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Recommendations on the post-acute management of the osteoporotic fracture - Patients with "very-high" Re-fracture risk

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ABSTRACT

Osteoporosis is a systemic skeletal disease where there is low bone mass and deterioration of bone micro-architecture, leading to an increased risk of a fragility fracture. The aim of this clinical guideline from Fragility Fracture Network Hong Kong SAR, is to provide evidence-based recommendations on the post-acute treatment of the osteoporotic fracture patient that presents for clinical care at the Fracture Liaison Service (FLS). It is now well established that the incidence of a second fracture is especially high after the first 2 years of the initial osteoporotic fracture. Therefore, the recent osteoporotic fracture should be categorized as "very-high" re-fracture risk. Due to the significant number of silent vertebral fractures in the elderly population, it is also recommended that vertebral fracture assessment (VFA) should be incorporated into FLS. This would have diagnostic and treatment implications for the osteoporotic fracture patient. The use of a potent anti-osteoporotic agent, and preferably an anabolic followed by an anti-resorptive agent should be considered, as larger improvements in BMD is strongly associated with a reduction in fractures. Managing other risk factors including falls and sarcopenia are imperative during rehabilitation and prevention of another fracture. Although of low incidence, one should remain vigilant of the atypical femoral fracture. The aging population is increasing worldwide, and it is expected that the treatment of osteoporotic fractures will be routine. The recommendations are anticipated to aid in the daily clinical practice for clinicians.

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The Translational potential of this article: Fragility fractures have become a common encounter in clinical practise in the hospital setting. This article provides recommendations on the post-acute management of fragility fracture patients at the FLS.

1. Introduction

Osteoporosis is a systemic skeletal disease where there is low bone mass and deterioration of bone microarchitecture, leading to an increased risk of a fragility fracture [1]. It is well known that the occurrence of an osteoporotic fracture leads to high morbidity and mortality. In fact, the condition often causes disability and poor quality of life for the patient. For hip fractures alone, it is projected that it will increase from 1,124,060 in 2018 to 2,563,488 in 2050 in Asia [2]. Globally, hip fractures also rank amongst the top 10 causes of disability, with 4.5 million patients disabled from the disease annually [3], and it is now a common encounter for clinicians [4]. A recent study showed that the approximate total costs for hospitalization of hip fractures showed a steep increase from USD 60 million to USD 380 million from 2012 to 2016 in China [5]. In Hong Kong, there is an increasing trend with more than 8000 osteoporotic fractures every year [6]. The number of osteoporotic fractures has been rising rapidly in Asia, posing a large socio-economic burden to our society [7,8]. Therefore, with the aging population, the diagnosis, treatment, and prevention of the osteoporotic fracture has been an ever-increasing burden.

Recent call-to-actions by numerous organizations have focused on addressing the fragility fracture crisis worldwide and preventing the subsequent imminent fracture [9]. The Fragility Fracture Network is an international organization with a global network of alliances of fragility fracture leaders [9]. The Fragility Fracture Network Hong Kong SAR (FFN-HKSAR) which was established in 2021, works together with FFN-China, and the importance to promote quality patient care, training, research, and education in the field of fragility fractures are emphasized. Our previously published medical practice guideline in 2019 has recommended the instrumental role and establishment of Fracture Liaison Services (FLS) in the hospital settings to bridge the healthcare gap [10], which is now already established in many public hospitals in Hong Kong. Ideally, patients 50 years or older presenting with an osteoporotic fracture in the hospital that provides definitive fracture care should be identified, investigated, provided information, treated and reviewed by the FLS. The FLS has proven improvement in BMD testing with Dual-energy X-ray absorptiometry (DXA), treatment initiation, adherence to treatment, re-fracture incidence and decrease in mortality [11,12]. The FLS consists of a dedicated coordinator or champion that provides proactive recruitment of all osteoporotic fracture patients [10], and has been shown to be cost-effective in the hospital settings [13]. Due to its structured service, the patient is assessed and treated in a holistic manner.

Recent new evidence and international guidelines have emerged in how to optimize the care and treatment of osteoporosis. The aim of this clinical guideline from FFN-HKSAR, is to provide evidence-based recommendations on the post-acute management of the osteoporotic fracture that presents for clinical care at the FLS.

2. Definition of the osteoporotic fracture and risk factors of occurrence

The osteoporotic fracture is defined as a fracture caused by low trauma events, in which the World Health Organization (WHO) has quantified this force equivalent to a fall from standing height or less [14,15]. The locations of the major osteoporotic fracture occur in the hip, spine, distal radius, and proximal humerus. On the other hand, the minor osteoporotic fracture typically occurs in the pelvis, sacrum, ribs, distal femur, distal humerus and ankle [16]. It is important to note that the term osteoporotic fracture does not require the presence of osteoporotic bone by bone mineral density (BMD) and an osteoporotic fracture together. In fact, many osteoporotic fractures occurs in patients that have a T-score higher than −2.5 as measured by the DXA scan, and 10% even occur in individuals with normal BMD [17]. These individuals have microarchitectural deterioration leading to the risk of the osteoporotic fracture.

Numerous risk factors have been identified, in which common ones include age, low body mass index, history of previous fracture, smoking, age, steroid use, falls, vitamin D deficiency, smoking, and alcohol [18]. More recently, the concept of the imminent risk of fracture has also been highlighted. According to the International Osteoporosis Foundation (IOF), the recent fracture is a major risk factor of another re-fracture, and the increase in risk is not constant with time [19]. A previous study in Hong Kong have shown that up to 50% of secondary fractures occur in the imminent fracture period of the first 2 years after the initial major osteoporotic fracture [6]. In another study with 905 women and 337 men in Australia, 41% of re-fractures in women and 52% of re-fractures in men occurred in the first 2 years [20]. With current evidence worldwide showing the high rates of re-fractures in the imminent fracture period, the allocation of healthcare resources and attention has been emphasized in the FLS [21]. Another important risk factor is sarcopenia, which is a progressive, age-related skeletal muscle disorder that leads to accelerated loss of muscle mass and function [22]. In severe circumstances, individuals can lose up to 50% of muscle mass at the age of 80. It is well established that sarcopenia significantly increases the risk of falls, fracture, and mortality [23], and our previous study have shown the prevalence in Hong Kong was approximately 40% in elderlies 65 years old or above [24]. The disease has a 12.9 times higher risk of osteoporosis compared to those without sarcopenia [25], and our previous systematic review also showed that the prevalence of sarcopenia after an osteoporotic fracture reached 95% in males and 64% in females [26], coining the term ‘osteosarcopenia’ [25,27].

3. Post-acute management of the osteoporotic fracture

3.1. Recommendation 1: a recent osteoporotic fracture should be categorized as “very-high” re-fracture risk

Numerous clinical guidelines have been available to guide the treatment of osteoporosis recently. The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) clinical practice guidelines have recommended patients with a recent osteoporotic fracture (e.g., within the past 12 months) as “very-high” fracture risk stratification [28]. Other “very-high” fracture risk factors include fractures whilst on osteoporotic therapy, multiple fractures, very low T-score (e.g. <-3.0), high risk of falls or history of falls, and very high fracture probability by FRAX® score (e.g. major osteoporosis fracture >30%, hip fracture >4.5%) [28]. For the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and IOF guidelines, patients with a fracture probability above the upper assessment threshold, which is set at 1.2 times the intervention threshold, after FRAX assessment would be defined as “very-high” risk. Similar to the AACE/ACE guidelines, an example of stratifying the patient as “very-high” risk would be a recent vertebral fracture (e.g., within the past 24 months) [29]. Deconditioning and muscle wasting during hospital stay, especially amongst osteoporotic

fracture patients occurs commonly. More importantly, approximately 50% of all refractures occur in the first 2 years [21]. With the increasing osteoporotic fractures [6], identifying a recent osteoporotic fracture (within 12–24 months) as "very-high" risk is an important pre-requisite for the subsequent clinical management of the patient to prevent the imminent fracture (Fig. 1).

3.2. Recommendation 2: vertebral fracture assessment should be incorporated into the assessment of the patient in the Fracture Liaison Service

It has been recently recommended by the IOF Fracture Working group that the vertebral fracture assessment (VFA) should be incorporated with the FLS [30]. The VFA provides an image of the thoracic and lumbar spine, and is a tool available with DXA machines and has proven abilities to detect the vertebral fractures, which are often clinically silent. There is also good agreement between DXA-VFA and spinal radiographs with studies showing values reaching 97% and kappa score of 0.95 [31]. Additionally, the advantages of VFA are the lower cost and lower radiation exposure compared to conventional spinal radiographs. The tool has also been shown to be cost-effective during screening of osteoporosis [32].

Approximately 1.4 million vertebral fractures occur worldwide each year [33] and the condition is one of the most common and early complications of osteoporosis [34,35]. In fact, the lifetime vertebral fracture risk reaches 30–50% in patients over 50 years of age. The condition leads to debilitating pain, spinal deformity, and long term morbidity leading to poor clinical outcomes [36]. The subsequent risk of a future hip and vertebral fracture is also 2 and 4 times, respectively [37] with the 3-year and 5-year mortality rates reaching 46.1% and 69.1% [36]. It has been shown in previous studies that in Asians, there is also a higher vertebral-to-hip fracture ratio compared to Caucasians. In fact, in the Chinese the prevalence of a vertebral fracture is over 50% at age 80 years or older [38].

With the use of VFA, it allows a reliable baseline measurement to define old and new vertebral fracture events and the need to change osteoporotic management as well. Therefore, the clinical implication of assessing for vertebral fracture is important, especially the potential change of treatment for the patient [30].

3.3. Recommendation 3: osteoporosis in "very-high" re-fracture risk patients should be treated with a potent anti-osteoporotic drug

The goal for osteoporotic fracture management is for the patient to recover to pre-fracture functional level and reduce fracture risk [39]. The use of more potent drugs should be considered for very-high fracture risk patients with a recent osteoporotic fracture to treat osteoporosis [40]. It is currently recommended by the ESCEO/IOF to optimize calcium and vitamin D status, have regular exercise and fall prevention, and to initially use an anabolic agent followed by an anti-resorptive agent to reduce fracture risk [29]. It is highlighted that the greater improvement of BMD can be maintained with the anti-resorptive drug once the anabolic agent is stopped as most treatments last only 12–24 months [29], showing the importance of sequential therapy. For the AACE/ACE guidelines, the use of the anabolic agents (e.g. Romosozumab, Teriparatide), Denosumab or Zoledronic acid can be used as initial therapy, but anabolic agents are preferable [28]. Following this guideline, a previous FLS study in Hong Kong showed that the imminent fracture rate was reduced to only 0.4% at 2 years [41]. A previous meta-regression analysis of 38 placebo-controlled trials of 19 therapeutic agents also showed that larger improvements in BMD are associated with greater reductions of osteoporotic fractures [42]. Therefore, the stimulation of bone formation provides a foundation for continued risk reduction of re-fractures upon sequential treatment [43]. It is also a common scenario that a patient that had previous oral bisphosphonates suffers from an osteoporotic fracture, and the clinician needs to decide on the subsequent osteoporosis management. A previous study showed superior BMD when transitioning from alendronate to Romosozumab over Teriparatide [44]. Several commonly used anti-osteoporotic drugs are shown in Table 1.

DXA scan can be repeated every 1–2 years for assessment of treatment response and serial change. Significant decrease in BMD or recurrent fractures whilst on therapy may be considered a failure, warranting reassessment and consideration of treatment change [28,45]. Ideally, the follow-up of the patients should be in the same location with same DXA system. Based on the American Society of Bone and Mineral Research (ASBMR) and the United States National Osteoporosis Foundation (NOF), in those with very-high risk of fracture, more aggressive treatment to goal to a T-score > -2.0 is preferable [46]. However, achieving these goals may be difficult and therefore this further highlights the importance of an appropriate initial therapy, such as an anabolic agent, followed by a

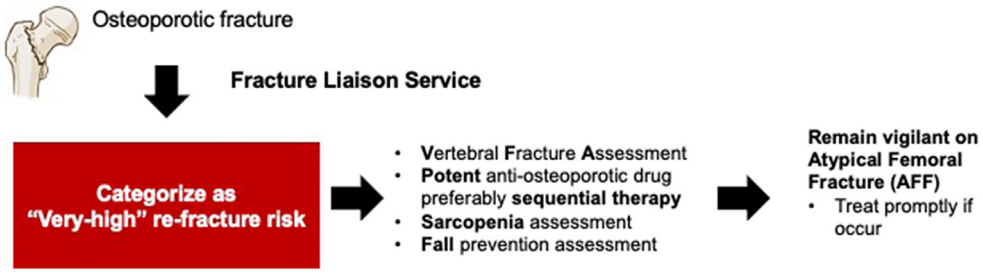

Fig. 1. Summary flowchart in the post-acute management of the osteoporotic fracture.

Table 1
Commonly used Anti-osteoporotic agents to treat Osteoporotic Fracture Patients.

Drug	Route	Frequency	Mechanism of Action	Note and Considerations
Alendronate	Oral	Weekly	Anti-resorptive by direct inhibition of osteoclast activity	Reassess fracture risk in 5 years [45]
Zoledronic Acid	I.V	Yearly	Anti-resorptive by direct inhibition of osteoclast activity	Reassess fracture risk in 3 years [45]
Denosumab	S.C	6-months	Anti-resorptive by inhibiting osteoclast activity by receptor activator of nuclear factor-kB ligand (RANKL) inhibition	Reassess fracture risk in 5–10 years [45]. If discontinue, should have transition to another osteoporosis agent [28]
Teriparatide	S.C	Daily	Stimulation of bone formation by direct effect on osteoblast	For 2 years [28,45]
Romosozumab	S.C	Monthly	Binds and inhibits sclerostin resulting in increased bone formation and reduced bone resorption	For 1 year [28,45]. Currently not approved for male osteoporosis.

potent antiresorptive agent for optimal response when resources are available.

3.4. Recommendation 4: fall prevention and sarcopenia should be addressed with a multi-disciplinary approach

It is estimated that one-third of elderlies aged 65 years or older fall each year [28] and these injuries are a leading cause of death. In fact, up to 95% of hip fractures are caused by falls. The role of orthogeriatric care is well-established in the management of fragility fracture patients [47]. Current clinical practice guidelines for fall prevention includes assessment of function, muscle strength and mobility, medication review, home and environment factors, feet and footwear, comorbid conditions e.g. vision, syncope, diabetes, cognitive, cerebrovascular and cardiovascular assessment for fall prevention [48–50]. Cognitive impairment is also highly prevalent in hip fracture patients [51]. The mainstay of treatment are exercise-based interventions, pain, chronic condition and medication management, visual corrections, education, calcium and vitamin D supplements via a multidisciplinary approach [50], which prevent falls and addresses other medical conditions.

Sarcopenia is also a major risk factor for falls [23] and recent guidelines have been published on the diagnosis of sarcopenia. A commonly used protocol is the Asian Working Group for Sarcopenia (AWGS) 2019 consensus, which diagnoses sarcopenia based on the presence of low appendicular skeletal muscle mass (DXA <7.0 kg/m^2 for men; <5.4 kg/m^2 for women; or bioelectrical impedance analysis (BIA) < 7.0 kg/m^2 for men; <5.7 kg/m^2 for women) and low muscle strength via handgrip strength (<28 kg for men; <18 kg for women) or low physical performance (6-m walk <1.0 m/s; short physical performance batter score ≤ 9; or 5-time chair stand test ≥ 12 s) [52]. On the other hand severe sarcopenia is diagnosed with the presence of all three low parameters [52]. A previous study of 2286 hip fracture patients in Hong Kong identified that those with good premorbid function and increased age was associated with deteriorating mobility [53]. In fact, in geriatric hip fracture patients, the prevalence of sarcopenia is high in Hong Kong, at 73.6% for males and 67.7% for females [54]. Therefore, the assessment of sarcopenia in the osteoporotic fracture patient is crucial in the recovery process. Unfortunately, there are no well-established drugs that have been approved for treating sarcopenia [22]. The mainstay of treatment for sarcopenia is therefore progressive resistance and balance exercises at least 2–3 times per week together with adequate nutrition [25,55]. Given the prevalent co-existence of 'osteosarcopenia', nutritional recommendations are protein 1.2–1.5 g/kg/day, vitamin D 1000 IU/day, calcium 1200 mg/day and creatine 3–5g/day for these patients [22,28].

3.5. Recommendation 5: remain vigilant on atypical femoral fractures and treat promptly if diagnosed

The occurrence of an atypical femur fracture is a rare event but can be challenging and difficult to manage, and therefore clinicians should remain vigilant [56,57]. Previous studies have shown the incidence to be low, with 1.8–113 cases per 100,000 person-years for bisphosphonate exposure of <2 years to 8–10 years, respectively [58]. Although Asians have a higher risk compared to Whites, the absolute risk remains low [59]. The ASBMR Task Force had revised the definition of atypical femoral fractures in 2013 [60]. To satisfy the criteria, the fracture is located along the femoral diaphysis just distal to the lesser trochanter to just proximal to the supracondylar flare. 4 out of 5 major features also need to be present, where minor features can be associated but are not required. Major features include the fracture, (i) associated with minimal or no trauma, (ii) originating at the lateral cortex and is mainly transverse and may be oblique at it progresses medially at the femur, (iii) complete fracture extends through both cortex and may have a medial spike or incomplete involving only the lateral cortex, (iv) noncomminuted or minimal comminution, and (v) localized periosteal or endosteal thickening at the lateral aspect of fracture site [60]. The 4 minor features are (i) generalized increase in cortical thickness of femur diaphysis, (ii) unilateral or bilateral prodromal symptoms, (iii) bilateral incomplete or complete fracture, and (iv) delayed fracture healing [60]. A recent study showed that the use of extended femur scans by DXA can aid in the detection of incomplete atypical femoral fractures and can be considered as a screening tool [61].

In the setting of an atypical femoral fracture, a thorough history and examination should be performed, and treatment performed promptly for pain relief and early mobilization [62]. Most orthopaedic surgeons would recommend the use of a long cephalo-medullary nail spanning the length of the femur for a complete atypical femoral fracture [63]. This is due to the fact that with prior bisphosphonate use, theoretically the osteoclast remodeling would be affected which affects intramembranous fracture healing that is required with extramedullary fixation [63]. However, there has been no large-scale randomized controlled trials to support the superiority of one fixation device to another. There is expert consensus that in the occurrence of an atypical femoral fracture, the ongoing anti-resorptive agent (e.g., bisphosphonate or denosumab) should be discontinued and teriparatide can be considered for patients with high risk of fragility fracture [62–64]. As of now, there is no clear evidence of the benefits of teriparatide in accelerating the healing of atypical femoral fractures [65]. It is also becoming increasingly accepted that for incomplete atypical femoral fractures a prophylactic surgery should be performed. This is due to the potential poor clinical outcomes that non-operative treatment can bring as well as the possibility of progression to a complete fracture [66], although the final decision depends on the patient [62]. Although the absolute risk of an atypical femoral fracture is low [59], it is a serious event and careful management is advised.

4. Future directions and research

Osteoporosis is a common disease that is influenced by many factors. Previous genome-wide association studies (GWAS) and meta-analyses have shown hundreds of loci associated with BMD, osteoporosis and osteoporotic fractures. Novel genes identified can become opportunities for new therapeutics. However, the majority of studies are of Caucasian descent, and therefore n further studies can be performed in Asians, which would be beneficial in the understanding of osteoporosis pathophysiology and drug developments [67,68]. Sarcopenia is a disease that often accompanies osteoporosis, and can have severe consequences from falls and fractures, but there is currently no well-established approved drug yet. The development and identification of biomarkers has also been researched [69]. Common markers include inflammatory markers and clinical parameters such as haemoglobin, serum albumin, and creatine [70]. The search for an accurate biomarker may be an effective tool in the early diagnosis and assessment of sarcopenia. In the future, clinical trials would be required to translate and validate these markers in drug trials. Fracture fixation in osteoporotic fractures can be challenging and the use of novel implants to enhance healing would be useful. Several studies have shown that the use of magnesium and hybrid titanium-magnesium implants can facilitate the healing of fractures [71,72]. Positive results during the translation of novel implants in clinical trials would benefit patients significantly.

5. Conclusion

The aging population is increasing worldwide, and it is expected that the treatment of osteoporotic fractures will be routine in daily clinical practices. FFN-HKSAR brings recommendations on the post-acute treatment of an osteoporotic fracture based on literature review. The

categorization of the recent osteoporotic fracture as "very-high" re-fracture risk, incorporation of VFA into the FLS, treating osteoporosis via sequential therapy, managing fall prevention and sarcopenia, and to remain vigilant on atypical femoral fractures and treat promptly if diagnosed, are essential to improving the care for our patients.

Ethical statement

No human or animals were involved in this article.

Author contribution

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Conception and design of study: R.M.Y. Wong, S.W. Law, S.K.H. Chow, W. Li, A.Y.C. Hsu, R.W.K. Ng, A.W.H. Ho, S.H. Choi, C.X. Fang, C.F. Chan, K.H. Leung, K.K. Chu, T.C.Y. Kwok, M. Yang, M. Tian, W.H. Cheung. Acquisition of data: R.M.Y. Wong, S.W. Law, S.K.H. Chow, W.H. Cheung. Analysis and/or interpretation of data: R.M.Y. Wong, S.W. Law, S.K.H. Chow, W.H. Cheung.

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Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Author names: Ronald Man Yeung Wong, Sheung Wai Law, Simon Kwoon Ho Chow, Wilson Li, Albert Yung Chak Hsu, Raymond Wai Kit Ng, Angela Wing Hang Ho, Shing Hing Choi, Christian Xinshuo Fang, Chun Fung Chan, Ka Hei Leung, Kwok Keung Chu, Timothy Chi Yui Kwok, Minghui Yang, Maoyi Tian, Wing Hoi Cheung.

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