducted and patients were randomized to receive to placebo (N = 173), risedronate 2.5 mg/day (N = 169) or risedronate 5 mg/day (N = 176) [41]. Results showed a significant reduction of VF (70%) in the risedronate 5 mg compared to placebo group (P = 0.01). ZOL is an IV bisphosphonate. In a pivotal RCT, the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) study [42], 833 patients using prednisolone (≥7.5 mg/day or equivalent) were treated with one dose of IV ZOL (5 mg) or oral risedronate (5 mg/day). Results showed that ZOL was noninferior and superior to risedronate for the increase in lumbar spine BMD at 12 months (primary outcome). The occurrence of new thoracic and lumbar VFs at 12 months, defined according to the semiquantitative method by Genant et al. [16], was very infrequent in both groups (ZOL [n = 5] and risedronate [n = 3]). Whether the low VF rate reflected the antifracture efficacy of both drugs has to be interpreted with caution given the short period of follow-up.

10.2. Teriparatide and VFs

The anabolic agent, teriparatide, is generally used as second line for treatment for GIOP, especially for patients with severe osteoporosis and those who are intolerance to the bisphosphonates. In the 18-month landmark double-blind RCT [43], 428 subjects (80% women) on long-term prednisone (≥5 mg/day for ≥3 months) were assigned to teriparatide (20 μg/day) subcutaneously or oral alendronate (10 mg/day). Results showed that there were fewer new radiographic VFs in the teriparatide than alendronate group (0.6% vs. 6.1%, P = 0.004). At 36 months, new VFs remained significantly less common in the teriparatide than alendronate group (1.7% vs. 7.7%, P = 0.007), with most occurring during the first 18 months [44]. Teriparatide is licensed for treatment of osteoporosis for 24 months only because of the potential risk of osteogenic sarcoma. Antiresorptive agents (e.g., oral bisphosphonate) should follow completion of PTH therapy to preserve the gain in BMD achieved during PTH therapy.

10.3. Denosumab and VFs

Denosumab is a human monoclonal antibody targeting the key bone resorption mediator RANKL (receptor activator of nuclear factor κB ligand). A small RCT recruited 42 women receiving long-term GC and oral bisphosphonates (≥2 years) who were assigned to continue bisphosphonates (N = 21) or switched to denosumab (N = 21) [45]. At month 12, BMD of the lumbar spine and hip increased by 3.4% ± 0.9% (P = 0.002) and 1.4% ± 0.6% (P = 0.03), respectively, in the denosumab group; whereas the corresponding change was 1.5% ± 0.4% (P = 0.001) and 0.80% ± 0.5% (P = 0.12) in the bisphosphonate-treated patients. This study suggested that switching from oral bisphosphonates to denosumab resulted in greater increase of the spinal BMD in GC users.

In a more recent multicenter double-blind double-dummy noninferiority RCT, 795 patients who were using GCs (≥7.5 mg prednisone daily or equivalent; 36.5% GC-initiating; remaining GC-continuing) were assigned to receive either denosumab (60 mg subcutaneous every 6 months) or risedronate (5 mg oral daily) for 24 months [46]. At 12 months, significantly greater increase in the lumbar spine BMD was observed in the denosumab than risedronate group (GC-continuing 4.4% [3.8%–5.0%] vs. 2.3% [1.7%–2.9%], P < 0.0001); GC-initiating 3.8% [3.1%–4.5%] vs. 0.8% [0.2%–1.5%], P < 0.0001). Incidence of adverse events, serious adverse events (including infections) and fractures was similar between the 2 groups. The 24-month data of this study showed that denosumab continued to be superior to risedronate in raising the BMD at the lumbar spine [47]. Although there were no differences in fracture rate between the 2 treatment arms, this study was not powered to detect this outcome and further extension studies the incidence of VFs are needed.

Recent studies showed the possible increase in VF as a result of rebound increase in bone turnover that leads to a rapid fall in BMD following discontinuation of denosumab [48–50]. This raises particular concern in GIOP as patients may discontinue GC and denosumab at some stage. Careful planning and counseling of denosumab discontinuation in GC users are important, particularly in high-risk patients for osteoporotic fractures [2]. After cessation of denosumab, it is recommended to switch to other anti-osteoporotic medications (e.g., bisphosphonates) for maintenance [50,51]. Due to the risk of increased VF after drug cessation, denosumab is considered as second-line treatment of GIOP when bisphosphonates and teriparatide are contraindicated or fails [2,48–50].

10.4. Raloxifene and VFs

There are limited data on the efficacy of raloxifene, a selective estrogen receptor modulator (SERM), in GIOP [52] to justify its first-line use for VF reduction in GC-treated patients. Raloxifene may increase the risk of arterial and venous thromboembolism [32] in postmenopausal women and should be considered when all other options are contraindicated. Newer generation SERMs, such as bazedoxifene, are being investigated in postmenopausal osteoporosis [53]. They reduce the risk of VF in postmenopausal women with additional favorable effects in lipids, uterine and breast tissue [54]. Further studies are needed to explore its efficacy in the prevention of VF in patients with GIOP.

11. Recommendations from the ACR

The ACR recommends that patients receiving ≥3 months of prednisolone (≥2.5 mg/day) should receive intervention to prevent osteoporosis [32]. In subjects aged more than 40 years (and not of childbearing potential) with a history of osteoporotic fracture (high-risk) or those without a fracture but had moderate to high risk of having a major osteoporotic (>10%) or hip fracture (>1%) at 10 years as assessed by the FRAX, initial treatment with an oral bisphosphonate is indicated. When oral bisphosphonates are not suitable (intolerance, contraindications, comorbidities, patient's

preference, or concerns about compliance), the IV bisphosphonates (e.g., zoledronic acid) should be considered as an alternative. When the bisphosphonates are not appropriate, other options include teriparatide (costly, inconvenience due to daily injection), denosumab (lacks fracture data) and raloxifene (lacks fracture data; for postmenopausal women only) may be considered.

There is little information regarding the efficacy of anti-osteoporotic medications in reducing fracture in younger patients less than 40 years of age. The ACR recommends treatment for moderate to high risk younger patients, defined as: (1) having a personal history of osteoporotic fracture or (2) rapid bone loss of ≥10% over one year at the spine (assessed by dual X-ray absorptiometry) or (3) those continuing GC treatment (≥6 months at a dose of ≥7.5 mg/day) with BMD Z-score < -3.0 at the spine/hip [32]. The choice of drugs is same as older patients ≥40 years of age except for raloxifene, which is not indicated in men and pre-menopausal women. In all cases, the order of the preferred treatments should be based on relative efficacy (fracture reduction), toxicity and cost.

12. Treatment for painful VFs

Calcitonin has been used to relieve acute pain due to VF but is regarded to have weak evidence by international clinical practice guidelines [55]. A meta-analysis has shown that short-term calcitonin is effective in reducing acute back pain related to a recent VF within 4 weeks but there is no convincing evidence to support the use of calcitonin for chronic pain (>3 months) associated with fractures of the same origin for a longer history [56]. Vertebral augmentation procedures such as percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PKP) has long been used to treat acute pain resulting from VF [57,58]. PVP involve the percutaneous injection of bone cement into a fractured vertebra, with the intent of stabilizing the vertebral body, whereas PKP involves the inflation of a small balloon to create a cavity within the vertebra that is then filled with bone cement [59].

Two RCTs of vertebroplasty for painful osteoporotic VFs with a control arm of sham procedure in 2009 did not report any demonstrable difference in pain control or function between the study groups [60,61]. These results have generated considerable controversy given the increasing number of PVP procedures being performed prior to these studies. Recent double-blind placebo-control RCTs continued to show contradictory results regarding the pain reduction efficacy of PVP [62,63]. A Cochrane systematic review of 6 trials comparing the efficacy of vertebroplasty to usual care showed a significant but small effect on pain reduction at various time points [64]. However, the effect of vertebroplasty on disability or quality of life were inconsistent. As none of these trials were blinded, the treatment effect might have been over-estimated due to the placebo response associated with procedures [64]. On the other hand, placebo-controlled trials of PKP are lacking but unblinded study has shown efficacy of PKP in pain reduction as compared to conservative treatment [65].

Several professional bodies have published their stance on vertebral augmentation [55,59,66–68]. The American College of Radiology [66] and the National Institute for Health and Care Excellence of the UK [55] stated a low level of evidence regarding PVP or PKP and the recommendation of these procedures for VF-related pain is not strong. The American Academy of Orthopedic Surgeons Clinical Practice Guideline recommends against vertebroplasty for VF-related pain [67]. In the recent report from the American Society for Bone and Mineral Research taskforce [59], it was suggested that PVP does not demonstrate clinically significant benefit over placebo in patients with acute and painful VF. There is also insufficient evidence to support kyphoplasty over nonsurgical management.

On the other hand, PVP and PKP may be less beneficial in GIOP than in primary osteoporosis as studies have shown that PVP and PKP might predispose patients to refracture through the shifting of the normal load transmission through the spine [69,70]. Some authors argue that these refractures are the result of the natural progression of osteoporosis in high-risk patients [71]. Tian et al. [72] reviewed the literature regarding PVP or PKP in GC-related osteoporotic VF from 1995 to 2013. One hundred and seventeen GIOP patients with VF from 11 studies were included [72]. It was perceived that PVP was a safe, effective and feasible procedure for pain relief in selected patients with repeated and/or multiple thoracic-lumbar VFs related to GCs. Noteworthy, 43% of patients treated with PVP sustained a refracture which required a repeat of the procedure. Almost all the refractures occurred within a year after PKP or PVP (41.8% were at adjacent level and 58.2% were at remote levels of the involved vertebrae).

Despite the controversies of the efficacy of PKP or PVP, these procedures were increasingly performed for VFs [73] in recent years. The American College of Radiology and a position statement from multiple US Societies suggested vertebroplasty should be used for patients who have failed or cannot tolerate conservative or traditional management [66,69]. Further RCTs are warranted in order to look into its pain alleviating effect on GIOP patients.

13. Summary

GC-related VF is one of the commonest types of osteoporotic fractures in clinical settings but has received little attention. Understanding its prevalence and risk factors would enable risk stratification and early primary and secondary prevention. Oral bisphosphonates remain the first-line pharmacological treatment whereas the IV bisphosphonates, teriparatide, denosumab and raloxifene may be considered for patients who are intolerant/contraindicated or refractory to oral bisphosphonates on an individual basis. Level of evidence for surgical procedures such as PVP and kyphoplasty to relieve VF-related acute pain is not strong. They should be considered as an option for pain relief for those who have failed or cannot tolerate conservative or traditional management. More high-quality and bigger placebo-controlled controlled trials are needed to conclusively define the effectiveness and safety of nonharmacological, pharmacological, and interventional approaches for the management of vertebral fragility fractures.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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