Improving patients' outcomes after osteoporotic fractures

As populations are aging, osteoporotic fractures are common and they are associated with high rates of mortality and morbidity, disability, pain and a high cost of treatment. In addition to primary prevention strategies, efforts should be made to improve patients' outcomes after a fragility fracture and optimize their overall management. Optimal surgical treatment of the fracture, when indicated, and high-quality postfracture care in terms of evaluation and appropriate medical treatment of osteoporosis, rehabilitation, lifestyle modifications and secondary fall prevention should be provided for optimal functional recovery, reduction of future fracture risk and improvement of overall quality of life. A multidisciplinary approach and the establishment of clinical pathways are mandatory to ensure optimization of treatment and adherence to prevention strategies of secondary fractures.

KEYWORDS: fragility fractures ■ osteoporosis ■ osteoporotic fractures ■ outcome ■ secondary prevention

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Osteoporotic fractures have become one of the most prevalent trauma conditions seen daily in clinical practice [1]. They are also known as 'fragility fractures' and they are defined as those occurring after a low-energy trauma, traditionally interpreted as a fall from a standing height or less [2]. Contributing factors are the susceptibility to falls and underlying osteoporosis, which is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility [3]. Fractures of the vertebrae (spine), proximal femur (hip) and distal forearm (wrist) have long been regarded as 'typical' osteoporotic fractures with a substantial variation in their incidence between populations, sexes, different age groups and even between urban and rural areas [4]. In 2000, there were an estimated nine million new osteoporotic fractures worldwide, with approximately 1.7 million forearm fractures, 1.6 million hip fractures and 1.4 million vertebral fractures [5]. Overall, it has been forecasted that 20% of 50-year-old men and half of 50-year-old women will suffer from at least one osteoporotic fracture during their remaining lifetime [6].

As populations are aging, the incidence of osteoporotic fractures is also increasing [4], representing a major public health problem and a substantial burden to healthcare services [6]. For example, in 2005, fragility fractures in the USA resulted in 2.5 million medical office visits, 430,000 hospital admissions and 180,000 nursing home admissions, with a direct cost of US$17 billion [7]. In the UK, over 300,000 patients present to hospitals with fragility fractures, with a medical and social cost of approximately £2 billion each year, most of which is the result of hip fractures [8].

In addition to their significant medical costs worldwide [4], osteoporotic fractures also represent a major cause of morbidity in older people, often necessitating hospitalization and operative treatment, and resulting in loss of patient's mobility and autonomy [4,6]. Hip fractures in particular are associated with high mortality [9]. Finally, besides the aforementioned main adverse outcomes of osteoporotic fractures including mortality, morbidity and cost of treatment [4], all fragility fractures, and particularly lumbar or multiple vertebral fractures and hip fractures, are also associated with pain and decrease of physical/social function and well being, compromising patients' quality of life [10].

Therefore, the treatment of osteoporosis and the prevention of osteoporotic fractures is a major public health issue; and numerous treatments as well as fall prevention strategies have been developed to reduce the risk of fracture in patients with osteoporosis [3,11]. The aim is to minimize the associated mortality, morbidity and disability. Appropriate medical treatment for osteoporosis, adequate fracture fixation, rehabilitation and lifestyle modifications (e.g., calcium and vitamin supplementation, weight-bearing exercises and minimizing the risk of falls) could facilitate optimal functional recovery, a reduction in future fracture risk and an overall improvement in health-related quality of life [12].

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Improvements in operative treatment of osteoporotic fractures

The operative treatment of osteoporotic fractures represents a challenge for the orthopedic surgeon. It often has unpredictable outcomes as a result of increased bone fragility and a high rate of failure of implant fixation [13]. In general terms, numerous techniques have been developed to optimize surgical treatment of osteoporotic fractures and allow early weight bearing when possible, including advances in implants and technique-related parameters [13]. For the latter, the aim is to decrease the risk of failure at the bone-implant interface before bony union has occurred by using techniques for relative stability with intramedullary nails and buttress fixation, controlled valgus bone impaction with tensioning internal fixation devices such as the dynamic hip screw, and bone augmentation techniques by using bone autograft or allograft, bone cement or bone substitutes [13,14].

Research is ongoing to improve orthopedic implants with biomechanically superior technologies to allow more secure and stable constructs, such as the use of fixed-angle devices and locking plates [13]. The use of locking plates in particular has expanded significantly over the last decade for the treatment of osteoporotic fractures [15]. However, because other issues have emerged including periprosthetic fracture risk in osteoporotic bone, due to stress concentrations at the plate end compared with conventional plating, hybrid plating (combining the use of locked and nonlocked screws) has been suggested to improve fixation strength of the construct in osteoporotic bone [16,17].

Biological processes to enhance the osteointegration of implants and improve fixation or to augment the healing potential of osteoporotic fractures have also been used [13]. These include coatings of the implants with hydroxyapatite [18], systemic or local administration of bisphosphonates [19], and implantation of growth factors including bone morphogenetic proteins, TGF-β or FGF [20].

Finally, endoprosthetic replacement of unstable comminuted osteoporotic fractures is also being used as an alternative to fracture fixation for osteoporotic fractures, aiming to allow early mobilization and improve pain and overall functional outcome. Such an approach has been undertaken in extracapsular hip fractures treated with hip arthroplasty [21,22], complex intra-articular fractures of the proximal tibia treated with primary knee replacement [23], as well as complex distal or proximal humeral fractures treated with total elbow arthroplasty [24] or shoulder arthroplasty respectively [25].

However, although there are numerous studies reporting on the use of various orthopedic devices and methods of biological enhancement to improve the operative treatment of osteoporotic fractures [13–25], the majority of studies are level III and IV studies [201] and therefore, no strong recommendations can be made regarding their use in the clinical practice. High-quality evidence from randomized trials or systematic reviews and meta-analyses are required to evaluate and establish their clinical applications as well as their cost–effectiveness.

Secondary prevention of osteoporotic fractures

As an osteoporotic fracture is the strongest indicator of risk for future fracture and an episode of osteoporotic fracture at least doubles the likelihood of further fractures, the implementation of strategies regarding the assessment and treatment of osteoporosis and the secondary prevention with a falls risk assessment is of great importance in an effort to reduce the risk of further fractures [1,8]. Since orthopedic surgeons are usually the first physicians to assess and treat the patient after a fragility fracture, their role therefore does not end in the treatment of the fracture; but they should also ensure that preventive measures are implemented using a multidisciplinary approach among clinicians, allied healthcare professionals (nurses, physical and occupational therapists and social workers) and administrative staff [26].

The need for a multidisciplinary approach for postfracture osteoporosis care to ensure treatment is provided routinely with continuity of care is well recognized. It has been shown that implementation of a coordinator-based program can improve postfracture osteoporosis care starting by early identification of these patients and documentation of osteoporosis to allow assessment, referral and appropriate treatment of underlying osteoporosis [26,27]. Such an approach can also be cost effective in avoiding future costs of subsequent fragility fractures [28]. Referrals for rheumatology or endocrinology consultation of postfracture patients can increase the percentage of patients receiving therapy for osteoporosis, and dedicated nurses, geriatricians or family physicians can improve outcomes by increasing, not only initiation, but also adherence to treatment [29]. However, despite the effectiveness of preventive measures, few patients currently receive such services [8].

Assessment & treatment of osteoporosis

Although fracture care is often the first opportunity for clinical management of osteoporosis, many patients do not receive any evaluation after a fracture. Several studies have indicated that investigation for osteoporosis after fracture is less than optimal and patients with low-energy fractures may not even be evaluated or receive any treatment for underlying osteoporosis [30]. Ideally, assessment for osteoporosis should be offered in all these patients as it has been shown that the risk of further fractures in those found to be in the 'osteoporotic range' can be reduced by half by antiresorptive therapy [1]. McLellan *et al.* demonstrated that by providing routine assessment and, where necessary, treatment for osteoporosis after a fracture as well as specific recommendations for secondary prevention, osteopenic or osteoporotic patients can be successfully identified and treated [31]. Routine diagnostic procedures in osteoporosis evaluation should include history and physical examination, bone density measurement with dual-energy x-ray absorptiometry scan and laboratory tests [32]. However, in older women and men with a fragility fracture over the age of 75 years, bone density measurement is not needed and treatment with bisphosphonates is recommended regardless of bone mineral density (BMD) [33].

Medical treatment

In general, after diagnosis of osteoporosis, a coordinated postfracture osteoporosis treatment program should be provided for patients with a fragility fracture [26] involving the orthopedic surgeon, rheumatologist or endocrinologist and the family physician. In summary, therapeutic options to reduce hip fracture risk include calcium and vitamin D repletion and osteoporotic medical treatment [34]. The primary goal of pharmacologic treatment of osteoporosis is to reduce the risk of subsequent fractures. Several classes of drugs are currently being used for the prevention and management of postmenopausal osteoporosis, including bisphosphonates, calcitonin, estrogens and/or hormone therapy, raloxifene, strontium ranelate and parathyroid hormone (PTH) [12].

Bisphosphonates are currently used as first-line treatment for osteoporosis, as they increase BMD by reducing the rate of bone resorption and they can be administered either orally or via intravenous infusion, with each mode of administration having associated benefits and costs [12,35]. Bisphosphonates are of proven benefit in the prevention of fragility fractures [36]. In addition to reduced fracture risk, interventions can improve quality of life and reduce mortality in patients with fragility fractures [37]. Recommendations for administration of bisphosphonates include postmenopausal women aged 65–75 years if osteoporosis is confirmed by dual-energy x-ray absorptiometry scan, and older women without the need for a scan. Bisphosphonates are also recommended for postmenopausal women younger than 65 years when they have a very low BMD or extra independent risk factors of further fragility fractures [36]. Regarding hormone replacement therapy, it is not recommended as a first-line therapy for the prevention of osteoporosis [202].

However, even though bisphosphonates are the most widely used antiresorptive agents for the treatment of osteoporosis, their long-term use has been associated with increased fracture risk for the so-called 'atypical fractures' secondary to suppressed bone turnover, affecting sites such as the subtrochanteric femur that are infrequently affected by osteoporotic fractures [37,38]. It remains unknown whether the pathophysiology of these atypical insufficiency fractures is related to the mode of action of bisphosphonates leading to the accumulation of microfractures and weakening of bone, or whether they represent an unusual osteoporotic fracture manifestation [38,39]. Overall, the optimal duration of bisphosphonate treatment is still unclear and the real risk of associated stress fractures needs to be elucidated. Recently, it has been found that there was no evidence of an increased risk of atypical femur fractures in bisphosphonate users compared with raloxifene/calcitonin users, but the possibility that long-term bisphosphonate use may increase the risk of these fractures cannot be excluded [40]. In the meantime, clinicians should be aware that patients on long-term treatment may develop such fractures and the decision to maintain a patient on therapy beyond 5 years should be taken on a case-by-case approach, guided by assessment of individual overall fracture risk, and the drug's efficacy and safety profile [39]. A 12-month interruption in therapy after 5 years in patients who are clinically stable has been suggested; and in those who sustained an atypical fracture while receiving bisphosphonate therapy, teriparatide treatment is advised [41].

Another alternative to the antiresorptive drugs that reduce bone turnover is the use of anabolic agents. Currently, teriparatide, a

recombinant formulation of PTH, is available as a bone-forming therapy for the treatment of osteoporosis and it has been found to reduce the incidence of vertebral and nonvertebral fractures in osteoporotic patients [42]. Teriparatide is recommended as an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are unable, have a contraindication or are intolerant to bisphosphonates [36].

Overall, preventive pharmacotherapy reduces the risk of vertebral fracture by 30–70%, depending on the agent and patient's compliance [43]. Furthermore, both calcitonin and teriparatide are also useful in decreasing the pain associated with vertebral fractures [44,45]. However, the effect on nonvertebral fractures is lower and varies by fracture site. For example for hip fractures, the relative reductions in risk in the osteoporosis trials range from 30 to 51% [46]. In a recent meta-analysis assessing the efficacy of different bisphosphonates in the prevention of osteoporotic fractures, it has been found that there is a 47% probability that zoledronic acid shows the greatest risk reduction of hip fractures, followed by alendronate (36%) and risedronate (11%) [47]. On the contrary, for wrist fractures, there were no particular antiosteoporotic agents with a significant protective effect versus the other agents or placebo [42].

Overall, when choosing a particular pharmacological agent it should be kept in mind that agents found to decrease vertebral, nonvertebral and hip fractures should be used preferentially over those that only demonstrate vertebral antifracture efficacy. As a general rule, therapeutic decisions should be based on a balance between benefits and risks of treatment for each particular patient, as no single agent is appropriate for all patients [46].

Even though it has been shown that treatments can reduce the risk of future fractures [1], when taken regularly and long term [48,49], they are usually being used irregularly and suboptimally despite prescription [50,51]. Generally, poor adherence and no persistence in antiresorptive medication regimens are common in patients with osteoporosis, and this can negatively affect patient outcomes and increase the risk of a subsequent fracture. Particularly for oral bisphosphonates, rates of adherence decline dramatically during the first year of treatment and continue to decline thereafter [52]. The alternative use of intravenous administration of zoledronic acid once a year may ensure that patients will have a full treatment effect for at least 12 months [48]. Lack of patients' adherence, including compliance and persistence to the osteoporotic treatment represents an important issue that affects outcome. Even in randomized, controlled clinical trials where patients are carefully monitored and in regular contact with healthcare professionals, the adherence rate varies between 60 and 81% [53]. Furthermore, in the everyday clinical practice, compliance and persistence by patients to treatment of osteoporosis is even lower, and clinicians may have a misconception of how adherent their patients are [53]. There are numerous reasons for lack of patients' adherence including complicated dosing regimens or dosing intervals and lack of knowledge about osteoporosis and the importance of the treatment for fracture prevention. For example, patients are more adherent to monthly versus weekly, and weekly versus daily bisphosphonates. Nevertheless, even with weekly or monthly treatment, patients still had suboptimal adherence [53]. The use of intravenous bisphosphonates such as ibandronate (quarterly dosing) and zoledronic acid (annual dosing) may lead to improved adherence by patients. Furthermore, adverse effects, such as osteonecrosis of the jaw or gastrointestinal irritation, which can be either real or perceived, represent important reasons why patients may not adhere to treatment [53,54]. To maximize adherence, it is important for patients to understand the nature and progression of osteoporosis, even though it may be asymptomatic. Additionally, a close relationship between healthcare providers and patients monitoring have been shown to improve adherence by 57% [55].

Finally, a novel antiosteoporotic agent, denosumab, has been recently added to the list of agents used for the treatment of osteoporosis and it is administered subcutaneously every 6 months. It is a human recombinant monoclonal antibody (an antireceptor activator of NF-κB ligand [RANKL] antibody) that inhibits osteoclastic-mediated bone resorption by binding to osteoblast-produced RANKL. By reducing RANKL binding to the osteoclast receptor RANK, it decreases bone resorption and turnover. This novel approach for the management of postmenopausal osteoporosis shows high adherence rate, excellent safety profile and global nonvertebral and vertebral osteoporotic fracture risk reduction [42,56]. Currently, denosumab is recommended as a treatment option for the prevention of osteoporotic fractures only in postmenopausal women at increased or high risk of fractures, risk of fracture but the patient cannot comply with the special instructions for

administering oral bisphosphonates, or have an intolerance of, or contraindication to, take other osteoporosis treatments [57,58].

Overall, improvements in treatment persistence and compliance are necessary to help reduce the risk of fractures [35]. Such measures include improved physician/patient communication and simplification of treatment regimens, close monitoring with the use of biochemical markers of response or BMD measurements, and early intervention in declining adherence, as well as a specific specialist to take responsibility for the follow-up [52,59]. Overall, after the initial management of the fragility fracture, it is crucial for the treating physician to ascertain patient's follow-up care, by providing a detailed plan highlighting the need for osteoporotic medical treatment, since long-term administration is required for effectiveness of the treatment [12] and treatment of osteoporosis at the time of a fracture represents a highly cost-effective intervention [60].

Nutrition, calcium & vitamin D supplementation, & bone health

Even though nutrition is only one of the several factors that influence bone mass and osteoporotic fractures, numerous nutrients and dietary components, such as calcium, vitamin D, vitamin K, phytoestrogens and nondigestible oligosaccharides can influence bone health [61]. Although the evidence base to support their role in bone health ranges from very firm to scant, depending on the nutrient/component [61], nutritional policies for the treatment of osteoporosis should be implemented in patients with a fragility fracture. In general, maintaining optimal levels of calcium and vitamin D is fundamental for osteoporosis treatment, especially in older patients who are at increased risk for vitamin D and calcium deficiencies because of changes in dietary intake and nutrient absorption [12].

The role and optimal level of calcium intake to compensate for skeletal calcium losses and for the treatment of osteoporosis and prevention of fractures remains unclear. The daily calcium doses for individuals older than 50 years of age vary widely from 700 to 1300 mg [62]. Recent guidelines recommend that the total daily intake of elemental calcium (through diet and supplements) for individuals over age 50 years should be 1200 mg. Regarding vitamin D, for healthy adults at low risk of vitamin D deficiency, routine supplementation with 400–1000 IU (10–25 µg) vitamin D3 daily is recommended, but for adults over age 50 years at moderate risk of vitamin D deficiency, the recommended daily dose is 800–1000 IU (20–25 µg). In general, daily doses up to 2000 IU (50 µg) are safe and do not necessitate monitoring. For patients receiving pharmacologic therapy for osteoporosis, serum levels of 25-hydroxyvitamin D should be measured after 3–4 months of adequate supplementation and should not be repeated if an optimal level (≥75 nmol/l) is achieved [43].

Research is ongoing to investigate associations between long-term dietary intake of calcium and risk of osteoporotic fractures and to define the optimum daily calcium intake. There is controversy about the efficacy of calcium supplementation for reducing fractures [63] and the potential adverse effects of high-dose supplementation [64]. Increased calcium intake was not found to be associated with a further reduction of osteoporotic fracture rate [62]. Nevertheless, postfracture use of prescribed calcium plus vitamin D supplements alone or with antiosteoporotic drugs in females was associated with lower mortality in older people hip fracture patients [65]. Vitamin D combined with calcium was also found to be associated with statistically significant reduction in the risk of falls, and this was more prominent in patients who were vitamin D deficient [66]. The dose of oral vitamin D (cholecalciferol, ergocalciferol) that appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized persons older than 60 years of age is between 700 and 800 IU/day, whereas a dose of 400 IU/day is not sufficient for fracture prevention [67].

Overall, for patients with a fragility fracture, the physician can prescribe calcium and vitamin D supplementation, but this should be in addition to agents that have a proven capacity to prevent fractures, such as bisphosphonates [12]. However, recent studies have shown that the role of calcium supplementation with or without vitamin D in osteoporosis management should be reassessed, as it was found to be associated with increased risk of cardiovascular events in healthy postmenopausal women, especially myocardial infarction as well as angina, stroke or even sudden death [68,69]. Therefore, this potential risk should be balanced against the likely benefits of calcium supplementation on bone and osteoporosis.

Finally, physical exercise and particularly high-intensity resistance training in postmenopausal women has a positive effect on BMD and bone health, by preventing postmenopausal bone loss [70]. Therefore, other healthcare-related professionals, such as rehabilitation professionals and

dieticians can also play a role in postfracture care and particularly in the nonpharmacological management of osteoporosis including physical activity and dietary supplementation.

Assessment of contributors to secondary osteoporosis & metabolic bone diseases

Secondary osteoporosis can result from various chronic diseases such as rheumatoid arthritis, medications and especially long-term oral corticosteroid use, increased alcohol consumption, or nutritional deficiencies that adversely impair bone metabolism, compared with primary osteoporosis, which is associated with aging [3,71]. To improve outcome in patients presenting with a clinical osteoporotic fracture, it is important to detect and appropriately treat previously undetected contributors to secondary osteoporosis and metabolic bone diseases (SECOB). Bours *et al.* evaluated their prevalence in patients with a recent clinical vertebral or nonvertebral fracture, by performing BMD and laboratory investigations, including serum calcium, inorganic phosphate, 25-hydroxyvitamin D, creatinine, intact PTH, thyroid-stimulating hormone, free T(4), serum and urine protein electrophoresis, and in men also serum testosterone [72]. They found that at presentation with a fracture, 26.5% of patients had previously unknown contributors to SECOB, such as monoclonal proteinemia, renal insufficiency grade III or greater, primary or secondary hyperparathyroidism, hyperthyroidism and hypogonadism in men. Furthermore, more than 90% of patients had an inadequate vitamin D status and/or calcium intake at any level of BMD. Since these conditions are treatable or at least they require regular follow-up, systematic screening of patients with a recent osteoporotic fracture will identify those in whom potentially reversible contributors to SECOB and calcium and vitamin D deficiency are present to improve their outcome [72].

Fall prevention

Since a personal history of fracture is one of the strongest clinical predictors of subsequent fractures [73], and most fragility fractures are the result of falls [7], prevention of falls is a fundamental step to reduce the risk of recurrent fractures. Fall prevention strategies should be discussed between the patient and the primary care physician or nurse, aiming to reduce the number and severity of falls by minimizing potential risk factors for falling such as poor lighting, visual impairment and use of certain medications [12]. Interventions to reverse risk factors, such as impaired vision, should be performed when possible [4]. Continued physical therapy and exercise after discharge from the hospital can not only improve or maintain long-term level of mobility, but can also reduce fall hazards in the home by strengthening exercises and balance training [12]. External hip protectors were found to be cost effective among residents of long-term care facilities in reducing hip fractures, but not in the community because of poor compliance [203]. However, there is controversy regarding their efficacy to prevent fall injuries and therefore there is insufficient evidence to recommend for or against their routine use [204]. Nevertheless, recommendations for their use in institutionalized older people may be made on other grounds, including the large potential benefit and limited adverse effects [204]. The use of an antislip shoe device was also found to reduce the rate of falls in icy conditions [74].

Additionally, a safe and 'fall-proof' environment should be ensured and the use of sedating or psychotropic medications should be avoided [35,74]. As there is an age-related increase in falls or an increased risk of falls in various diseases [4], more aggressive implementation of fall prevention strategies and interventions such as pacemakers in people with carotid sinus hypersensitivity and cataract surgery should be considered [74]. Overall, recent studies have demonstrated that a thorough assessment and multifactorial interventions can reduce the rate of falls in older people living in the community [75] as well as in nursing care facilities and hospitals [75]. There is also evidence that such fall prevention strategies can be cost saving, but further research is needed to confirm the contexts in which these are effective [74].

Specific considerations to improve patients' outcomes based on the fracture site

Hip fractures

Hip fractures have been characterized as the 'international barometer' of osteoporosis, as they are strongly related to low BMD, they are almost always treated in hospital and are more costly, they are associated with major morbidity, loss of independence, and even increased mortality than other common types of osteoporotic fractures [4,34]. Mortality following hip fracture is mainly attributed to complications such as deep vein thrombosis, pulmonary embolism, pneumonia, deconditioning and poor rehabilitation [76]. Mortality rates increase with patient age (4% for

each patient year), the time required to have the hip repaired (<2 days, 4%; >4 days, 6.1%), and comorbid conditions at admission (10-year mortality rate for chronic obstructive pulmonary disease, 27%; congestive heart failure, 40%) [77–79]. Mortality rates have also been found to be higher in men compared with women [80]. In a recent systematic literature review, it has been shown that patients with osteoporotic hip fracture are at considerable excess risk for death compared with nonhip fracture/community control populations ranging from 8.4 to 36% for the first year after fracture, and that the increased mortality risk may persist for several years thereafter [9]. Overall, there is an increased relative risk for mortality following hip fracture that was at least double that for the age-matched control population, which however, becomes less pronounced with advancing age and is highest in the days and weeks following the index fracture [9].

Even though an initial hip fracture was found to be associated with an increased risk for subsequent osteoporotic fracture up to sixfold [81], which is associated with poorer prognosis than the first one [82], current postfracture care for these cases remains problematic, with only 5–25% of patients being discharged with prescriptions for osteoporosis treatment [35]. Furthermore, hip fracture patients may experience a second hip fracture, especially within the first year [83]. Therefore, it is essential to implement and adhere to clinical strategies immediately after the first hip fracture to lower the risk of subsequent fractures [34,84].

Regarding the effect of surgical timing in patients with osteoporotic hip fracture, most studies focus on mortality with conflicting findings [85–90]. Such discrepancies on the effect of surgical delay on outcomes among studies may be due to the diversity of the reasons of delay or a differential effect on patient risk subgroups, as a recent prospective study of 2250 elderly patients with hip fracture has shown that the reported association between late surgery and higher morbidity and mortality in patients with hip fracture is mostly explained by medical reasons for surgical delay [88]. Nevertheless, even if the timing of the operation remains controversial and potential residual medical and nonmedical confounding factors may limit definitive conclusions, operative delay beyond 48 h after admission may increase the odds of all-cause mortality [87]. Additionally, a delay of more than 4 days was found to increase mortality even more [89]. Conversely, a recent study has shown that although a 1-week delay in the surgical treatment of elderly patients with hip fractures increased the incidence of postoperative complications, it did not increase the mortality rate or prolong the period of recovery [90].

Regarding the functional outcome, Orosz *et al.* investigated the association of timing of surgical repair of hip fracture with function and other outcomes in osteoporotic patients, and found that early surgery was not associated with improved function or mortality [86]. Nevertheless, it was associated with reduced pain, length of stay and probably with major complications among medically stable patients. Overall, further research is required in this field, but meanwhile medically stable patients with hip fractures should receive early surgery when possible [86], to improve the short-term clinical outcome including the ability to return to independent living, shorten length of stay and reduce risk for development of pressure ulcers, and possibly to minimize overall mortality rates and postoperative complications [91]. The aim is to shorten the period of higher levels of pain and avoid prolonged delay and fasting period, which may aggravate the postfracture catabolic phase [91]. Obviously, important factors such as patient's medical and cognitive status as well as preinjury walking ability and activities of daily living should also be considered when evaluating patient's outcome and time to surgery in patients with osteoporotic hip fractures. The availability of operating rooms and support services needs to be optimum to avoid system-related causes of a delay of surgery.

The role of postoperative management after a hip fracture

The postoperative management after a hip fracture in older patients is fundamental for the final outcome, since optimal management can minimize potential perioperative causes of morbidity and mortality. In summary, important parameters to be considered during postoperative management include appropriate pharmacologic treatment with monitoring and adjustment of medications, as well as physiotherapy (as appropriate including chest physiotherapy) [12]. Regarding the pharmacologic treatment, medications prescribed depend on the type of fracture treated and they may include thromboprophylaxis to prevent deep vein thrombosis, antibiotics to prevent infection and analgesics to control pain [12]. Adequate analgesia in particular during the early postoperative period, is particularly important for facilitating physical therapy sessions and mobilization, but narcotic use should

be carefully monitored as they may increase adverse events and the risk for falls. However, it has been reported that postoperative pain is often inadequately managed [92], and this can persist not only for the early postoperative period, but also for a short period after discharge, ranging from discomfort to more severe pain associated with movement [93]. In a recent systematic review on the efficacy and safety of pharmacologic and nonpharmacologic interventions for managing pain after a hip fracture including nerve blockade, spinal anesthesia, systemic analgesia (narcotics, NSAIDs), multimodal pain management, transcutaneous electrical neurostimulation and complementary and alternative medicine, it has been shown that nerve blockades are effective in reducing acute pain after hip fracture; however, evidence was insufficient on the benefits and harms of most interventions in managing acute pain [94].

Nerve blockade has also been found to be effective in reducing postoperative delirium [95], which constitutes a common and troublesome complication in older patients with hip fractures [95]. Its incidence during hospitalization varies from 13% [96] up to 34% [95] even in patients cognitively intact at admission. Risk factors for development of delirium are older age, more than four prescribed drugs at admission, cognitive dysfunction as well as pain intensity [95,96]. The latter highlights the need for adequate pain management pre- and post-operatively. Furthermore, it has been shown that the implementation of a multifactorial program with intensified prehospital and perioperative treatment and care could reduce the incidence of delirium during hospitalization by 35% [96].

Finally, the role of orthogeriatrics for an efficacious postoperative management should also be affirmed, since older patients with hip fracture often have complex comorbid conditions or develop severe complications during hospitalization. Therefore, timely and high-quality care must be provided with continuous orthogeriatric input to prevent and address these complex problems [97,98]. It has been demonstrated that daily comanagement of these patients by geriatricians and orthopedic surgeons leads to improved outcomes including shorter times to surgery, shorter length of stay, fewer cardiac complications and fewer cases of thromboembolism, delirium and infection, although no difference in in-hospital mortality or readmission rate was noted [97]. Overall, different models have been implemented and evaluated to improve orthogeriatric services [99]. Although the best model is yet to be elucidated, there is a trend toward an integrated approach including a geriatrician in the trauma unit, a multidisciplinary team, prioritization of the geriatric fracture patients and development of guidelines to improve outcomes of older patients with hip fracture [99].

Osteoporotic vertebral fractures

A considerable proportion of osteoporotic vertebral fractures escape clinical diagnosis and severe vertebral deformities alone produce symptoms that lead to diagnosis, with less than 10% of fractures necessitating admission to hospital [4]. This implies that many patients with an osteoporotic vertebral fracture seldom receive preventive osteoporotic treatment [100]. However, it is essential to identify the occurrence of one vertebral osteoporotic fracture, even an asymptomatic one detected incidentally on a routine radiograph, as it increases the likelihood of additional fractures by at least fourfold [101]. Early recognition of these fractures will allow prompt initiation of osteoporotic treatment and secondary prevention to reduce future fracture risk.

Moreover, as most osteoporotic vertebral fractures are precipitated by routine everyday activities (e.g., bending or lifting light objects) and only a quarter of them result from falls [4], it is important to investigate the spine for such fractures in patients who already sustained a fragility fracture and complain of back pain, even if there is no history of trauma, in order to provide appropriate treatment. Such fractures are regarded as *prima facie* evidence of osteoporosis and their incidence rises rapidly with age in both sexes [4]. After the age of 60 years, women have approximately a two- to three-fold greater incidence of vertebral fractures than men [4,102].

In general, acute osteoporotic vertebral compression fractures are treated conservatively with bracing, analgesics and functional restoration, whereas open surgical management with decompression and stabilization is reserved for the rare patient with neural compression and progressive deformity with neurologic deficits [102]. Percutaneous vertebral body augmentation (vertebroplasty or balloon tamp reduction) is indicated in patients with chronic pain in nonsurgically treated patients who fail to improve over 8–12 weeks after fracture, in an effort to improve pain and function, but the exact indications remain unclear [102]. Newer materials for augmentation may provide more favorable clinical results and may be used in the future for prophylactic vertebral augmentation with biologic agents that locally improve bone density

and strength, offering long-term functional improvement in treated patients [103].

Recently, clinical practice guidelines approved by the American Academy of Orthopaedic Surgeons (AAOS) on the treatment of symptomatic osteoporotic spinal compression fractures have been published [103], aiming to help physicians in their clinical decision-making and improve patient outcome. In summary, the use of vertebroplasty for the treatment of these fractures is not recommended (strong recommendation) as it has not shown any significantly improved outcome, whereas the use of calcitonin for 4 weeks following the onset of fracture is recommended for pain reduction (moderate recommendation). Also, for the prevention of additional symptomatic fractures, ibandronate and strontium ranelate can be administered, and for pain management, the use of L2 nerve root blocks to treat the pain associated with L3 or L4 fractures is recommended. Finally, kyphoplasty can be performed to improve pain in patients, who are neurologically intact, with subacute or chronic symptomatic fractures (weak recommendations). Insufficient evidence exists to support the use of bracing or the implementation of an exercise program for patients who present with an osteoporotic spinal compression fracture. Future research is required to determine the effectiveness of modalities such as bracing, physical therapy/exercise and kyphoplasty in the treatment of these fractures [103].

Distal radius fractures

Although distal radius fractures have no impact on mortality rate and have minimal morbidity compared with other osteoporotic fractures [12,104], the history of prior wrist fracture may represent a risk factor for recurrent osteoporotic fractures, especially in men [105]. However, the risk of recurrent fractures was found to be substantially lower than that following other osteoporotic fractures, but significantly higher than for those who no previous fracture [106]. Therefore, patients with osteoporotic wrist fractures should be evaluated as candidates for preventive measures. A recent diagnostic meta-analysis of the ability of distal radius to predict a future hip fracture has shown low sensitivity and high specificity for predicting future fragility fracture [107].

Among the clinical practice guidelines recently published on the treatment of distal radius fractures in adults [108], there is inconclusive evidence to recommend for or against surgical treatment of older people (>55 years) patients with distal radius fractures. The available evidence could not demonstrate any statistically significant difference regarding pain and overall mental or physical outcomes between casting and surgical fixation in these patients. On the other hand, adjuvant treatment of distal radius fractures with vitamin C is recommended to prevent disproportionate pain and improve functional recovery (moderate recommendation) [107].

Osteoporotic pelvic & acetabular fractures

Even though osteoporotic pelvic fractures, including pubic rami and sacral fractures, are less frequent fragility fractures, an increase in their incidence has been observed [108]. In general, osteoporotic pelvic fractures requiring initial hospitalization share most characteristics of hip fracture with high morbidity and mortality and loss of autonomy in terms of outcome [109]. Although the vast majority of osteoporotic pelvic fractures are classified as stable injuries and their management involves conservative treatment and pain management, the pain-related immobility and the long healing period that is often required may lead to a possible increased risk of morbidity and mortality especially in patients with severe pre-existing comorbidities [109,110]. Recently, operative treatment in certain cases with reconstruction of the pelvic ring using external fixation with supra-acetabular screw positioning was found to reduce the pain and allow an earliest possible rehabilitation without prolonged immobilization or secondary pelvic insufficiency instability [111]. Finally, a high rate of vitamin D deficiency associated with a secondary hyperparathyroidism has been observed among patients with osteoporotic pelvic fractures [109] and therefore it should be treated to improve outcome.

Regarding the acetabular fractures in older individuals with severe osteoporosis, the outcome can be improved by aggressive operative treatment if the physiological status of the patient allows it. Techniques common to revision of failed acetabular components can be used to reconstruct the osteoporotic acetabular fracture in combination with total hip replacement with satisfactory outcome similar to those achieved for reconstruction of osteoarthritis and early mobilization [112].

Specific considerations for vulnerable elderly patients

This group of patients usually comprises patients over the age of 80 years, minimally ambulatory, with multiple medical comorbidities and cognitive impairment [113]. It is a

greater challenge to improve final outcome for these patients after an osteoporotic fracture as there are patient-related barriers to initiate and maintain effective osteoporotic treatment and implement rehabilitation or secondary prevention strategies. Such barriers include among others coexisting dementia, severe medical comorbidities and polypharmacy, postoperative delirium, and inadequate social support in patients who live alone or have low socioeconomic status [113]. The advanced age itself in combination with the history of the fracture dramatically increases their risk for subsequent fracture and it is associated with a higher rate of comorbidities and polytherapy.

Often physicians who treat these patients may be discouraged to initiate osteoporotic treatment and secondary prevention due to risk of complications with some medications, lack of adherence with treatment, inadequate caregiver supervision or support, and shorter life expectancy [113]. They may even overlook calcium and vitamin D supplementation, in an effort to minimize the sum of daily medications. Nevertheless, efforts should be made to improve outcome in the vulnerable elderly patients by initiating treatment and prevention strategies through complex care paths or specialist referrals for these patients. These need to be initiated early and require coordination. Particularly in the rehabilitation hospital, where the patients are in a more stable condition, there are better opportunities to initiate these strategies and to promote adherence [113].

Rehabilitation, long-term pain management & improving quality of life after an osteoporotic fracture

In addition to fall prevention and treatment of osteoporosis, rehabilitation also improves the functional outcome in patients after an osteoporotic fracture by reducing the level of disability and/or maintaining the level of mobility [12]. Prompt physical therapy in terms of mobilization, muscle strengthening and chest physiotherapy, postoperatively or after conservative management, ensures early recovery, maximizes mobility and reduces complications from prolonged immobilization [77]. Continued physical therapy after discharge from the hospital is also central in order to ensure and retain optimal functional recovery. In osteoporotic patients, long-term mobility and weight-bearing exercises are important to help maintain and improve bone health. The importance of physical exercise is not only that it improves the outcome after a recent fragility fracture, but it also has a positive effect on the rest of the patients' lives [12].

Particularly for older patients with hip fractures, rehabilitation interventions to improve their recovery and physical and psychosocial functioning have been a topic of intense research as they often result in reduced mobility. Care programs including strategies for mobilization with early weight bearing and gait retraining, exercises and physical training, and even home exercise programs [114], used at various stages during rehabilitation [115] have been implemented. However, there is insufficient evidence to determine the effectiveness of the various mobilization strategies at enhancing mobility that start either in the early postoperative period or during the later rehabilitation period [84], and to recommend practice changes [116]. A review on the effects of multidisciplinary rehabilitation for these patients has shown that although there was a tendency to a better overall result when multidisciplinary inpatient rehabilitation was provided in patients, these results were not statistically significant [117]. Similarly, regarding the distal radius fractures, the effects of rehabilitation interventions on outcome in adults after conservative or surgical treatment have been studied, but the current evidence is insufficient to establish their relative effectiveness [118]. Therefore, future trials are needed to establish the effectiveness as well as the cost–effectiveness of different rehabilitation strategies.

In addition to increased morbidity and mortality after an osteoporotic fracture, there is also an associated compromise in various aspects of quality of life, including pain, decreased physical, mental and social well being [10]. Quality of life can be measured in these patients using generic questionnaires such as Short Form (36) Health Survey and European Quality of Life-5 Dynamics or one of the available osteoporotic-specific questionnaires.

Significant loss of quality of life has been reported with hip fractures and with prevalent vertebral fractures, especially with lumbar fractures compared with thoracic ones or with multiple vertebral fractures [10,119]. As quality of life was found to be dependent on comorbidities, mobility, independence of activities of daily life and fracture complaints [10], it is central to optimize treatment modalities, pain management, rehabilitation strategies and overall patients' medical management to improve outcomes as evaluated by quality of life

questionnaires. Recently, it has been demonstrated that osteoporotic fractures also have an impact on quality of life over time [120], implying that evaluation and management of patients with fragility fractures should be continuing for a better outcome.

Especially after hip fractures, up to 42% of older patients may experience persistent pain 3–4 months postoperatively [121]; and around a quarter of hip-fractured patients continued to experience moderate to very severe pain from 6–12 months after discharge, with a significant impact on their quality of life [93]. Consequently, more attention should be given to ensure continuing adequate pain control strategies when required postoperatively in patients with fragility fractures, to prevent further declines in their outcomes in the long term, such as ambulation, morbidity and return to community [122].

Finally, modifications of lifestyle factors such as quitting smoking and minimizing alcohol intake can also improve patients' general health and quality of life [12].

Conclusion

As populations are aging, osteoporotic fractures have become one of the most prevalent trauma conditions seen daily in clinical practice. Therefore, these fractures represent a major public health problem, as they are associated with high rates of morbidity, disability and pain, and even mortality and high cost. Therefore, in addition to primary prevention strategies, efforts should be made to improve patients' outcomes after fragility fractures and optimize their overall management. By providing adequate fracture fixation and postfracture care in terms of evaluation and appropriate medical treatment of osteoporosis,

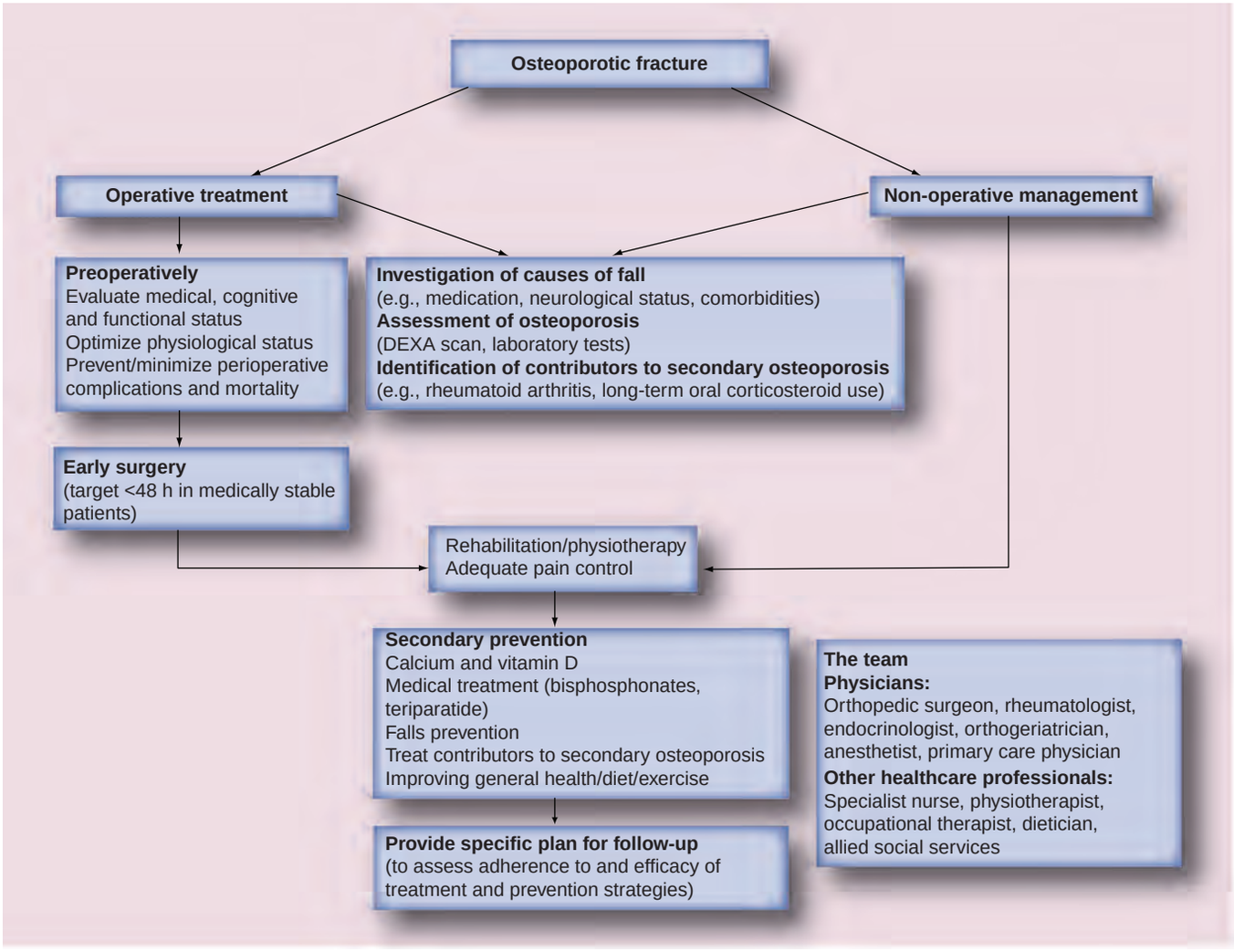

Figure 1. Summary of the overall management of patients after an osteoporotic fracture aiming to improve outcome.
DEXA: Dual-energy x-ray absorptiometry.

rehabilitation, lifestyle modifications and fall prevention (Figure 1), the aim is to attain optimal functional recovery, reduce future fracture risk, and improve bone health and overall quality of life. The need for a multidisciplinary approach and the establishment of clinical pathways is obvious to ensure high-quality care and adherence to medical treatment and other secondary prevention strategies.

Future perspective

Advances that are made in implant technology, operative and anesthetic techniques as well as rehabilitation strategies and their effectiveness on improving outcomes in patients after osteoporotic fractures will be evaluated in the years to come. Moreover, with the increased understanding of the pathophysiology of osteoporosis at the molecular level, research is ongoing to develop novel and more effective therapeutic targets for osteoporosis, in an effort to overcome side-effects and limitations of current treatments, and inadequate compliance and to improve outcome and possibly reverse osteoporosis in the future. The most promising novel treatments include odanacatib (a specific inhibitor of the osteoclast protease cathepsin K), and antibodies against the proteins sclerostin and dickkopf-1 (two endogenous inhibitors of bone formation) [123]. In the future, the role of the genetic susceptibility to bone fragility and osteoporosis will be further elucidated [124], allowing early identification of patients at risk for osteoporosis or poor outcome, identification of genes and pathways as molecular targets for the design of novel more efficacious treatments and the development of individualized treatment modalities to improve outcomes.

Physicians and all healthcare professionals need to be actively educated about the existing guidelines, and the 'barriers' for adequate post-fracture care need to be identified and addressed within the different medical, rehabilitative, nursing home and home-care services [125]. Finally, further efforts should be made on the secondary prevention following the first osteoporotic fracture [84] and a standardized discharge plan may help to achieve long-term adherence to treatment [29].

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Executive summary

- Osteoporotic or fragility fractures are common and contributing factors are the susceptibility to falls and the underlying osteoporosis. Fractures of the vertebrae, the hip and the distal radius are the 'typical' osteoporotic fractures. They are associated with increased treatment cost, pain, morbidity and mortality.
- As populations are aging and the incidence of osteoporotic fractures is increasing, efforts should be made to improve patients' outcomes and optimize their overall treatment management.
- Improvements in implants and surgical techniques facilitate early mobilization and improved function and pain scores.
- Secondary prevention of future osteoporotic fractures is central and includes assessment and treatment of underlying osteoporosis, and fall prevention strategies.
- Medical management of osteoporosis includes calcium and vitamin D repletion and medical treatment such as bisphosphonates and parathyroid hormone. The primary goal is to reduce the risk of subsequent fractures. However, treatment persistence and compliance is currently low and should be maximized to improve outcomes. Contributors to secondary osteoporosis and metabolic bone diseases must be detected and treated appropriately.
- Fall prevention strategies are a fundamental step to reduce the risk of recurrent fractures. Potential risk factors for falling should be assessed and interventions against reversible risk factors should be performed.
- For osteoporotic hip fractures, as they are associated with high mortality and morbidity, early surgery should be targeted in medically stable patients to improve the short-term clinical outcome and reduce complications and possibly mortality rates.
- Osteoporotic vertebral fractures are frequent and they are associated with chronic pain. Current clinical practice guidelines on their treatment assist the physicians in the clinical decision-making.
- Extra attention should be given in the vulnerable elderly patients with an osteoporotic fracture, as they represent a challenging group regarding administration of osteoporotic treatment and implementation of rehabilitation or secondary prevention strategies.
- Optimal rehabilitation and adequate pain management can improve function and overall quality of life after an osteoporotic fracture.

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