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Fragility Fracture Prevention: Review from a Japanese Perspective

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Osteoporosis has been named "the silent disease" because there are no symptoms until a fragility fracture occurs. With the rapid rise in the elderly population, the number of patients with osteoporosis and fragility fractures has increased in most developed countries. Fragility fractures increase societal burdens in terms of mortality and quality of life, as well as economic costs. Fragility fractures of the hip have the most impact on the ambulatory status of the elderly and its incidence is reported to be lower among Asians or Africans than Caucasians. Increases in the age-specific and gender-specific incidence of hip fracture with time have been reported in Asian countries, including Japan; however, studies in North America, Europe and Oceania have reported decreases in the incidence. A new fragility fracture increases fracture risk, resulting in possible recurrence or other new fractures. The most important strategy for preventing such fractures is a systematic approach to educating and following patients in the immediate postoperative period after the initial fragility fracture.

Key words: hip fracture; osteoporosis; secondary fracture prevention

Japan currently has the largest aged population, and it is expected to increase until 2050 while the total population decreases (Fig. 1). Even among the developing countries, graying of the population will become a serious concern in the future. With the rapid increase in the elderly population, the number of patients with osteoporosis and fragility fractures has increased in most developed countries. Fragility fractures increase societal burdens with respect to mortality, quality of life (QOL), and economic costs. The combined annual cost of all osteoporotic fractures has been estimated to be $20 billion in the Uninted States and €30 billion in the European Union (Cummings and Melton, 2002; Cooper et al., 2011). Fractures account for about 1–2% of the total health care costs, of which inpatient care costs dominate. Although fractures affect older people to a larger extent, indirect costs, such as the loss in productivity due to sick leave, also play an important role that has been estimated at approximately 10% of the total costs (Zethraeus et al., 2007). In Japan, the annual cost for the treatment of hip fractures is estimated to be approximately ¥130 billion, excluding the cost of patient care after discharge (Committee for Osteoporosis Treatment of The Japanese Orthopaedic Association, 2004).

A new fragility fracture does not only reduce daily activity but can also increase fracture risk, resulting in possible recurrence or other new fractures: "fracture begets fracture." However, it is reported that the vast majority of patients who experience a hip fracture do not receive anti-osteoporotic therapy after the fracture (Cadarette et al., 2008; Roerholt et al., 2009). In Japan, there is a paucity of data available on the proportion of patients with a

Abbreviations: AFF, atypical femoral fractures; FLS, Fracture Liaison Service; ONJ, osteonecrosis of the jaw; POSHIP, Prevention of Second Hip Fracture study; QOL, quality of life new fragility fracture who are started on an intervention (Hagino et al., 2012). Novel strategies are required to disseminate and implement best practices at the point of care to reduce the risk of recurrent fractures. In this review, the current status of osteoporosis and fragility fractures and strategies to reduce their burden are discussed.

What are osteoporosis and fragility fractures?

Osteoporosis

Osteoporosis has been named "the silent disease" since there are no symptoms until a fracture occurs after minimal trauma. Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects a combination of bone density and bone quality (NIH Consensus Development Panel, 2001). A fragility fracture occurs when a failure-inducing force such as trauma is applied to osteoporotic bone (NIH Consensus Development Panel, 2001). Bone density is expressed as grams of mineral per area or volume, which is measured by bone densitometry. Bone quality refers to its architecture (macro and micro), turnover, damage accumulation (e.g., microfractures) and mineralization. Bone quality is thought to be the part of bone strength that is not explained by bone density, which is estimated to be 30% of total bone strength (NIH Consensus Development Panel, 2001).

In 2005, there were an estimated 13 million patients with osteoporosis in Japan. This number was calculated from the data on bone density in healthy Japanese subjects and the diagnostic criteria for primary osteoporosis.

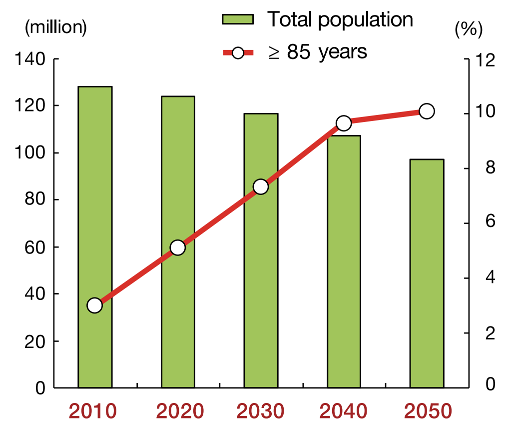

Fig. 1. Population projections for Japan. The total population of Japan is projected to decrease until 2050 but a substantial increase in the proportion aged 85 years and over is expected. (Data source: National Institute of Population and Social Security Research; http://www.ipss.go.jp/syoushika/tohkei/newest04/sh2401smm.html)

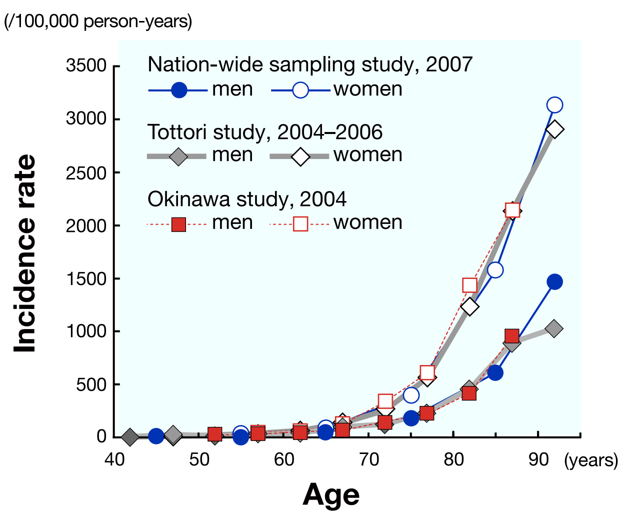

Fig. 2. Age-specific and gender-specific incidences of hip fractures in Japan. The age-specific and gender-specific incidence of hip fractures increases exponentially with age after 70 years in both men and women. Adapted from: Hagino et al., 2009a; Orimo et al., 2009; Arakaki et al., 2011.

Fragility fractures

Fragility fractures are thought to be osteoporosis-related geriatric fractures, as opposed to traumatic fractures. However, there is no conclusive definition for fragility fracture. Based on the recent papers, fragility fractures are those due to mild injuries, such as a fall from standing height, and not occurring as a result of significant trauma, such as a motor vehicle collision (ASBMR Task Force on Osteoporotic Fracture Secondary Prevention, in press).

Incidence of fragility fractures

Among the Japanese population, the age-specific and gender-specific incidence of hip fractures increased exponentially after 70 years of age (Fig. 2)

(Hagino et al., 2009a; Orimo et al., 2009; Arakaki et al., 2011). Based on the incidence in Tottori Prefecture, Japan, the annual number of patients with new hip fractures is estimated to be approximately 190,000 in 2012 and 320,000 in 2040 (Fig. 3).

There have been many epidemiological surveys of hip fractures worldwide. One of the conclusions derived from these studies is that the incidence of hip fractures is lower among Asian or African populations than Caucasian populations. Table 1 compares the incidence of hip fractures among different populations based on studies from Japan , China (Yan et al., 1999), Korea (Lim et al., 2008), Turkey (Tuzun et al., 2011), Argentina (Morosano et al., 2005), Finland (Lönnroos et al., 2006) and Norway (Bjørgul and Reikerås, 2007). Incidences for both genders in Asian populations, including Japanese, are substantially lower than those in Caucasian populations living in Northern Europe or South America. Since Asians are known to have similar or lower bone mass than Caucasians, differences in bone mass do not explain the differences in the incidence of hip fractures. Elucidating the causes for ethnic differences in the incidence of hip fractures may suggest preventive measures that could protect against fragility fractures. Therefore, several approaches have been tried to explain why hip fracture incidence is lower in Asian populations. One hypothesis is the different risk of falls between Asians and Caucasians (Aoyagi et al., 1998), presumably based on differences in lifestyles. It was reported that aspects of the Japanese lifestyle, such as drinking Japanese tea and the use of a futon, are effective for preventing fractures (Suzuki et al., 1997; Hagino et al., 2004). However, there have been no conclusive explanations for the differences observed.

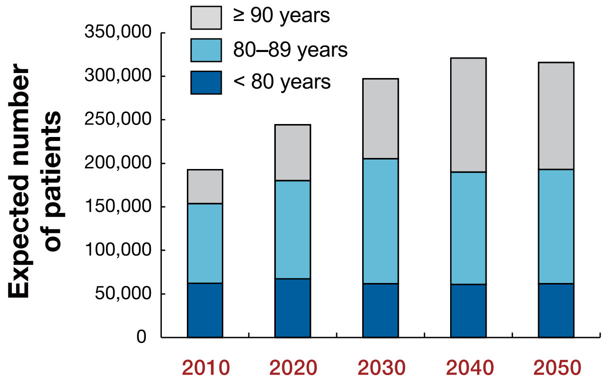

Fig. 3. Expected number of patients with hip fractures in Japan. Approximately 190,000 hip fractures are expected to occur in 2012, and the estimate increases up to more than 300,000 for 2040 based on the incidence in Tottori Prefecture, Japan. (Data source: National Institute of Population and Social Security Research; http://www.ipss.go.jp/syoushika/tohkei/newest04/sh2401smm.html)

Recent data from Asia, including Japan, showed an increase in the age-specific and gender-specific incidence of hip fractures over time (Hagino et al., 2009a; Arakaki et al., 2011; Xia et al., 2011). In Japan, a steady increase has been observed for 20 years in Tottori (Hagino et al., 2009a) and Okinawa (Arakaki et al., 2011) Prefectures (Fig. 4). In Beijing, China, the incidence of hip fractures rose very rapidly from 2002 to 2006, about 10% per year (Xia et al., 2011). It is speculated that the increased risk of hip fracture is due to the changes in lifestyle with urbanization. On the other hand, studies in North America, Europe and Oceania have generally reported increases in hip fracture incidence through the second half of the 20th century, but those continuing to follow trends over the last 2 decades have found that rates have stabilized with age-adjusted decreases being observed in certain centers (Cooper et al.,

Table 1. Comparison of the incidence of hip fractures among different populations

	Geographic area	Survey year	Men	Women
Japan	Tottori Prefecture	2004–2006	94.9	326.6
Japan	Okinawa Prefecture	2004	89.8	329.0
Japan	Nationwide	2007	94.2	324.5
China	Shenyang	1994	72.2	65.2
Korea	Nationwide	2001–2004	164.5	290.4
Turkey	12 regions	2009	89.8	432.3
Argentina	Rosario	2001–2002	116.7	479.4
Finland	Central Finland	2002–2003	195.6	399.6
Norway	Southeastern Norway	1998–2003	264.4	615.5

Data are incidences (per 100,000 person-years) adjusted to the population structure for all of Japan in 2010 (≥ 35 years).

2011). However, no conclusive cause has been elucidated for why the incidence in North America, Europe and Oceania are decreasing and why those in Asia are increasing.

In contrast to the incidence of the limb fractures, epidemiological surveys found a higher incidence of incident vertebral fractures evaluated morphometrically among the Japanese (Fujiwara et al., 2003) than in European counterparts (Van der Klift et al., 2002; European Prospective Osteoporosis Study Group, 2002). The prevalence of vertebral fractures is also higher among the Japanese population than the Caucasian population in the United States (Ross et al., 1995). It is suspected that small bone size or lifestyle differences, including low calcium intake, are responsible for this difference; however, there are no studies to explain this difference.

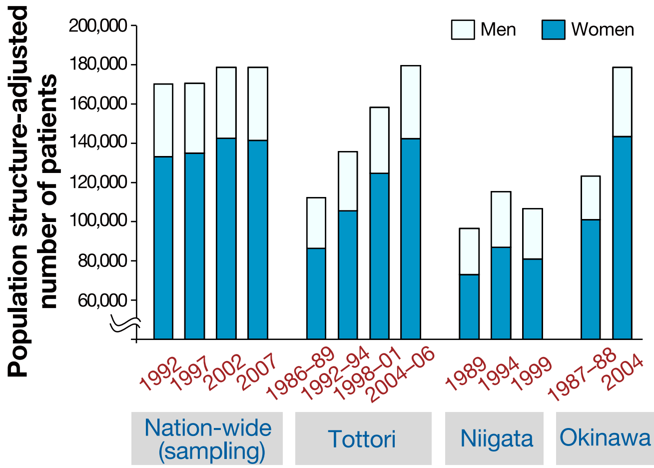

Fig. 4. Recent changes in the incidence of hip fractures in Japan. The number of patients with hip fractures calculated from previous surveys from Tottori (Hagino et al., 2009a), Niigata (Morita et al., 2002) and Okinawa (Arakaki et al., 2011) Prefectures and throughout the country (Orimo et al., 2009) are shown. Data are adjusted to the population structure (2010 Japan).

Risk of a second fracture

Investigators from Rochester, Minnesota described the epidemiology of hip fractures in their locality during the period between 1965 and 1974. They found that 68% of women and 59% of men had experienced at least 1 other fracture prior to breaking their hip (Gallagher et al., 1980), suggesting that almost one-half of today's hip fracture patients have suffered prior fractures (ASBMR Task Force on Osteoporotic Fracture Secondary Prevention, in press). Very little data is available on the risk of sustaining a second hip fracture after an initial hip fracture in the Asian population, although there is a large difference in the incidence of fragility fractures between Asians and Caucasians. Recently we performed a registry-based study consisting of 2,328 patients with first hip fracture treated in 25 hospitals in Japan (Prevention of Second Hip Fracture study; POSHIP) (Hagino et al., 2012). The 1-year incidence rate as determined in the POSHIP study was 3.40% and rate ratio of a second hip fracture compared to the general population in Japan was as high as 4.0.

The likelihood of sustaining a second hip fracture tended to rise during the first 6 or 8 months after the first hip fracture and then plateau (Yamanashi et al., 2005; Hagino et al., 2012). A recent nationwide study in Denmark involving a large number of hip fracture patients demonstrated that the risk of a second hip fracture was 12-fold higher at 1 month and more than doubled at 1 year (Ryg et al., 2009). These findings indicate that the period immediately following the first fracture is a window of opportunity for implementing a fracture prevention strategy.

Burden of fragility fractures

Changes in ambulatory ability

Hip fracture is the fragility facture with the highest impact on the ambulatory status of the elderly. A fixed-point observation project involving core orthopedic hospitals throughout Japan examined a larger number of variables including the 1-year prognosis (Sakamoto et al., 2006). In this study, a total of 10,992 hip fractures were enrolled from 1999 to 2001 and a 24.1% decrease in the number of patients who were independently ambulatory was observed at 1 year after fracture. In a recent large prospective study, changes in ambulatory ability after hip fracture were evaluated (Fukui et al., 2012).

In this cohort, patients who sustained hip fractures suffered obvious deterioration in ambulatory ability and the number of ambulatory subjects in the community setting was nearly halved 6 months after surgery, whereas that of patients who cannot walk unaided was almost doubled. In a retrospective 10-year observational study, the proportion of patients who were able to walk outdoors alone, with or without an assistive device, was 68% before a hip fracture and 56% at 1 year afterwards, and remained stable for 10 years (Tsuboi et al., 2007).

Mortality

In a prospective study in Japan, the 1-year mortality rate for the entire hip fracture patient population was 10.1% (Sakamoto et al., 2006). In a retrospective study, the survival rate decreases rapidly for 2 years after fracture before stabilizing (Tsuboi et al., 2007). However, the survival rate was still well below that of the general population for up to 10 years and the increased mortality risk was approximately double that of the general population.

A comparative study of hip fractures with a median follow-up duration of 276 days after surgery demonstrated that the survival rate was 89.5% in Japan and 77.2% in the United States (Kondo et al., 2010). Japanese patients had a significantly longer length of hospital stay after surgery but higher survival rates than American patients, and longer length of hospital stay after surgery was associated with a lower risk of mortality after discharge after adjusting for patient characteristics and country.

Quality of life

In a prospective observational study, health-related QOL was evaluated by Euroqol (EQ5D) in elderly women following incident hip, vertebral and wrist fractures (Hagino et al., 2009b). The reduction in EQ5D values was greatest in the hip fracture group during the observational period. EQ5D values at 6 months after fracture in the wrist fracture group showed recovery; however, at 6 months the hip and vertebral fracture groups had EQ5D scores that were significantly lower than pre-fracture scores. At 1 year after fracture, EQ5D values were not significantly different from pre-fracture values for the vertebral and wrist fracture groups; however, they remained significantly lower for the hip fracture group. Another recent study demonstrated that men and women with hip and clinical vertebral fractures and women with rib fractures had adverse changes in their QOL but forearm and pelvic fractures did not appear to substantially influence QOL scores (Papaioannou et al., 2009).

Prevention of fragility fractures

Who are the targets?

It is well established that a history of a prior fracture at any site is an important risk factor for future fractures (Klotzbuecher et al., 2000). Patients with a history of a prior fracture, therefore, should receive further evaluation and treatment for osteoporosis to prevent subsequent fractures. However, it is reported that the vast majority of patients who experience a hip fracture as well as other fragility fractures do not receive anti-osteoporotic therapy after fracture (Cadarette et al., 2008; Roerholt et al., 2009). Among patients who begin anti-resorptive osteoporosis treatment after fracture, adherence to treatment decreases over time and remains suboptimal (Roerholt et al., 2009; Rabenda et al., 2008). It was recently reported that the situation has not improved; in 2007 to 2008, fewer than 20% of untreated individuals with a low-trauma fracture received intervention despite increased attention to gaps in post-fracture osteoporosis management in the last 10 years (Leslie et al., 2012). The POSHIP study found a high risk of a second hip fracture during the 1-year period after the initial fracture; however, anti-osteoporosis pharmacotherapy was given in only 18.7% and 53.3% received no treatment (Hagino et al., 2012). Thus, inadequate treatment after the first hip fracture is now evident as well as other fragility fractures.

Fracture liaison service

A systematic approach is important for educating and following patients in the immediate postoperative period after a hip fracture as well as for other fragility fractures in order to provide adequate intervention for patients at high risk for subsequent fracture (Gardner et al., 2005; Rozental et al., 2008). In the United Kingdom, Canada and the United States, a consensus on systematic and multidisciplinary approaches to secondary fragility fracture prevention, called the Fracture Liaison Service (FLS), has been developed over the last decade (Mitchell, 2011). The FLS is operated by mainly nurse specialists supported by a lead clinician in osteoporosis. They identify patients with new fragility fractures who are either admitted to the orthopedic inpatient ward or managed as outpatients through the fracture clinic and then arrange for appropriate patients to attend the FLS clinic where bone density is measured. After bone mass measurement, the nurse specialist assesses future fracture risk by taking the patient's history. If necessary, the nurse informs the patient of the risk for osteoporosis, and then provides a letter to give to the primary physician. Such systematic approaches have been started globally in campaigns such as "Capture the Fracture" (International Osteoporosis Foundation).

Fig. 5. Case of an atypical femoral fracture. An 81-year-old women suffered a right femoral shaft fracture upon falling on the road. She has been on alendronate for 6 years. Complete fractures extend through both cortices and a medial spike of the right femur was observed on a radiograph (left panel). An increase in the cortical thickness of the diaphysis of the lateral cortex of the left femur is noted (right panel; arrow).

Anti-osteoporosis drugs

The recent development of anti-osteoporosis drugs, especially anti-resorptive agents, has revolutionized the field of fracture prevention. It is now known that oral bisphosphonate treatment for 3 years (Osaki et al., 2012) or an annual infusion of zoledronic acid for 1.9 years (Black et al., 2007) after a hip fracture is associated with a reduction in the rate of new clinical fractures including hip fracture, as well as an improvement in survival (Lyles et al., 2007). Since bisphosphonates can reduce the incidence of fragility fractures, including hip fractures, in patients with osteoporosis, they have become first-line drugs for the treatment of osteoporosis. Though bisphosphonates have a relatively good safety record and are well tolerated by most patients, serious adverse events have been associated with their use. Over the past few years, there has been growing concern about the potential relationship between long-term use of bisphosphonates and osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) (Fig. 5). Regarding AFF, recent nationwide population-based analyses were reassuring for patients receiving bisphosphonates (Schilcher et al., 2011). Recently, a survey of AFF was conducted in Japan (Hagino, 2011). The 3,116 hospitals surveyed reported 398 cases of AFF, of which 29.9% were associated with previous bisphosphonate therapy. Although there seems to be a higher prevalence of current bisphosphonate use among patients with AFF or ONJ, the absolute risk of these complications is very small and the beneficial effects of bisphosphonates far outweigh these risks.

In addition to anti-resorptive agents, an anabolic agent, teriparatide, is available and widely used globally. Many clinical trials have found that teriparatide can reduce the incidence of new fractures (Neer et al., 2001). Recently, weekly teriparatide became available in Japan for the treatment of osteoporosis. Teriparatide has a potential for desired effects in secondary fracture prevention (Nakamura et al., 2012).

Conclusion: A rapid increase in the number of patients with fragility fractures is projected in many Asian counties, including Japan. The most important strategy for preventing such fractures is a multidisciplinary approach for educating and following patients in the immediate postoperative period after the initial fragility fracture.

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