

Review article

Osteoporosis in East Asia: Current issues in assessment and management

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Abstract

The greatest burden of hip fractures around the world is expected to occur in East Asia, especially China. However, there is a relative paucity of information on the epidemiology and burden of fractures in East Asia. Osteoporosis is greatly under-diagnosed and under-treated, even among the highest-risk subjects who have already suffered fractures. The accessibility to bone densitometry, the awareness of the disease by professionals and the public, and the use and reimbursement of drugs are some of the areas which need improvement especially. Cost-effective analysis on screening strategy and intervention thresholds based on local epidemiology data and economic status are available only in Japan. In addition, clinical risk factor models for the assessment of fracture probability may be ethnic specific. Further research is needed to develop a cost-effective risk assessment strategy to identify high-risk individuals for screening and treatment based on local data. Moreover, inadequate calcium and vitamin D intake is still an issue faced by this region.

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1. Introduction

As classified by the United Nations, East Asia contains Hong Kong, Japan, Macau, Mongolia, North Korea, the People's Republic of China, South Korea and Taiwan. In this region, osteoporosis is increasingly being recognised as a growing problem [1,2] because of the rapidly increasing size of the elderly population. In particular, China has the largest aged population in the world, as the population aged ≥ 60 years will reach 400 million (approximately 30% of the total population) by 2050 [3]. In Japan, the percentage of the population aged ≥ 65 years rose from 10.3% in 1985 to 20.1% in 2005 [4]; this percentage is expected to double by 2050 [4]. The corresponding percentage in Taiwan increased from 4.3%

in 1980 to 10.74% in 2010 [5]. As in the West, there is an exponential increase in the incidence of hip fractures after the age of 65 in Asian populations [6]. For example, the hip fracture incidence has more than doubled for each successive 5-year age group in Hong Kong [7].

In this review, we highlighted the differences and similarities in the assessment and treatment between the East and West. We focused mainly on hip and vertebral fractures because they account for the majority of fracture-related mortality and morbidity as well as health care expenditure. We identified data for this review by a systematic search of Medline with the MeSH terms “Osteoporosis” and “East Asia” for peer-reviewed clinical studies and other studies of clinical significance. This search was not restricted to reports written in English; articles written in a native language but that included an English abstract were included as well. The review included articles published between June 1996 and November 2015. Bibliographies of identified articles, guidelines and conference proceedings of professional societies

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were reviewed for additional references. Review articles and book chapters were cited to provide readers with additional details and references. In this discussion, we gave more weight to randomised controlled trials and meta-analyses than evidence of lower quality. Data presented here are from China, Hong Kong, Japan, South Korea and Taiwan. When selecting a study or studies over others to represent the epidemiology of a region or country, we chose national rather than regional data, if available. We used the most recent studies and also studies which examine greater number of subjects.

2. Epidemiology

While the burden of hip fractures is increasing markedly throughout the world, the greatest impact is expected to be felt in Asia; specifically, the percentage of hip fractures in Asia is expected to rise from 26% in 1990 to 37% in 2025 [8]. By the year 2050, half of all hip fractures in the world are projected to occur in Asia, particularly in China [9].

In a recent systematic review of hip fractures incidence worldwide, the age-standardised annual incidence of hip fractures was reported to be higher in Hong Kong, Japan, South Korea, and Taiwan than in the USA and some European countries [10]. This is in contrast to a study 2 decades ago which showed the hip fractures incidence to be higher in USA compared to Hong Kong [11]. The recent decline and increase in hip fracture incidence in USA and East Asia, respectively, may partly account for this [2]. For women, Taiwan was in the high-incidence category (incidence >300/100,000), ranking number 9 among all 61 countries/regions. Hong Kong, Japan and South Korea were in the medium-incidence category (200–300/100,000), ranking 23, 32 and 34, respectively. China was in the low-incidence category (<200/100,000). For men, Japan, Korea and Taiwan were among the high-incidence countries (>150/100,000), while China and Hong Kong were in the moderate-incidence category (100–150/100,000). The data used to compute hip fracture incidence in China, Hong Kong, Japan, South Korea and Taiwan in this study were from publications in the years 2011, 2009, 2006, 2008 and 2009, respectively. Updated incidence rates of hip fractures were reported from Japan and South Korea in 2009 [12] and 2011 [13], respectively. These specific hip fractures incidence rates are summarised in Table 1 [7,12–15].

Following the trend in to the West [2], the age-specific incidence of hip fractures seems to have been stabilising in the past decade, especially in the age group <80 years in Hong Kong [16], Japan [12] and South Korea [13]. The increase in BMD, healthier lifestyles (more exercise and higher vitamin D levels) and longer reproductive periods may be responsible for this [17]. Nonetheless, the overall number of hip fractures is still increasing in China [15], Japan [12,18] and South Korea [13]. It is attributable largely to the ageing populations, but may partly due also to improved reporting [19]. In Japan, the estimated number of hip fractures for both sexes per year for all age groups increased 2.78-fold from 53,200 in 1987 to 148,100 in 2007 [12]. In South Korea, from 2005 to 2008, the total number of hip fractures for subjects aged ≥ 50 years

Table 1
Annual age specific hip fracture incidence in East Asia.

Place	Sampling method	Years of study	Incidence per 10,000	Ref	
China	Beijing hospital discharge record	2002–2006	12.9	$\geq 50M$	[15]
			22.9	$\geq 50F$	
HK	Region-wide public hospitals database	2000–2004	21.22	70–74M	[7]
			36.44	70–74F	
			45	75–79M	
			83.08	75–79F	
			87.14	80–84M	
			150.38	80–84F	
Japan	Nation-wide estimate	2007	165.44	$\geq 85M$	[12]
			283.76	$\geq 85F$	
			18.12	70–79M	
			39.71	70–79F	
			61.03	80–89M	
			157.14	80–89F	
South Korea	Nation-wide	2005–2008	146.62	90 + M	[13]
			313.58	90 + F	
			2.38	50–59M	
			1.81	50–59F	
Taiwan	Nation-wide	2002	60.58	80–100M	[14]
			105.25	80–100F	
			36.23	70–74M	
			51.13	70–74F	
			59.2	75–79M	
			99.1	75–79F	
			93.83	80–84M	
			178.37	80–84F	
			153.03	$\geq 85M$	
			274.55	$\geq 85F$	

nation-wide increased by 21% (from 16,866 in 2005 to 20,432 in 2008) [13].

Comparison of the prevalence of vertebral fractures between populations is difficult due to the lack of a gold standard for the definition of vertebral fracture and also because of the different age groups included in these studies (Table 2). Similar to the situation in the West [20], about three-fourths of vertebral fractures in East Asia [21–24] were not diagnosed clinically. The updated age-specific prevalence of vertebral fractures among female populations in various East Asia countries and White Caucasian women using different methods is summarised in Table 2 [25–34]. The age-specific data on men is sparser [28,35,36]. The prevalence of hip fractures in men was considered to be higher in Japan [37], followed by Hong Kong and Taiwan [28]. Prior vertebral fracture was an important risk factor for future vertebral fractures [28,37,38] and hip fractures [38,39].

3. Impact

There is significant underestimation of the burden of osteoporosis in East Asia. While hip fractures is a useful surrogate to quantify the socioeconomic burden of osteoporosis, the incidence of hip fractures in East Asia may not be as well documented as in some Western industrialised countries where well-maintained large population databases are available. Large population databases are available in South Korea (Korean National Health Insurance Program) and Taiwan

Table 2
Age specific vertebral deformity prevalence among East Asia women using different assessment methods (%).

Place	Sampling method	Method	40–49	50–59	60–69	70–79	> / = 80	Ref
China	Beijing	Rochester		4.9	16.2	19	36.6	[28]
	Random sample	SOF		3.9	10.5	15	31.2	
Hong Kong	Convenience Sample	SOF			19	44	68	[25]
	Convenience Sample	Genant's SQ system			10.8 (65–69y)	17.4	29.5	[30]
Japan	Random Sample	McCloskey-Kanis Criteria		2.7	13.8	17.5		[29]
Korea	large scale	Rochester	4.4	8.7	20.9	26.3		[26]
	Community based Cohort							
Taiwan	nation-wide	Rochester	1.5(40–44), 2.7(45–49)	4.5(50–54), 4.8(55–59)	6.7(60–64), 13.9(65–69)	20.7(70–74), 24.3(75–79)	29.7	[27]
USA.SOF		Rochester				24.7	36.5	[28,31]
		SOF				22	33.9	[28,31]

Adapted from Tables 2 and 3 in Ref. [25] and Table 4 of Ref. [30].

SOF, Study of Osteoporosis Fractures (Ref. [31]); SOF method, method used in this study, adopted from DM et al. (Ref. [32]); SQ, semi-quantitative.

Rochester, method published by Eastell and colleagues (Ref. [33]).

McCloskey-Kanis criteria (Ref. [34]).

(National Health Insurance Research Database, NHIRD). These databases have high coverage for >90% of the population. In Korea, the coverage is 100%. In Japan, a nationwide survey has been implemented every 5 years since 1987 to estimate the hip fractures incidence [12]. Recent data on hip fracture incidence in China [15] and Hong Kong [7] are from regional statistics and convenience samples, respectively.

Substantial under-reporting is anticipated in some East Asia countries. A significant amount of patients in rural areas with hip fractures may not be known to medical system because of long distances to the hospital. The facilities for surgical management are also limited in local health care facilities. Moreover, these patients may not have the money to pay for prosthetics. Therefore, many are managed at home or die without access to the medical system. Means to improve accuracy in documentation will enable a more precise estimation of the impact and may help facilitate better health-care planning.

The mortality after hip fracture was generally lower in East Asia [40–43] compared to the USA [44] and UK [45]. However, the increased mortality was still substantial [46]. The 1-year mortality rate following a hip fracture in Japan, South Korea and Taiwan were reported to be 11.5% [40], 16.55% [41] and 14% [42], respectively. In Hong Kong, the age-adjusted 360-day mortality rate was 22.4% and 16.4% for men and women, respectively, in 2009 [43]. The mortality after a hip fracture was higher in Korea for males, those in the lower socioeconomic status, those living in places other than the capital city, those not taking anti-osteoporosis drugs after the fracture, and those who received operations from more specialised hospitals [41], which might reflect more severe fractures. In Taiwan, a higher mortality rate was noted in more elderly subjects (HR 7.34 for aged >84 vs. <70 years), individuals with certain medical conditions (HR 2.4–6.12) and cases of delayed operations (HR 2.86 for delay >48 h vs. ≤24 h) [42]. Functional level deteriorated in 60% of hip

fracture patients [47]. An improved model of care may lower the mortality rate and improve the clinical outcomes [48].

Vertebral fractures also increase mortality [49] and lead to decline in functional state [50]. Mortality is correlated with the number of vertebral fractures [49]. Even morphometric vertebral fractures [47] or osteoporosis in general [51] were associated with a higher mortality rate in the Japanese population.

Osteoporosis leads to deterioration in quality of life (QOL) and quality-adjusted-life-year (QALY) loss. Quantitative analysis of the QOL among osteoporosis subjects has been carried out in China [52], Hong Kong [53], Japan [54–56], South Korea [57] and Taiwan [58]. These studies showed that, among East Asia populations, osteoporosis was associated with a decrease in QOL, which improved with treatment. Data on QALY loss due to fractures was only available for Japan [59]. The cost-effective of drug intervention is usually expressed as fracture risk reduction or QALY gained. Treatment for osteoporosis was considered more cost-effective if offered to subjects at higher risk of fracture. This threshold for treatment also depends on the willingness to pay of different societies. Similar to many western countries [60], with a threshold of US dollars 30,000 per QALY gained, intervention for osteoporosis was considered to be cost-effective in Japan [59].

Data on health-care costs of fractures are sparser for East Asia societies compared to the West. Even within East Asia, the socioeconomic situation is diverse, and willingness to pay for prevention and treatment for osteoporotic fractures varies within the region. In western China, the annual total cost of hip fracture was RMB 27,283 per person-year while that for vertebral fracture was RMB 21,474 in 2010. The annual rate of increase in cost is 6%, so the cost is expected to be five times these figures by 2050 [61]. In Hong Kong, the acute hospital care cost of hip fractures in 1996 amounted to 1% of the total annual hospital budget, or US \$17 million, for a population of 6 million [62]. Medical expenditures related to hip fractures

were US \$3.1 billion in Japan in 1997 [63]. The expenditure for all fractures in Japan was USD \$4863 million in 2002. Reimbursement records in Korea showed that the number of patients receiving medical treatment related to osteoporosis increased from 1,034,399 to 1,392,189 for women and from 120,496 to 171,902 for men between 2004 and 2008 [64].

4. Unmet needs

4.1. Under-diagnosis and under-treatment

Osteoporosis is greatly under-diagnosed and under-treated in this region, even among the highest-risk patients who have already suffered fractures. A recent study [65] was conducted using patient surveys and medical charts of postmenopausal women discharged after hip fractures from treatment centres in China, Hong Kong, Singapore, South Korea, Malaysia, Taiwan, and Thailand. Bone mineral density (BMD) measurement was only performed in 28.2% of patients prior to hip fractures; 51.5% were informed that they had osteoporosis after hip fractures, and 33.0% received medications for osteoporosis in the 6 months after discharge. The International Osteoporosis Foundation (IOF) Asian Pacific Regional Audit also highlighted that osteoporosis was greatly neglected [1]. The number of dual energy X-ray absorptiometry (DXA) machines is inadequate across the region and in most cases not reimbursed. In Hong Kong, history of prior spine or hip fractures is required for reimbursement of anti-osteoporosis drugs in public sector. Fracture liaison services are not common across the region. The barriers to screening, assessment and treatment of high-risk subjects are discussed below.

4.2. Paucity of data

The exact burden of hip fractures is not well delineated in some East Asia countries/regions. There is scant data on post-acute care expenses and productivity loss after hip fracture. Corresponding data for vertebral and other fractures are even sparser. The lack of solid epidemiological and economic data is a major hindrance in convincing health authorities about the importance of osteoporosis under resources constraints.

4.3. Suboptimal awareness/knowledge and financial constraints

The awareness of osteoporosis among the public and professionals is generally suboptimal. College students in China knew less about osteoporosis and had a greater barrier to reduce their risk via lifestyle changes, compared to college students in USA [66]. In Hong Kong, 91% of doctors considered osteoporosis to be under-diagnosed because of its asymptomatic nature, the inaccessibility to care, and the high cost of diagnostics [67]. 33% of doctors were not aware of the guidelines for BMD testing [67]. Only <30% and 55% of doctors would perform BMD and prescribe medication, respectively, when faced with patients with fractures [67]. Another survey in Hong Kong reviewed that majority of subjects were willing to pay for

anti-osteoporotic treatment if the price could be lowered [68]. In Japan, only 61% of doctors in various specialities know about the diagnostic criteria for osteoporosis [69]. Among Korean women with osteoporosis, only 37.5% were aware of their diagnosis and 23.5% received treatment. Easily identifiable risk factors (e.g., history of fracture, falls, height loss, family history) were not associated with increased awareness and treatment [70]. In most East Asia countries/regions, government policies for the prevention and treatment of osteoporosis are lacking, although non-government organisations are active in this area. In China, the osteoporosis prevention and awareness program is restricted to urban areas. DXA machines are only available in the more economically developed areas of the country, but still many people cannot afford to pay for the test. The use of pharmaceutical therapies for osteoporosis varies markedly between urban and rural areas and from the north to south of the country.

4.4. Lack of cost-effectiveness analysis

There is a general lack of studies on cost-effective screening and intervention thresholds. Related to this, support towards reimbursement for screening and treatment is not optimal. Screening of osteoporosis is supported by policy only in Japan [12]; screening was considered to be not suitable in Hong Kong [71]. The criteria for screening and threshold for treatment need to be developed for individual populations based on their own epidemiology data and economic situation. The World Health Organization (WHO) recommended the use of QALYs gained and willingness-to-pay to determine the intervention thresholds for osteoporosis on a country-to-country basis [72]. Both QALYs gain and willingness-to-pay depend on the gross domestic product (GDP) of individual countries/regions and vary widely. The GDP per capita (USD, 2012) for China, Hong Kong, Japan, South Korea and Taiwan is 6076, 36,667, 46,736, 23,113 and 20,328, respectively, compared to 49,922 for the US [73]. A treatment that gains one QALY at a cost equivalent to under two times the per capita GDP is normally considered to be a cost-effective treatment [74]. The cost-effectiveness of screening followed by treatment based on local data is available only for Japan [75]. According to this study, it was cost effective to provide BMD measurement to women aged 70 years and over who had a vertebral fracture in the preceding 2 years and treat those who were osteoporotic, assuming a cost per QALY threshold of 100,000 US dollars.

5. Risk factors for fractures

5.1. Bone mineral density

Low BMD is an important determinant for fractures and treatment guidelines have traditionally been based on BMD [76]. The use of population-specific databases can adjust in part for significant differences in body size between Asians and Caucasians. The BMD of Asian women differed little from that of Caucasian women after adjustment for body size

[77]. Population-specific BMD normative databases are available for China [78,79], Hong Kong [80], Japan [81], South Korea [82] and Taiwan [83]. The International Society for Clinical Densitometry (ISCD) recommended the development of a uniform Asian male and female database [84]. However, when compared across populations, the WHO recommended using the third US National Health and Nutritional Examination Survey (NHANES III) reference database as a standardised international hip reference for women and men of all ethnic groups [84]. In Japan, 80% and 70% young adult mean [85] for subjects with or without prior fractures, respectively, are used to define osteoporosis instead of using the T-score. A BMD 25% lower than the peak BMD has also been used as criteria for diagnosis of osteoporosis in China [86]. In East Asia, there is currently an uneven geographic distribution of DXA, which is the gold standard for measurement of BMD. There are also differences in the availability of qualified staff to operate the scanners and inadequate running cost.

Limited access to DXA in East Asia has led to Quantitative ultrasonometry (QUS) measurements of the calcaneus as an accepted alternative tool [87–90]. QUS has the potential for widespread use owing to its portability, low cost, and lack of ionising radiation. Studies on the ability of QUS to predict fractures among East Asia populations were only available in Hong Kong and Japan. QUS can predict non-vertebral fractures in Japanese men and women [91], but its ability to predict major fractures was inferior to DXA among Chinese men [90]. The economic evaluation of QUS as a pre-screening test for the identification of patients with osteoporosis is available in the West [92], but not in East Asia.

Screening tools based on risk factors have been used to identify subjects, who are likely to be osteoporotic, for DXA. The Osteoporosis Self-Assessment Tool for Asians (OSTA), based on only age and weight, was developed for Asians and later validated for Caucasians. The OSTA has been evaluated in China [93,94], Hong Kong [95,96], Japan, Korea and Taiwan [97]. The OSTA cut-off of -1 had a sensitivity of 59.1–91% and a specificity of 45–66%, depending on the population, sex and whether a femoral neck or lumbar spine T-score was used as a reference. Usage of this simple pre-screening tool allows for a more sensible use of DXA under limited resources, but no cost-effectiveness analysis of such an approach has been performed.

5.2. Clinical risk factor

Many clinical risk factors for fractures have been identified in various East Asia populations (Table 3). In order to improve fracture prediction, effort has been invested to find out clinical risk factors which predict fractures independent of BMD. Likely candidates include age, prior fracture, concomitant diseases, history of fall and factors leading to increased propensity to fall.

The increased fracture risk in subjects with concomitant disease may due to frailty and increase susceptibility to fall [104]. However, it may also be related to worsen bone quality. This observation mainly comes from Japanese literature. Saito

et al. and others have published extensively on bone quality markers (homocysteine, pentosidine) as well as collagen cross-links and suggested their relationship with bone strength and fractures [105,106]. Pentosidine (serum or urine) and homocysteine (serum) levels have been suggested to be useful for fracture prediction in osteoporotic and diabetic subjects [105,107]. According to the Japanese guidelines [76], a vigorous assessment for osteoporosis is recommended in patients with diabetes and chronic renal disease. Osteoporosis associated with diabetes and chronic renal failure is mainly related to deterioration in bone quality, whereas BMD is relatively well-preserved. Treatment was recommended as soon as the T-score falls in the osteoporotic range.

History of fall and factors leading to increase propensity to fall can predict fracture independent of BMD [100]. However whether this risk is amendable by medication is questionable according to western literature [108]. Fall prevention programmes should be offered to this group of subjects with increased fall risk.

6. Assessment of fracture risk

6.1. DXA as screening

Currently, DXA is offered every 5 years for women between 40 and 70 years old under the Health Promotion Law in Japan, regardless of clinical risk factor [76]. However, the screening rate was only 4.6% in 2005 [76]. In Hong Kong [109] and Taiwan [110], the screening recommendations by professional bodies are based on the 2010 Asia–Pacific Panel Consensus Meeting of the ISCD [84] and the 2008 National Osteoporosis Foundation (NOF) guidelines [111]. The screening recommendations in these two regions are actually similar. BMD testing is indicated for women aged 65 or men aged 70 and older, postmenopausal women under age 65 with risk factors for fracture, perimenopausal women with clinical risk factors or high-risk medication use, men aged between 50 and 70 with clinical risk factors, adults with a fragility fracture, adults with a disease or condition or prescribed medications associated with low bone mass or bone loss, anyone being considered for pharmacologic therapy or being treated to monitor treatment effect. However, these screening strategies were not based on local cost-effective analysis as in the Western countries [112]. Except in Japan, DXA is only reimbursed under certain criteria; for example, DXA is only reimbursed in the event of endocrine disorders or prior fractures in Taiwan. The cost of DXA is often too high for an average wage earner without reimbursement. According to a cost-effective analysis in Japan, providing DXA to women ≥ 70 years with vertebral fracture over the past 2 years and treatment with risedronate for osteoporotic subjects was cost-effective, assuming a cost per QALY threshold of US \$100000 [75].

6.2. Clinical risk factor models for calculation of absolute fracture risk

Although BMD is the foundation for diagnosis of osteoporosis, use of BMD alone as an intervention threshold is

Table 3
Clinical risk factors for fractures.

Place	N	Sex	Type of study	Setting	Risk factors	Outcome	Ref
China	273	M + F	Prospective	Hospital based	age (>75 y, HR1.23, >85, HR1.68) female sex HR1.6 prior VF HR1.62 prior HF HR 1.27 BMD T-score < -3.5 HR 1.38 weaken motor skill HR 1.27	Refracture	[98]
Beijing, China	402	PMF	Cross-sectional	Random sample	age per 5 years OR 1.5 prior fracture OR 2.2 BMD OR/SD 2.4–2.5 history of heavy physical labour OR 0.1	Morphometric VF	[23]
Hong Kong	1810	M	Prospective	Convenience, those attend education fair	history of fall* RR = 14.5 FN T-score </ = -2.5 RR = 13.8 L1-4 T-score </ = -2.5 RR 4 history of fraility fracture RR4.4 outdoor activity <60 min/d RR 4.1 BMI<20 HR3.6 difficulty bending forward RR 3.6 use of walking aid RR 2.7 age ≥ 65 RR 2.7	All low-trauma fracture except skull, fingers/toes	[99]
Hong Kong	1435	PMF	Prospective	Convenience, those attend education fair	use of walking aid* RR = 4.2 ≥1 falls in 12 mths RR = 4 Housebound RR = 3.7 Dietary calcium intake <400 mg/d RR = 3.1 age (per 10y) RR = 2.2 fracture history RR = 2.2 BMI <19 kg/m ² RR = 1.8 FN BMD per SD RR = 2 L1-4 BMD per SD RR = 1.5	All low-trauma fracture except skull, fingers/toes	[100]
Hong Kong	2178	PMF	Cross-sectional	Convenience, those attend education fair	age every 5 years OR 1.6 BMI OR 1.05 menarche age OR 1.2 years since menopause OR 1.08 current smoking or drinking OR 1.99 calcium intake <400 mg/d OR 1.46 fracture history OR 3.8 fall in last 12 months OR 3.27 BMI OR 1.05 T-score at L1-4 or FN OR 1.5	Morphometric VF	[25]
Japan (FRISC)	1787	PMF	Prospective	Hospital based cohort	age + 10 years RR 1.62 weight + 10 kg RR 1.25 prior fracture RR 2 back pain RR 1.58 LS BMD + 1 T-score 0.85	Major osteoporotic fracture	[101]
Korea	1541	F	Cross-sectional	Voluntary sample	age T-score </ = -2.5 RR 2.31 vs > -2.5 parental hip fracture RR 3.29	Fractures at any site	[102]
	1155 1529	M F	Cross-sectional		age hip circumference OR 1.682 low T-score prior fracture OR 2.288 low income low education for women: menopause, years since menopause, number of deliveries/pregnancies	Morphometric VF	[26]
Taiwan	228 497 control	M + F	Case controlled		low milk intake/peak flow rate/hand grip strength in F low mini-mental state examination in M low BMD in both sexes		[103]

Only studies which include BMD measured by DXA in the analysis are quoted here.

BMI, body mass index; PMF, Postmenopausal female; FN, femoral neck; BMD, bone mineral density; LS, lumbar spine; VF, verman fossa; DXA, dual-energy X-ray absorptiometry.

suboptimal. This is because although BMD is specific, it is not sensitive enough for fracture prediction, as a significant percentage of fractures occurred in non-osteoporotic subjects. There has been a paradigm shift from using BMD alone to guide treatment to the combine use with clinical risk factors to calculate the absolute fracture risk for an individual. Due to the barrier to the usage of DXA as a screening tool in East Asia, efforts were made to investigate whether it is possible to use clinical risk factors only to identify high-risk subjects for treatment, as is the case for the National Osteoporosis Guideline Group (NOGG) guideline in the UK [113].

Various algorithms for prediction of 5- and 10-year fracture risk have been developed [114–116]. Among them, FRAX is probably the one that is used most widely. The FRAX[®] model was developed using nine cohort studies, including the Japanese Hiroshima cohort [117]. It is validated by 11 independent cohort studies, including the Japanese Miyama cohort [118]. FRAX is a major achievement in terms of the measurement of absolute fracture risk. However, there have been some controversies as to the applicability of FRAX on different ethnic groups [119]. The development of FRAX was largely based on data collected from Caucasian populations. The only Asian population present in the derivation and validation cohorts of FRAX was from Japan. However, it was also shown that FRAX underestimated the fracture risk in Japanese populations [120]. This was because the gradient of risk/SD for hip fractures in the Miyama cohort for subjects aged 70 years was significantly higher than in FRAX [120]. Moreover, FRAX assumes the relationship between BMI and mortality is constant across ethnic groups [121]. The ratio of hip fractures to other fractures is also assumed to be similar to Sweden for those countries where this ratio is not available [122]; however, this was shown not to be the case [123]. The hip fracture rates for Hong Kong and Japanese men and women age ≥ 65 years were less than half of that in Sweden. However, the vertebral fracture rates were higher, giving rise to a higher vertebral fracture to hip fracture ratio. The incidence of vertebral fractures in a retrospective cohort in Korea was also higher than that predicted by FRAX [124]. In this study, they used probability for major osteoporotic fracture as a surrogate for vertebral fracture. Using lumbar spine BMD instead of femoral neck BMD in the FRAX model can potentially improve the prediction [124]. The clinical risk factors are weighted in FRAX [119]. However, these risk factors may have different ‘weights’ in East Asia since the prevalence of many clinical risk factors in FRAX is lower among Asians compared to Caucasians [120,125].

Despite these limitations, FRAX is still a useful tool to guide the decision for treatment and has been widely used in East Asia populations. Population-specific FRAX algorithm, calibrated to local data on fracture rate and mortality, is available for China, Hong Kong, Japan, South Korea and Taiwan. The difference in 10-year probability of major osteoporotic fracture between various EA countries/regions (Table 4) not only reflects the difference in fracture risk but also differences in heterogeneity in mortality [10]. The FRAX probability from China may be an under-estimation because

the data used for this calculation were quite old and mostly from regional statistics.

Some studies in East Asia showed that models using fewer clinical risk factors might have predictive abilities similar to that of the full FRAX model. This finding was also evident in the Western literature [126]. In the Japanese Population-Based Osteoporosis Cohort Study (JPOS) [120], the predictability for major osteoporotic fracture was evaluated with 10-year follow-up data. The AUC for the model based on age, weight, and femoral neck BMD was similar to that of the full FRAX model. In another prospective population-based community cohort study in Japan, with a follow up time of 4 years and including 2613 men and women at a mean age of 65 in Hiroshima, the model of FRAX plus vertebral fracture status appeared to provide greater prognostic information regarding future major osteoporotic fracture compared to FRAX. The gradient of risk/SD for the 2 models were 2.73 and 2.54, respectively. However, a simpler model containing age, BMD, prior fracture, and vertebral fracture status already captured most of the predictive information with a gradient of risk/SD of 2.67 [127]. The AUC of FRAX was similar to that of a simple model using age + femoral neck BMD in a Hong Kong cohort [125].

The predictive value of FRAX with and without femoral neck BMD for major osteoporotic fracture and hip fracture, based on AUC, seems to be similar in Japan [120] and Hong Kong Chinese [125] populations. This concurs with the recommendation of Kanis et al. [128] that FRAX without BMD is suitable for fracture prediction in countries where DXA facilities are sparse because the prediction with or without BMD is comparable. However, there is currently no direct prospective evidence of treatment efficacy based on individuals with increased fracture risk who are not known to have low BMD.

An ethnic specific risk factor model, which had a 10% higher sensitivity than FRAX at a specificity of ≥ 0.8 [125] for the prediction of major osteoporotic fracture, was developed for Hong Kong postmenopausal women. These clinical risk factors increased the fracture risk even in the absence of BMD data [100]. These clinical risk factors reflect poor muscular function and coordination (Table 3). Fracture risk calculators, such as the Garvan calculator [115] and QFracture Scores

Table 4
Comparison of 10-year FRAX probabilities for major osteoporotic fractures.

		FRAX probability		
		<10%	10–15%	>15%
China	men	5.4		
	women	6.9		
Hong Kong	men		12	
	women		14	
Japan	men		13	
	women			17
South Korea	men		11	
	women		15	
Taiwan	men			16
	women			19

Adapted from Ref. [10].

The clinical scenario is an individual aged 65 years with a prior fragility fracture (and no other clinical risk factor), a T-score of -2.5 and body mass index of 24 kg/m^2 .

algorithm [116], also include factors related to frailty and fall risk. A simple indicator of general muscle strength, handgrip strength, was found to have a comparable predictive power to BMD for major osteoporotic fracture among Chinese [129].

7. Treatment

7.1. Importance of adequate calcium and vitamin D intake

A recent review suggested possible optimal dietary strategies for long term skeletal health [130]. These include adequate animal protein intake coupled with dietary calcium intake of 1000 mg/day and, maintain normal vitamin D level, increase fruits and vegetables, increase potassium while reducing sodium intake, increase intake of foods rich in vitamins K1 and K2 as well as including bones in the diet.

Traditionally calcium and vitamin D have been viewed as very important for bone health. However, there have been recent data challenging this belief. The systematic review conducted by Bolland et al. concluded that dietary calcium intake was not associated with risk of fracture in observational and intervention studies [131]. On the other hand, calcium supplements lowered the risk of any fracture by a modest but statistically significant 11% ($n = 58,573$; RR 0.89, 95% CI 0.81 to 0.96). In this review, only 5 studies comes from East Asia. 3 [132–134] out of these 5 studies showed low calcium or milk intake to be related to fracture. Another intervention study showed that milk supplement retard bone loss but was not powered to conclude on fracture outcome although the treatment group did have fewer fracture [135]. According to a recent Cochrane systematic review, there is high quality evidence showing that vitamin D (not including analog) plus calcium (compared with control or placebo) reduce the risk of any fracture, new non-vertebral fracture and hip fracture [136]. On the whole East Asian populations have lower calcium intake as compare to Western populations [137]. This is suggested that for the prevention of fractures in elderly people and simultaneous avoidance of possible serious adverse events related to a high calcium intake, emphasis should be placed on people with a low intake of calcium rather than increasing the intake of those already consuming satisfactory amounts [130].

Vitamin D deficiency and inadequate calcium intake are prevalent in China [138,139], Hong Kong [140,141], Japan [142,143], Korea [144,145] and Taiwan [146,147].

The situation is most severe in China. In Shanghai, during the winter season, the prevalence of vitamin D insufficiency (<30 ng/mL) was 84% in males and 89% in females while the corresponding figures for vitamin D deficiency (<20 ng/mL) was 30% and 46%, respectively [138]. The average calcium intake in China was less than 400 mg in 2002 [139]. The average calcium intake per day is 400–600 mg in Hong Kong, Japan, Korea and Taiwan, according to surveys at different times and for different age groups [141,143,145,147]. 62.8% of subjects in Hong Kong having levels <30 ng/ml [140]. However, despite this, a substantial amount of physicians and patients are still unaware of the importance of calcium and

vitamin D in osteoporosis prevention and treatment [148–150]. Vitamin D deficiency also worsens fragility and increases the risk of falls [151]. Guidelines have highlighted the importance of calcium and vitamin D [76,109,110,152,153], but effort is needed to improve the implementation of these guidelines [150,154]. In Asia, 50–100% of the population is lactose intolerant [155] and thus may be at risk for calcium inadequacy. Apart from supplements, fish can be a good source of calcium [156], and a higher fish intake results in a higher BMD [157,158]. Fatty sea fish is especially a good source of vitamin D and n-3 polyunsaturated fatty acid which are beneficial for bone health. The fish highest in calcium content are those canned with edible bone such as sardine and salmon, some other sea fish such as cod, anchovy and pike are also high in calcium content.

We agree with the guidelines that daily intake of 1000 mg calcium and 800IU vitamin D is beneficial to bone health. Higher intake will be necessary for elderly, malabsorptive and osteoporotic subjects especially those who are institutionalized may need up to 2000 IU vitamin D per day. However, as pointed out by Avenell et al. [136], what is more important is indeed the food not the nutrient. E.g. calcium citrate or carbonate may not the best for bone health. Calcium hydroxyapatite, in the form of bone, may be better [136].

7.2. Indications for treatment (Table 5) and intervention threshold

Treatment guidelines for osteoporotics are available in China [152], Hong Kong [109], Japan [76], South Korea [153] and Taiwan [110]. The treatment guidelines in Hong Kong and Taiwan were based on the National Osteoporosis Foundation recommendations. The guidelines in Hong Kong, Japan and Taiwan incorporate FRAX and recommend treatment for subjects without other indications for treatment (such as prior fractures or BMD below a cut-off) if their FRAX value get above a fixed value regardless of age.

7.3. Efficacy of drugs

The efficacy of various anti-osteoporotic drugs to increase BMD and reduce risk of hip fractures and vertebral fractures has been evaluated in East Asia populations (Appendix A).

Health economic appraisals for the primary and secondary prevention of fractures have been performed for most anti-osteoporotic drugs in the Western world [159,160]. These studies showed that alendronate [159], etidronate [159], risedronate [159], raloxifene [159], teriparatide [159] and strontium [160] are cost-effective in treating postmenopausal osteoporosis under well-defined scenarios but with different gain in QALYs. The size of the QALY gain for each intervention was strongly related to the age and pre-existing risk of the patient. However, such data are only available in Japan and there only for risedronate [75]. In a budget impact and economic effect stimulation study in South Korea, continuous reimbursement coverage for patients with osteoporosis was shown to reduce total health budget expenditure through saving fracture cost [162].

Table 5
Screening and treatment guideline.

Guideline	Prior fracture, treat if	DXA screening	Treat if	Ref
Hong Kong (use NOF guidelines)	Fracture at proximal femur or vertebrae (use NOF guidelines)	ISCD guideline	T-score ≤ -2.5 at LS or FN osteopenia + FRAX MOF risk $\geq 20\%$ osteopenia + FRAX Hip risk $\geq 3\%$ (use NOF guidelines)	[109]
China	Postmenopausal women and men ≥ 50 years old with fracture at proximal femur or vertebrae		T-score ≤ -2.5 at LS or FN osteopenia + OSTA# high risk + FRAX MOF risk $\geq 20\%$ osteopenia + OSTA# high risk + FRAX Hip risk $\geq 3\%$	[61]
Japan	Fracture at proximal femur or vertebrae other sites + BMD $<80\%$ YAM*	for 40–70 years old female if $<80\%$: further exam $\geq 80\%$ but $<90\%$: advice $\geq 90\%$ + RF:advice	BMD $<70\%$ YAM $\geq 70\%$ but $<80\%$ + FH proximal femoral fracture $\geq 70\%$ but $<80\%$ + FRAX (MOF) $\geq 15\%$	[76]
Korea	Radiographic evidence of an osteoporotic fracture.		minimum T-score of ≤ -3.0 at LS or femur	[153]
Taiwan	Osteoporotic fracture after age 50	≥ 65 both sexes <65 with CRF both sexes	FRAX MOF risk $\geq 20\%$ FRAX HF risk $\geq 3\%$	[110]

LS, lumbar spine; FN, femur neck; MOF, major osteoporotic fracture; HF, hip fracture; YAM, young adult mean; FH, family history; RF, risk factors; CRF, clinical risk factors; OSTA, osteoporosis self assessment tool for Asians.

Concerning treatment the subjects at risk but without osteoporosis or prior hip or vertebral fracture, the National Osteoporosis Foundation guideline recommended treatment if FRAX value $\geq 20\%$ for major osteoporotic fracture or $\geq 3\%$ for hip fracture. However, the National Osteoporosis Foundation guidelines are based on cost-effectiveness that produces a 35% prevention rate for 5 years according to the epidemiology and mortality data in the USA [111]. Direct application of the National Osteoporosis Foundation guidelines in other countries is not optimal. Fujiwara et al. [161] reported that FRAX would underestimate the risk of major osteoporotic fracture in the Japanese population. A FRAX cut-off value of 15% for major osteoporotic fracture (MOF) was recommended as the treatment threshold in subjects with low bone mass in Japan [163] instead of 20% used by National Osteoporosis Foundation.

7.4. Osteoporosis in men

There is much less research in men than in women in Asia. Thus, further studies are necessary to find a cost-effective screening method and intervention threshold in men [164].

7.5. Difference in prescription habits

There are several anti-osteoporotic drugs that are only available in Japan and not in other countries. These include Eldecalcitol (vitamin D3 analog), Menatetrenone (Vitamin K derivatives) and Minodronic acid (bisphosphonate developed in Japan) [165]. Aledronate and Risedronate are used at half-dose in Japan because of the assumption that Asians have a small body size and smaller skeleton. Bazedoxifene is only used in Japan and South Korea, but not in other EA countries. Herbal medicine is often used in China and Hong Kong for treatment of osteoporosis. A recent Cochrane review, which involved 10,655 participants, showed that Chinese herb Migu decoction (when compared with placebo) was associated with an increase in lumbar BMD of 0.16 g/cm³ (CI 0.06–0.26). Qianggu soft extract (vs no intervention) produced an increase in femoral neck BMD of 0.09 g/cm³ (CI 0.03–0.13).

Xianlinggubao plus caltrate (vs caltrate) produced increase in femoral neck BMD of 0.3 g cm³ (CI 0.25–0.35) [166]. No fracture data was available. All the studies included were small in sample size and tested different herbal medicine. More studies are required in this area.

Vitamin D analogs are widely used in Japan. For patients aged ≥ 65 years with existing fractures, 22% of doctors chose activated vitamin D as the first-line treatment compared to 55% who selected bisphosphonates [12]. Among vitamin D analogs, eldecalcitol was shown to be superior to alfacalcidol in increasing the BMD and reducing vertebral fractures and wrist fractures among the Japanese population [167]. A review from the West showed that adding calcitriol to other anti-osteoporosis drugs has additional bone-preserving effects [168]. However, in a recent Japanese study, alendronate plus alfacalcidol was no more effective than alendronate alone for overall vertebral fracture prevention, while subgroup analysis showed that alendronate plus alfacalcidol was more effective for fracture prevention in high-risk patients and for non-vertebral weight-bearing bone fracture prevention [169].

7.6. Vitamin K derivatives

The importance of vitamin K for bone health was highlighted in the Japanese guidelines [76].

Studies showed the possible association between intakes of vitamin K, such as in fermented soybeans, which is commonly consumed among Japanese and Koreans, and the risk of hip fracture [170,171] and vertebral fracture [172]. Intervention trials also showed that Vitamin K could increase the BMD in Korean postmenopausal women [173] and prevent fractures in Japanese individuals [174]. A recent review has addressed the importance of vitamin K especially K2 on bone health [130]. A large meta-analysis [175] concluded that high vitamin K2 levels were associated with 60% reduction in vertebral fracture risk, 77% reduction in hip fracture risk and 81% reduction in non-vertebral fracture risk. The beneficial effect of vitamin K may not be due to increase in bone mineral density but improved bone strength [176]. The natto (soybean fermented

with *Bacillus subtilis* var natto), named “Kinnotsubu honegenki”, was granted a health claim [177,178] in Japan.

7.7. Non-adherence

Adherence to anti-osteoporotic regimens is also seen as a problem in East Asia. Data are available from the West concerning the clinical and economic impact of non-adherence [179,180], but only the former was available in the East Asia literature [181,182]. In a study conducted based on a claims database in Taiwan, the overall adherence to anti-osteoporotic regimens was judged to be sub-optimal. Only 50.8% of patients continued to receive therapy at 1 year and 36.1% at 2 years [181]. Even among patients already with vertebral or hip fracture, only 38% of subjects in Taiwan remained compliant on alendronate during the first year of treatment. Over the 4-year follow-up period, the risk of hip fracture among the compliant patients was 70% lower than the noncompliant ones [182].

8. Conclusion

The greatest burden of hip fractures in the world is expected to rest in East Asia, especially China. However, osteoporosis is greatly under diagnosed and under treated in East Asia, even for patients who already had fractures. Efforts should be directed to improve the assessment and management of at-risk individuals via the following directions. Firstly, we should aim at better documentation of the epidemiology of all kinds of osteoporotic fractures and the related social and economic burden. Secondly, awareness of and knowledge on osteoporosis among both the professionals and public should be improved. Such an increased awareness among public may potentially improve the drug adherence. Thirdly, clinical risk factor models may be ethnicity-specific and differ between Asians and Caucasians. More research is needed to determine the optimal fracture risk assessment model for East Asia populations. Before this is available, we may use FRAX as an alternative. Fourthly, cost-effective screening methods and treatment strategies based on epidemiological and economic data for specific regions should be developed. Finally, more research on bone quality and treatment modalities specific to Asian populations needs to be performed.

Conflicts of interest

None.

Appendix A. Supplementary Table. Anti-osteoporotic drugs examined in East Asia countries/region

Alendronate: China

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Alendronate: HK

- Lau EM, Woo J, Chan YH, Griffith J. Alendronate prevents bone loss in Chinese women with osteoporosis. *Bone* 2000;27:677-80
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- Ho AY, Kung AW. Efficacy and tolerability of alendronate once weekly in Asian postmenopausal osteoporotic women. *Ann Pharmacother* 2005;39:1428-33.

Alendronate: Japan

- Kawate H, Ohnaka K, Adachi M, Kono S, Ikematsu H, Matsuo H, et al. Alendronate improves QOL of postmenopausal women with osteoporosis. *Clin Interv Aging* 2010;26:123-31.
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postmenopausal women with osteoporosis. *J Bone Miner Metab* 2011;29:458-65

Alendronate: Korea

- Kim SW, Park DJ, Park KS, Kim SY, Cho BY, Lee HK, et al. Early changes in biochemical markers of bone turnover predict bone mineral density response to antiresorptive therapy in Korean postmenopausal women with osteoporosis. *Endocr J* 2005;52:667-74
- Rhee Y, Kang M, Min Y, Byun D, Chung Y, Ahn C, et al. Effects of a combined alendronate and calcitriol agent (Maxmarvil) on bone metabolism in Korean postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Osteoporos Int* 2006;17:1801-7

Alendronate: Taiwan

- Yen ML, Yen BL, Jang MH, Hsu SH, Cheng WC, Tsai KS. Effects of alendronate on osteopenic postmenopausal Chinese women. *Bone* 2000;27:681-5.
- Lin TC, Yang CY, Yang YH, Lin SJ. Alendronate adherence and its impact on hip-fracture risk in patients with established osteoporosis in Taiwan. *Clin Pharmacol Ther* 2011;90:109-16.

Risedronate: Japan

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Risedronate: Korea

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Ibandronate: China

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Ibandronate: Japan

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Ibandronate: Korea

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Zoledronic acid: China

- Hwang JS, Chin LS, Chen JF, Yang TS, Chen PQ, Tsai KS, et al. The effects of intravenous zoledronic acid in Chinese women with postmenopausal osteoporosis. *J Bone Miner Metab* 2011;29:328-33.

Zoledronic acid: Korea

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Raloxifene: China

- Nakamura T, Liu JL, Morii H, Huang QR, Zhu HM, Qu Y, et al. Effect of raloxifene on clinical fractures in Asian women with postmenopausal osteoporosis. *J Bone Miner Metab* 2006;24:414-8.

Raloxifene: HK

Kung AW, Chao HT, Huang KE, Need AG, Taechakraichana N, Loh FH, et al. Efficacy and safety of raloxifene 60 milligrams/day in postmenopausal Asian women. *J Clin Endocrinol Metab* 2003;88:3130-6.

Raloxifene: Japan

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Bazedoxifene: Japan

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Teriparatide: China

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Teriparatide: HK

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Teriparatide: Japan

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