Maturitas 78 (2014) 131–137

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

EMAS position statement: The management of postmenopausal women with vertebral osteoporotic fracture

Ioannis K. Triantafyllopoulos[a,*], Kalliopi Lambropoulou-Adamidou[b], Cleopatra C. Nacopoulos[c], Nikolaos A. Papaioannou[a], Iuliana Ceausu[d,e], Herman Depypere[f], C. Tamer Erel[g], Faustino R. Pérez-López[h], Karin Schenck-Gustafsson[i], Yvonne T. van der Schouw[j], Tommaso Simoncini[k], Florence Tremollieres[l], Margaret Rees[m], Irene Lambrinoudaki[n]

[a] Laboratory of Research for the Musculoskeletal System (LRMS), School of Medicine, University of Athens, 10 Athinas Street, 14561 Kifissia, Greece
[b] Medical School, University of Athens, KAT General Hospital, 2 Nikis Street, 14561 Kifissia, Greece
[c] Medical School, University of Athens, 10 Athinas Street, 14561 Kifissia, Greece
[d] Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania
[e] Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania
[f] Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
[g] Department of Obstetrics and Gynecology, Istanbul University, Cerrahpasa School of Medicine, Valikonagi Cad. No. 93/4, Nisantasi, 34365 Istanbul, Turkey
[h] Department of Obstetrics and Gynecology, Zaragoza University Facultad de Medicina, Hospital Clínico, Zaragoza 50009, Spain
[i] Department of Medicine, Cardiology Unit and Head Centre for Gender Medicine, Karolinska Institutet and Karolinska University Hospital, Thorax N3:06, SE 17176 Stockholm, Sweden
[j] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[k] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100 Pisa, Italy
[l] Menopause and Metabolic Bone Disease Unit, Hôpital Paule de Viguier, F-31059 Toulouse cedex 09, France
[m] Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK
[n] Second Department of Obstetrics and Gynecology, National and Capodestrian University of Athens, Greece

ARTICLE INFO

Article history:

Keywords:
Osteoporosis
Vertebral fracture
Diagnosis
Conservative treatment
Surgical treatment

ABSTRACT

Introduction: Osteoporotic vertebral fractures are associated with significant morbidity, excess mortality as well as health and social service expenditure. Additionally, women with a prevalent osteoporotic vertebral fracture have a high risk of experiencing a further one within one year. It is therefore important for the physician to use a diagnostic and therapeutic algorithm for early detection and effective treatment of vertebral fractures.
Aims: The aim of this position statement is to provide and critically appraise evidence on the management of women with a vertebral osteoporotic fracture.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: The management of women with osteoporotic vertebral fractures includes measures to reduce pain providing early mobility, to support the affected spine ensuring fracture healing, as well as starting treatment for osteoporosis itself. Any other underlying pathology should be sought and treated. Early detection and treatment is essential as there is an increased risk of further fractures in patients with vertebral fractures. Treatment will depend on the underlying causes of bone loss, efficacy in any particular situation, cost and patient preference.

1. Introduction

In osteoporotic women, the risk of spinal fragility fracture increases linearly after the age of 60. Vertebral osteoporotic fractures (VOFs) are associated with significant morbidity and mortality as well as with health and social service expenditure [1,2].

* Corresponding author at: Dimitros 6, Marousi GR-15124, Greece. Tel.: +30 210 6124007; fax: +30 210 6124007; mobile: +30 6937266639.
E-mail address: sportdoc@otenet.gr (I.K. Triantafyllopoulos).

http://dx.doi.org/10.1016/j.maturitas.2014.03.002
0378-5122/

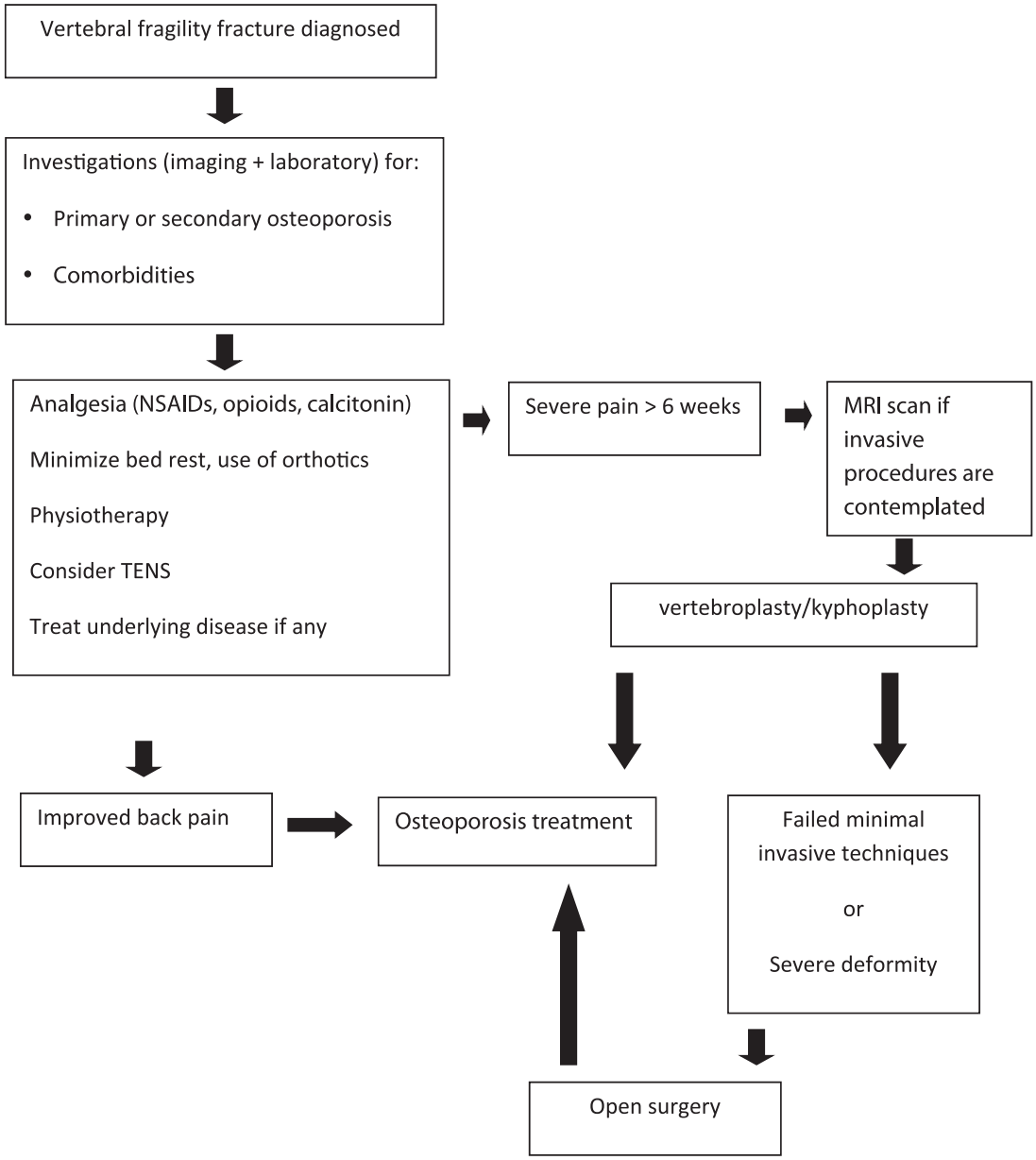

Fig. 1. Care pathway for the management of postmenopausal women with vertebral osteoporotic fracture.

Furthermore, in women with a VOF, there is an increased risk of further fragility fractures [3,4]. Prompt management is thus essential not only to deal with the current fracture but also to prevent subsequent ones. The aim of this position statement is to provide evidence-based advice and guidelines on the management of women with VOF (Fig. 1).

2. The burden of vertebral osteoporotic fracture

The incidence of VOF is underestimated as only about a third of people with the condition seek medical attention [5]. Those with acute back pain (*vertebral fracture type-1*) tend to present earlier than those who gradually lose height or become kyphotic (*vertebral fracture type-2*)

Up to 20% of women with an incident vertebral fracture will experience a second one within a year [6]. In addition low BMD and prevalent vertebral fractures are independently related to new vertebral fractures over 15 years of follow-up [7]. Women with previous VOF also have a 3.8-fold increased risk of hip fracture, compared with the background female population [8,9]. It is therefore important that vertebral fractures are detected early, and treatment considered as soon as possible. Furthermore, the cause of osteoporosis and contributory factors must be understood to try and minimize damage. Diseases that also cause vertebral collapse such as myeloma, hyperparathyroidism or neoplastic metastases must be excluded [10].

VOFs have a high impact on patient's quality of life in terms of reduced mobility, pain, poor sleep and fear of future fractures [11]. In most patients with a VOF, back pain decreases significantly with conservative therapy, predominantly in the first 6 months [12]. However, almost 2 years after an acute VOF, a third of patients still have severe pain necessitating analgesia and physical therapy. Mortality is increased and is directly related to the number of fractures [1,2]. The mechanism of the increased fracture-associated mortality

remains uncertain: it may be related to co-morbid conditions (such as cardiovascular disease) or subsequent hip fracture and gender differences have been noted [13,14].

3. Assessment of a vertebral osteoporotic fracture

Initial assessment of VOFs is important to ensure that appropriate management is instigated. It has been estimated that underlying pathology is present in about one third of women with symptomatic VOFs [6]. A detailed medical history, physical examination and appropriate investigation are mandatory for all patients with non-traumatic vertebral fractures. Imaging [15] and laboratory tests [10] are the first line diagnostic tools.

3.1. Imaging

The usual location of VOFs is the lower thoracic and upper lumbar spine and these can be seen on conventional chest X-rays. The international standard for the classification of vertebral osteoporotic fractures is the semiquantitative grading system was developed by Genant in 1993 [16]. According to this grading system, a vertebral deformity of T4-L4 with more than 20% height loss and a 10–20% area of height reduction is defined as a fracture. Four grades are differentiated: grade 0, no fracture; grade 1, mild fracture (reduction in vertebral height of 20–25%, compared with adjacent normal vertebrae); grade 2, moderate fracture (reduction in height of 25–40%); and grade 3, severe fracture (reduction in height of more than 40%). Wedge-shaped and biconcave fracture deformities are most common in osteoporosis, while posterior vertebral fractures are suggestive of neoplastic disease. Multidetector-CT can be used to diagnose incidental VOFs. The role of Dual-energy X-ray absorptiometry (DXA) measurement is of limited benefit as the diagnosis of osteoporosis can be assumed in the presence of a fracture especially in women aged over 75 [17]. However, DXA can be used to assess vertebral fracture [18]. Radionuclide bone scan and MRI scan are valuable diagnostic tools when there is suspicion of skeletal metastasis [19]. MRI with STIR sequencing can diagnose additional acute or chronic lesions not evident in plain X-rays. Therefore, it should be considered before cement augmentation procedures [20].

3.2. Laboratory tests

Initial investigations should include full blood count, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), thyroid, renal and liver function tests; serum protein electrophoresis, calcium, albumin, phosphate and alkaline phosphatase [10]. Serum 25-hydroxyvitamin D (25OHD) and parathyroid hormone (PTH) measurements are useful for vitamin D deficiency and parathyroid disorders. Iron metabolism, as well as serum testosterone and SHBG should be also assessed in men. Finally, coeliac disease can be excluded with endomysial antibodies.

4. Initial management of vertebral osteoporotic fractures

There is no consensus as to the best management. A care pathway is detailed in Fig. 1. In general, initial management includes bed rest, analgesia, physiotherapy and bracing. According to the UK National Institute for Health and Care Excellence percutaneous vertebroplasty, and percutaneous balloon kyphoplasty without stenting, are recommended as options for treating osteoporotic vertebral compression fractures only in people who have severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management and in whom the pain has been confirmed to be at the level of the fracture by physical examination and imaging [21].

Finally, where neurological deficit or severe spinal instability has developed, spinal fusion may be considered.

4.1. Physical support of the spine

After an initial short period of bed rest, mobilization should be encouraged with the use of physical supports. Corsets are no longer advocated, as they immobilize the spine and thus aggravate bone loss and muscle atrophy. Alternatively, a spinal orthosis such as a Jewett brace can be used (a) to stabilize the fracture area and therefore prevent further collapse or spinal deformity, (b) to provide stable positioning needed for faster bone healing, and (c) to allow immediate mobilization of the patient. Finally, walking aids will help compensate for loss of sagittal balance and impaired proprioception and reduce fall risk.

4.2. Pain management

Analgesia should begin with simple pain-killers such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). If stronger analgesia is required, opiates or opioids such as oxycodone can be used in combination with paracetamol. If pain becomes chronic, tricyclic antidepressants may be useful. Finally, in severe pain, intercostal nerve blocks give satisfactory but short-term relief. Pain relief should be undertaken in consultation with a specialized pain management team and non-pharmaceutical options such as TENS should be considered [22,23].

Calcitonin appears to be effective in the management of acute pain associated with acute VOF by shortening time to mobilization [24]. Salmon calcitonin (not available in all countries) administered intramuscularly, intranasaly or subcutaneously, for a period of two to four weeks, leads to a greater reduction in pain intensity compared to placebo [25]. However, there is no convincing evidence to support the use of calcitonin for chronic pain associated with older fractures of the same origin [26].

Intravenous bisphosphonates such as pamidronate or clodronate can also be used for the acute pain management of VOFs [27,28]. Furthermore zolendronic acid as a single annual 5 mg intravenous infusion significantly reduces the number of days with back pain compared to placebo [29]. Finally, subcutaneous daily teriparatide also significantly improves back pain due to osteoporotic fractures, although this medicine is not recommended for the sole purpose of analgesia and use varies between countries [30,31].

4.3. Percutaneous vertebroplasty and kyphoplasty

Percutaneous vertebroplasty and kyphoplasty are used in patients with severe ongoing pain after a recent, unhealed vertebral fracture despite optimal pain management, and in patients who develop significant deformity (e.g. >30% of kyphosis) [21,32].

Vertebroplasty involves the percutaneous injection of bone cement into the vertebral body under fluoroscopic guidance and can be performed as one-day or overnight procedure. Kyphoplasty is a similar technique, it involves, however, an additional step in which an inflatable tamp or balloon is first inserted percutaneously into the collapsed vertebral body under fluoroscopic guidance. The tamp is then inflated, compressing the cancellous bone and elevating the endplates. The fracture is then fixed by the injection of bone cement in a similar manner to vertebroplasty [33].

Both procedures seem to be equally effective but kyphoplasty seems to be safer than vertebroplasty [34]. In vertebroplasty and kyphoplasty, pain relief results from stabilization of the fracture, although thermal and chemical ablation of the nerve endings in the vertebral body may also contribute. In general, apart from pain

relief, these two techniques, when applied in carefully selected patients, offer significant functional recovery [35,36].

4.4. Open surgery

Open surgical treatment of VOFs is challenging and tends to be reserved (1) for those cases where less-invasive approaches have not provided a satisfactory result in terms of relief of chronic pain and (2) as the initial surgical procedure for people with severe deformity, with or without vertebroplasty or kyphoplasty at the time of open surgery [33,35,36]. It is often difficult to achieve reliable fixation, and bone grafts frequently collapse into the weak osteoporotic bone. Careful patient selection is critical to achieve satisfactory results. Preoperative health status must be carefully evaluated when deciding whether open surgery is a reliable option. Anterior, posterior, or combined anterior and posterior approaches can be used, depending on the exact configuration of the fracture(s). The aim is to eliminate movement by enabling the fractured vertebra to fuse to the adjacent vertebrae by using a combination of bone graft, screws, and plates. Extension osteotomy of the spine may be considered to compensate for loss of sagittal balance. It is associated, however, with high complication rates.

5. Treatment of underlying osteoporosis

5.1. General measures and advice

Women with a VOF should be advised on lifestyle measures to decrease bone loss. Such measures include eating a balanced diet rich in calcium, stopping smoking, avoiding excess alcohol consumption, maintaining regular physical activity and sunlight exposure [37]. Patients with limited sunlight exposure or low dietary calcium should be advised to take calcium and vitamin D supplementation [38]. Strategies for reducing falls should be instigated [39]. There is some evidence to support the use of individualized tailored exercise rehabilitation aimed at strengthening back muscles to maintain bone density and reduce further fracture incidence [40]. Of note, hip protectors seem to be an ineffective intervention for those living at home and their effectiveness in an institutional setting is uncertain [41]. Finally, underlying causes of secondary osteoporosis should be treated where possible.

The options discussed are calcium and vitamin D, menopausal hormone therapy, tibolone, selective estrogen receptor modulators, bisphosphonates and anabolic agents. While calcitonin is effective, its prolonged use has been associated with an increase in cancer rate. Thus, calcitonin is currently indicated only for the short term management of acute pain following a vertebral fracture in the European Union [42]. Strontium ranelate reduces the risk of vertebral fractures by 40%, an effect evident across multiple levels of risk, including women with VOF [43]. The European Medicines Agency concluded its review of strontium in February 2014 and recommended restricting its use to patients with no history of cardiovascular disease who cannot be treated with other medicines approved for osteoporosis. In addition these patients should continue to be evaluated regularly every 6–12 months by their doctor and treatment should be stopped if patients develop heart or circulatory problems, such as uncontrolled high blood pressure or angina [44].

5.2. Calcium and vitamin D supplementation

Calcium and vitamin D play a key role in bone metabolism and correction of nutritional deficiencies is therefore advised as part of osteoporosis management [45,46]. However, caution has been expressed in using calcium supplements in women whose diet is replete. Excess calcium supplementation may be associated with an increased risk of kidney stones and cardiovascular events. Thus it has been estimated that treatment of 1000 people with calcium supplements over a period of five years results in 26 fewer fractures, 14 more myocardial infarctions, 10 more strokes and 13 more deaths [47]. Therefore, it seems reasonable to encourage individuals of all ages to obtain their calcium needs from the diet and use supplements with caution.

Calcitriol or alfacalcidol, the active vitamin D metabolites can be used in glucocorticoid-induced osteoporosis [48]. These agents, however, have limited efficacy in decreasing vertebral fracture risk or the risk of a subsequent vertebral fracture [49]. Furthermore, the potential risk of hypercalcaemia and the need for regular monitoring of calcium and renal function limit the use of calcitriol in the management of osteoporosis.

Many housebound elderly are Vitamin D deficient. Vitamin D is essential for musculoskeletal health as it promotes calcium absorption from the diet, enables mineralization of newly formed bone and plays an important role in muscle function [38,50]. Vitamin D deficiency may result in bone loss and an increased risk of falls and fractures, whereas more severe deficiency leads to osteomalacia. In view of the key role of vitamin D, the UK National Osteoporosis Society produced a practical clinical guideline in 2013 on estimating vitamin D status, treatment (oral vitamin D3 being the preparation of choice), loading doses, maintenance therapy and monitoring [50]. The guidelines point out that serum calcium should be checked one month after loading to exclude the rare unmasking of primary hyperparathyroidism.

5.3. Menopausal hormone therapy

Menopausal hormone therapy (MHT) is the treatment of choice for the management of bothersome menopausal symptoms and urogenital atrophy. According to the Women's Health Initiative (WHI) trial, MHT decreased the risk of vertebral fractures by 35% in women in their sixties receiving either estrogen or estrogen–progestin treatment [51,52]. The same effect was apparent in the observational Million Women Study [53]. Long-term estrogen–progestogen combined MHT is associated with a small but significant increase in the risk of breast cancer [51,53]. Thus a recent consensus concluded that 'MHT is effective and appropriate for the prevention of osteoporosis-related fractures in at-risk women before age 60 years or within 10 years after menopause.' [54].

5.4. Tibolone

Tibolone is a synthetic steroid with estrogenic, progestogenic and androgenic activity indicated for the management of menopausal symptoms and of urogenital atrophy in postmenopausal women. In the LIFT trial undertaken in women aged 60–85 years, tibolone (1.25 mg daily) decreased the occurrence of new vertebral fractures by 45% compared to placebo after 3 years of treatment. However tibolone increased the risk of stroke [55] and the study was discontinued prematurely. Thus in some, but not all, EU Member States tibolone is indicated for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products authorized for the prevention of osteoporosis.

5.5. Selective estrogen receptor modulators (SERMs)

SERMS are compounds that act through the estrogen receptor, but depending on the tissue target they exert either estrogen-agonist activity (e.g. bone) or estrogen-antagonist activity (e.g. breast). In bone tissue they inhibit bone resorption and reduce bone turnover [56,57].

Raloxifene and bazedoxifene are two SERMs approved for the treatment of osteoporosis. Raloxifene is the first SERM approved for the treatment of postmenopausal osteoporosis. Raloxifene, taken orally on a daily basis, increases bone mineral density and reduces the incidence of vertebral fracture by 50% in women with no previous fracture and by 30% in women with prevalent fractures, as documented in its pivotal trial (MORE) [58]. There is no documented efficacy of raloxifene in non-vertebral or hip fractures. In addition it reduces the risk of breast cancer [59]. Raloxifene increases the risk of venous thromboembolism and hot flushes.

Bazedoxifene is a newer SERM approved for the treatment of postmenopausal women at risk of fracture. It is not available in all countries. It increases bone mineral density and decreases the risk of vertebral fracture by 35–40%. In primary analyses bazedoxifene was not shown to be effective in preventing non-vertebral or hip fractures. In subgroups of women at high risk of fracture, however, bazedoxifene also reduced the incidence of non-vertebral fractures. Like all other SERMS, it increases the risk of venous thromboembolism and hot flushes [60].

5.6. Bisphosphonates

Bisphosphonates are potent antiresorptive agents that are administered orally on a weekly (alendronate, risedronate) or monthly basis (risedronate, ibandronate) or intravenously every three months (ibandronate) or annually (zoledronic acid). Bisphosphonates reduce the risk of vertebral fractures by 40–70% in high risk populations including women with VOF [61]. Upper gastrointestinal irritation with oral agents and flu-like symptoms with the intravenous preparations are the most common side effects. Rare complications include osteonecrosis of the jaw and atypical femur fractures occurring at the shaft, the latter reported after prolonged treatment. Given their documented efficacy in patients with prevalent vertebral fractures, their favorable safety profile and their low cost, bisphosphonates should be considered as a first line option in women with VOF [10].

5.7. Denosumab

Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL), a bone resorbing cytokine. It is administered as a subcutaneous injection every six months. Denosumab reduces the risk of all vertebral fractures by 68% and the risk of new clinical vertebral fractures by 69% after 3 years of use, an effect persistent after 5 years [62,63]. The effect of denosumab is particularly evident in high risk populations such as women with previous osteoporotic fractures [64]. Side effects are rare and include topical skin reactions and very rarely cellulitis. Although its cost may be an issue, denosumab is included among the first line options for women with prevalent VOF.

5.8. Anabolic agents

Teriparatide (recombinant human parathohormone PTH 1–34) or the intact PTH molecule (1–84) increase bone density and decrease vertebral fracture incidence. Treatment of high risk postmenopausal women with teriparatide for a median of 20 months increased lumbar spine BMD by 9–13% than placebo group and reduced the risk of a new vertebral fracture by 65%. [65]. Intact PTH reduces vertebral fractures by 40% [66]. Teriparatide increase cortical bone formation, promoting thus bone strength [67].

The anti-fracture efficacy of teriparatide appears to be largely independent of age, initial BMD and the presence or absence of prevalent vertebral fractures [68]. In general, teriparatide is particularly useful in the management of women with severe osteoporosis who have a number of previous vertebral fractures or those who failed to respond to anti-resorptive treatments. Furthermore, its use in the first 18 months after spondyloplasty or kyphoplasty reduces the risk of second fragility fractures in adjacent vertebral bodies (*domino effect)* [69].

6. Follow-up of patients with vertebral fractures

Patients with prevalent VOF should be closely monitored for subsequent VOF, as they are, as stated earlier, at particularly high risk. Relapse or new onset of back pain, height reduction or kyphosis should alert the physician toward a new VOF. Bone mineral density is useful to assess response to osteoporosis treatment and possibly to detect incident VOF, by the Vertebral Fracture Assessment (VFA) algorithm [69]. However biochemical markers of bone turnover levels respond rapidly to both anabolic and antiresorptive treatments [70].

7. Conclusions

Treatment of osteoporosis should be multidisciplinary dealing with the acute event, managing the underlying osteoporosis and endeavors to return to previous levels of activity. In postmenopausal women with a VOF, management starts with targeted analgesia, early mobilization of the patient and anti-osteoporotic treatment tailored to individual needs and medical problems. Underlying pathology such as multiple myeloma or metastatic disease should be sought and treated accordingly. Vertebroplasty and kyphoplasty may prove useful in selected patients unresponsive to conventional pain relief. Open surgical treatment is reserved for patients with severe spine deformity or when minimally invasive percutaneous cement augmentation techniques have failed. In addition the use of specific orthotic devices may help to reduce kyphosis, improve mobility and reduce pain.

8. Summary recommendations

- The management of postmenopausal women with a VOF includes measures to reduce pain and improve mobility as well as treatment of osteoporosis itself and the underlying disease in cases of secondary osteoporosis.
- It is essential to investigate and treat any non-osteoporotic vertebral pathology that could cause a fragility fracture such as metastatic disease or multiple myeloma.
- Medical treatment of osteoporosis with effective agents such as menopausal hormone therapy, SERMS, bisphosphonates or denosumab, depending on age and concomitant medical conditions, need to be started as soon as possible.
- The woman must be calcium and vitamin D replete.
- Sufficient pain relief, physiotherapy and falls assessments need to be in place to facilitate rehabilitation and return to normal activities.
- In most patients, non-operative interventions combined are sufficient. However, surgery such as vertebroplasty or kyphoplasty may be required.
- Treatment is best provided by a multidisciplinary team.

Contributors

IT prepared the initial draft, which was circulated to EMAS board members for comment and approval, production was coordinated by MR, IL and IT.

Competing interest

The authors have no conflicting interests to declare.

Funding

None was sought or secured for writing this statement.

Acknowledgement

The authors would like to thank Dr. Sally Hope, Nuffield Orthopaedic Centre, Oxford for her helpful comments.

References

[1] Strom O, Borgstrom F, Kanis JA, et al. Osteoporosis: burden health care provision and opportunities in the EU. Arch Osteoporos 2011;6:59–155.
[2] Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.
[3] Ensrud KE, Schousboe JT. Clinical practice. Vertebral fractures. N Engl J Med 2011;364:1634–42.
[4] Donaldson MG, Palermo L, Schousboe JT, Ensrud KE, Hochberg MC, Cummings SR. FRAX and risk of vertebral fractures: the fracture intervention trial. J Bone Min Res 2009;24:1793–9.
[5] Wong CC, McGirt MJ. Vertebral compression fractures: a review of current management and multimodal therapy. J Multidiscip Healthcare 2013;6:205–14.
[6] Briggs AM, Greig AM, Wark JD. The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. Osteoporos Int 2007;18:575–84.
[7] Cauley JA, Hochberg MC, Lui LY, et al. Long-term risk of incident vertebral fractures. JAMA 2007;298:2761–7.
[8] Buckens C, de Jong Pim A, Mali WP, et al. Prevalent vertebral fractures on chest CT: higher risk for future hip fracture. J Bone Min Res 2014;29:392–8.
[9] Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int 2011;22:2395–411.
[10] Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013;75:392–6.
[11] Borgstrom F, Lekander I, Ivergard M, et al. The International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS)—quality of life during the first 4 months after fracture. Osteoporosis Int 2013;24:811–23.
[12] Klazen CA, Verhaar HJ, Lohle PN, et al. Clinical course of pain in acute osteoporotic vertebral compression fractures. J Vasc Interv Radiol 2010;21:1405–9.
[13] Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301(February (5)):513–21.
[14] Puisto V, Rissanen H, Heliövaara M, et al. Vertebral fracture and cause-specific mortality: prospective population study of 3,210 men and 3,730 women with 30 years of follow-up. Eur Spine J 2011 Dec;20(12):2181–6.
[15] Link TM. Osteoporosis imaging: state of the art and advanced imaging. Radiology 2012;263:3–17.
[16] Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137–48.
[17] NICE pathway: osteoporosis overview. http://pathways.nice.org.uk/pathways/osteoporosis [accessed 12.02.14].
[18] Schousboe JT, McKiernan F, Fuehrer JT, Binkley N. Use of a performance algorithm improves utilization of vertebral fracture assessment in clinical practice. Osteoporos Int 2013;(October). PubMed PMID: 24121999 [epub ahead of print].
[19] Lecouvet FE, Larbi A, Pasoglou V, et al. MRI for response assessment in metastatic bone disease. Eur Radiol 2013;23:1986–97.
[20] Park SY, Lee SH, Suh SW, Park JH, Kim TG. Usefulness of MRI in determining the appropriate level of cement augmentation for acute osteoporotic vertebral compression fractures. J Spinal Disord Tech 2013;26:E80–5.
[21] NICE technology appraisal guidance TA279. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for treating osteoporotic vertebral compression fractures. Issued: April 2013 TA279. http://publications.nice.org.uk/percutaneous-vertebroplasty-and-percutaneous-balloon-kyphoplasty-for-treating-osteoporotic-vertebral-ta279 [accessed 12.02.14].
[22] Manchikanti L, Helm S, Singh V, et al. ASIPP. An algorithmic approach for clinical management of chronic spinal pain. Pain Physician 2009;12:E225–64.
[23] Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. Pain Physician 2008;11(2 Suppl.):S5–62.
[24] Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. Osteoporos Int 2005;16:1281–90.
[25] European Medicines Agency. Assessment report for calcitonin containing medicinal products EMA/109665/2013, Referral under Article 31 of Directive 2001/83/EC. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Calcitonin_31/WC500146172.pdf [accessed 12.02.04].
[26] Knopp-Sihota JA, Newburn-Cook CV, Homik J, Cummings GG, Voaklander D. Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Osteoporos Int 2012;23:17–38.
[27] Pappagallo M, Breuer B, Lin HM, et al. A pilot trial of intravenous pamidronate for chronic low back pain. Pain 2014;155:108–17.
[28] Kim S, Seiryu M, Okada S, et al. Analgesic effects of the non-nitrogen-containing bisphosphonates etidronate and clodronate, independent of anti-resorptive effects on bone. Eur J Pharmacol 2013;699:14–22.
[29] Cauley JA, Black D, Boonen S, et al. Once-yearly zolendronic acid and days of disability, bed rest, and back pain: randomized, controlled HORIZON Pivotal Fracture Trial. J Bone Miner Res 2011;26:984–92.
[30] Rajzbaum G, Grados F, Evans D, Liu-Leage S, Petto H, Augendre-Ferrante B. Treatment persistence and changes in fracture risk, back pain, and quality of life amongst patients treated with teriparatide in routine clinical care in France: results from the European Forsteo Observational Study. Joint Bone Spine 2013;(June), http://dx.doi.org/10.1016/j.jbspin.2013.05.001, pii: S1297-319X(13)00120-6 [epub ahead of print].
[31] Francis RM. Back pain in osteoporotic vertebral fractures. Osteoporos Int 2008;19:895–903.
[32] Boonen S, Wahl DA, Nauroy L, et al. Balloon kyphoplasty and vertebroplasty in the management of vertebral compression fractures. Osteoporos Int 2011;22:2915–34.
[33] BMJ Best Practice. Osteoporotic spinal compression fractures. http://bestpractice.bmj.com/best-practice/monograph/819/highlights/summary.html [accessed 17.02.14].
[34] Robinson Y, Olerud C. Vertebroplasty and kyphoplasty – a systematic review of cement augmentation techniques for osteoporotic vertebral compression fractures compared to standard medical therapy. Maturitas 2012;72:42–9.
[35] Patil S, Rawall S, Singh D, et al. Surgical patterns in osteoporotic vertebral compression fractures. Eur Spine J 2013;22:883–91.
[36] Dodwad SN, Khan SN. Surgical stabilization of the spine in the osteoporotic patient. Orthop Clin North Am 2013;44:243–9.
[37] Lambrinoudaki I, Ceausu I, Depypere H, et al. EMAS position statement: diet and health in midlife and beyond. Maturitas 2013;74:99–104.
[38] Pérez-López FR, Brincat M, Erel CT, et al. EMAS position statement: vitamin D and postmenopausal health. Maturitas 2012;71:83–8.
[39] Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. Maturitas 2013;75:51–61.
[40] Giangregorio LM, Macintyre NJ, Thabane L, Skidmore CJ, Papaioannou A. Exercise for improving outcomes after osteoporotic vertebral fracture. Cochrane Database Syst Rev 2013;31(1):CD008618.
[41] Parker MJ, Gillespie WJ, Gillespie LD. Effectiveness of hip protectors for preventing hip fractures in elderly people systematic review. BMJ 2006;332:571.
[42] European Medicine Agency. Calcitonin. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Calcitonin/human_referral_000319.jsp&mid=WC0b01ac0580024e99 [accessed 12.02.14].
[43] Cianferotti L, D'Asta F, Brandi ML. A review on strontium ranelate long-term antifracture efficacy in the treatment of postmenopausal osteoporosis. Ther Adv Musculoskelet Dis 2013;5:127–39.
[44] European Medicine Agency. Protelos and Osseor. European Medicines Agency recommends that Protelos/Osseor remain available but with further restrictions. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Protelos_and_Osseor/human_referral_prac_000025.jsp&mid=WC0b01ac05805c516f [accessed 27.02.14].
[45] Moyer VA, U.S. Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2013;158:691–6.
[46] Rizzoli R, Boonen S, Brandi ML, et al. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 2013;29:305–13.
[47] Reid IR, Bolland MJ. Calcium risk-benefit updated—new WHI analyses. Maturitas 2014;77:1–3.
[48] Lekamwasam S, Adachi JD, Agnusdei D, et al. A framework for the development of guidelines for the management of glucocorticoids-induced osteoporosis. Osteoporos Int 2012;23:2257–76.
[49] O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab 2008;26:531–42.
[50] National Osteoporosis Society. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management; 2013. http://www.nos.org.uk/page.aspx?pid=1074 [accessed 25.02.14].
[51] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
[52] Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–12.
[53] Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
[54] De Villiers TJ, Gass ML, Haines CJ, et al. Global consensus statement on menopausal hormone therapy. Maturitas 2013;74:391–2.
[55] Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008;359:697–708.

[56] Komm BS, Chines AA. An update on selective estrogen receptor modulators for the prevention and treatment of osteoporosis. Maturitas 2012;71:221–6.
[57] Palacios S, Brincat M, Erel CT, et al. EMAS clinical guide: selective estrogen receptor modulators for postmenopausal osteoporosis. Maturitas 2012;71:194–8.
[58] Seeman E, Crans GG, Diez-Perez A, Pinette KV, Delmas PD. Anti-vertebral fracture efficacy of raloxifene: a meta-analysis. Osteoporos Int 2006;17:313–6.
[59] Moyer VA, On behalf of the U.S. Preventive Services Task Force. Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2013;159:698–708.
[60] Silverman SL, Chines AA, Kendler DL, et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int 2012;23:351–63.
[61] Khosla S, Bilezikian JP, Dempster DW, et al. Benefits and risks of bisphosphonate therapy for osteoporosis. J Clin Endocrinol Metab 2012;97:2272–82.
[62] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65.
[63] Bone HG, Chapurlat R, Brandi ML, et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clin Endocrinol Metab 2013;98:4483–92.
[64] McCloskey EV, Johansson H, Oden A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. J Bone Min Res 2012;27:1480–6.
[65] Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.
[66] Uihlein AV, Leder BZ. Anabolic therapies for osteoporosis. Endocrinol Metab Clin North Am 2012;41:507–25.
[67] Ma YL, Zeng QQ, Chiang AY. Effects of teriparatide on cortical histomorphometric variables in postmenopausal women with or without prior alendronate treatment. Bone 2014;59:139–47.
[68] Marcus R, Wang O, Satterwhite S, Mitlak B. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. J Bone Miner Res 2003;18:18–23.
[69] Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom 2013;16:455–66.
[70] Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. Nat Rev Rheumatol 2012;8:379–89.