

Bone Fragility in Asian and Caucasian Men

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Abstract

Hip and vertebral fractures are a public health problem in men of Asian and Caucasian origin. Inferences regarding gender and racial/ethnic differences in fracture rates must be made cautiously as problems in case ascertainment and classification of hip fractures, and problems in defining what constitutes a vertebral 'fracture' have not been solved. However, methodological issues probably do not entirely account for the heterogeneity of fracture patterns. There is likely to be a wide variation in fracture rates from country to country in Asia as reported in studies in Europe. The reasons for this heterogeneity are unknown.

Caucasian men lose similar amounts of bone as Caucasian women during ageing from the endosteal surface of the bone. Net bone loss is less in men than women because men form more periosteal bone during ageing than do women. The extent of periosteal and endosteal bone modelling and remodelling have not been studied in Asian men and women. Nor have there been hypothesis-driven studies designed to compare periosteal apposition and endosteal bone loss in Asian males compared to Caucasian males.

Sex hormone deficiencies contribute to abnormalities in skeletal size and mass during growth, remodelling imbalance and bone loss during ageing in men. The larger peak bone size and greater periosteal apposition with ageing in men compared to women is most likely to be androgen-dependent in Caucasians and Asians. Androgen deficiency may also partly account for reduced bone formation and negative bone balance at the basic multicellular unit (BMU). Oestrogen deficiency during growth is associated with reduced bone mass and increased leg length in males and females. Oestrogen deficiency during ageing may account for trabecular bone loss in men by increasing remodelling rate. There have been no anti-fracture efficacy studies done in Asian males.

Studies on the pathophysiology of osteoporosis in males have given insight into the pathophysiology of osteoporosis in females. Similarly, collaborative research efforts between groups around the world will facilitate comparative studies in Asian and Caucasian communities. The results of this work will provide important insights into the pathophysiology of bone fragility in both groups.

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Introduction

Bone fragility in men has been receiving greater attention during the last few years. Epidemiological studies have been done in Caucasian and Asian populations. However, the structural basis for gender and racial differences of fracture rates is not well defined. The purpose of this article is to review recent progress in the epidemiology, fracture risk assessment and pathogenesis of bone fragility in Caucasian and Asian men, and to define areas of ignorance that require further research.

Epidemiology in Asian and Caucasian populations

Fractures of the Proximal Femur

About one-third of hip fractures occur in men. Worldwide, the number of hip fractures in men is predicted to increase from 0.5 to 1.8 million in 2050 due to an increase in

longevity and a secular increase in the age-specific incidence of hip fractures.¹⁻⁸

Similar to women, the incidence of hip fractures in men increases with age. However, the age-specific annual incidence (per 100,000 persons over 50 years) is lower in Asians than Caucasians.^{5,7,9-15} Wong et al⁹ reported rates of 100 in men and 75 in women in Singapore; 20% to 50% that in Caucasians. Rates in the Japanese were about 50% that in American Caucasians.¹⁰ Low rates were reported in Korea and in Northern China.^{7,11,13} Xu et al⁷ and Yan et al¹³ reported rates of 100 for men and 90 for women in Northern Chinese. Intermediate rates of hip fracture were reported in Malaysia, Thailand and the Middle East^{15,16} (Fig. 1). Low rates have also been reported in Asian-Americans compared to American Caucasians.¹⁷ In contrast, higher rates were reported in other studies. Koh et al⁸ reported rates of 168 in

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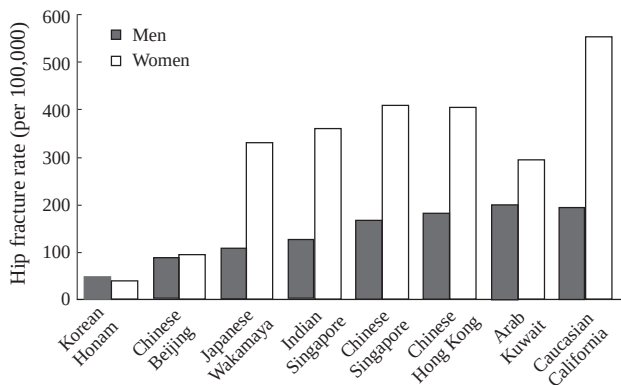


Fig. 1. The age-standardised hip fracture rates are lower in Asians compared to Caucasians in most of the studies but vary greatly within genders, racial groups and from country to country in Asia. Adapted from Koh et al.⁸

men and 410 in women in Singapore Chinese. Lau et al¹⁵ reported rates of 180 in men and 459 in women in Hong Kong. These wide annual incidence rates across Asian countries may reflect ascertainment problems, but these are likely to be real differences as well (Fig. 2).

There is a secular increase in hip fracture incidence in Asia. Among Hong Kong Chinese, rates have increased 2-fold during the last two decades.¹² From 1988 to 1992, the rates in Northern China increased by 33% in men and 34% in women.⁷ In Singapore, rates have increased by 0.7% per year in men and 1.2% per year in women from 1991 to 1998.⁸ Compared to the hip fracture rates in the 1960s, they were 1.5 to 5-fold higher during the 1991 to 1998 period.⁸

Vertebral Fractures

Several cross-sectional studies have suggested that the prevalence of vertebral fractures is similar in both Caucasian men and women.¹⁸⁻²² The Dubbo Osteoporosis study in

Australia reported that the prevalence of vertebral fractures was higher in men than women aged 65 years and over [17% vs 12% using the 4 standard deviation (SD) criterion].¹⁸ Davies et al²² reported that the prevalence was 29% in men and 10% in women aged 50 to 59 years, and 39% in men and 45% in women aged 80 years and over in Nebraska, USA. The European Vertebral Osteoporosis Study reported that the prevalence of vertebral fractures was 12% in men and women aged 50 to 79 years.¹⁹

However, these prevalence data are suspect even though they were replicated in several locations. The higher prevalence of vertebral fractures in men may be due to more trauma in youth in men than women rather than bone fragility.¹⁹ In addition, misclassification of spinal deformity has been reported to be more common in men than women.²³

The prevalence of vertebral fractures is similar or only modestly lower in Asian men compared to Asian women.²⁴⁻²⁶ Tsai et al²⁴ reported a prevalence of 20% for Chinese women and 12.5% for Chinese men aged 65 years and over. In Hong Kong, vertebral fractures were found in 16% of men and 30% of women, and in 37% of men and 35% of women with mild spinal deformities aged over 70 years.²⁵ In Beijing, the prevalence was about 10% in men and women aged 60 to 69 years, 16% in men and women aged 70 to 79 years, and 24% in men and 31% in women aged 80+ years.²⁶ (Fig. 3). These observations may have been biased by traumatic fractures in youth being counted as fragility fractures in old age. Limited data suggest that the age-specific prevalence is similar in Asian and Caucasian men.^{12,24-26} (Fig. 4) Vertebral fracture prevalence is reported as being similar or slightly lower in Asian women than Caucasian women.²⁷⁻²⁹

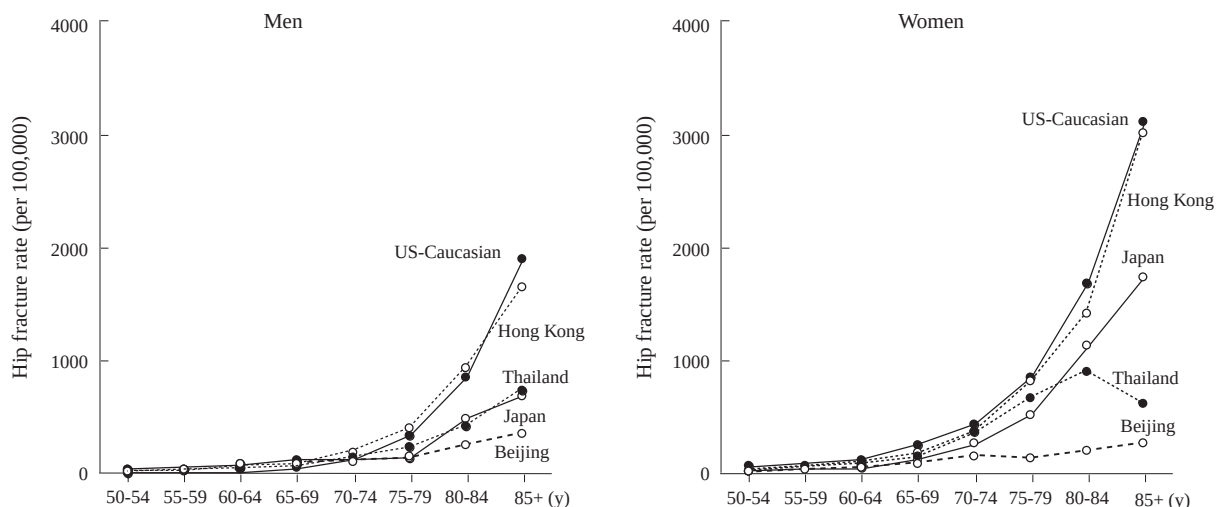


Fig. 2. The age-specific rates of hip fracture in men and women are lower in Asians compared to Caucasians but are similar in Hong Kong Chinese compared to Caucasians. Adapted from Lau et al,¹⁵ Ross et al¹⁰ and Xu et al.⁷

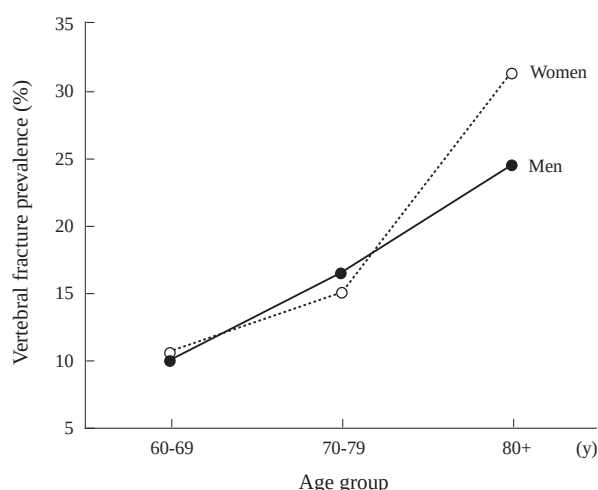


Fig. 3. The age-specific prevalence of vertebral fractures increased with age in men and is similar to that in women in Beijing, China. Adapted from Nevitt.²⁶

Prospective studies are few but suggest that the incidence of vertebral fractures is lower in men than women.³⁰⁻³³ The incidence of vertebral fractures in men was about half that in women in Rochester, Minnesota (0.73 vs 1.45).³⁰ In a prospective study in Hawaii, the rate was 3 times higher in Caucasian women compared to Caucasian men (16 vs 4%).³² Incidence figures for vertebral fractures are not documented in Asia. More studies giving meticulous attention to standard morphometric definitions of vertebral fracture are needed before any inferences concerning gender or racial differences in vertebral fracture rates can be made with confidence.

Morbidity, Mortality and Cost

Morbidity and mortality from hip fractures were reported to be higher in Caucasian men compared to Caucasian women and showed an increase with age.³⁴⁻³⁶ More than 50% of men and women with hip fractures required residential care or needed assistance with daily living. Poor

et al³⁴ reported that the total mortality in men was 3-fold higher than women (14% vs 5.4%). Neither fracture nor illness alone accounted for the excess mortality. An interaction between fracture, its consequences and coexisting illnesses may be responsible. Morbidity and mortality rates associated with hip fractures in men and women have not been reported in Asia.

Increased morbidity and mortality associated with vertebral fractures have been reported in men.^{37,38} However, it is difficult to ascertain the morbidity following vertebral fractures when the time of fracture is unknown and there is no single definition of vertebral fracture. In Hong Kong, Lau et al²⁵ reported that the prevalence of back pain was higher in men than women with vertebral fractures (68% vs 50%). A Philadelphia geriatric morale score did not differ between the vertebral deformity groups for men. Nevitt et al²⁶ and Xu et al²⁸ reported that vertebral fracture was associated with limited physical function (time to stand up from chair increased) in Chinese men and women in Beijing. No association between chronic back pain and vertebral fracture was detected in men and women, even those with severe or multiple fractures. Mortality associated with vertebral fractures was higher in men than women.³⁸

The annual cost associated with osteoporotic fractures was about \$21.7 billion in the US.³⁹ In Australia, hip fractures accounted for about 1% of the annual health services expenditure.⁴⁰ Men contributed up to about 20% of the annual expenditure for treatment of osteoporosis-related fractures.⁴¹ Hip fractures accounted for a larger proportion of the total expenditure in men compared to women (73% versus 61%). The cost associated with treatment of osteoporotic fractures has not been reported in Asia. Unpublished data have shown that the annual cost related to the treatment of hip fractures in Hong Kong was \$HK130 million, accounting for 1% of an annual total hospital care expenditure.¹²

Areal BMD and Fracture Risk

Areal bone mineral density (aBMD) predicts fracture risk similarly in Caucasian men and women.^{32,42-49} The absolute risk for spine fracture for a given aBMD at the calcaneus and proximal radius is similar in men and women.⁴⁷ The age-specific absolute risk for hip fracture (i.e. number of cases per 10,000 per year) at a given aBMD is similar in men and women of the same age.⁴⁹ The relative risk for spine and hip fractures conferred by a 1 SD decrease in aBMD at any site increases similarly, by 1.5 to 2-fold, in both men and women.³²

aBMD is also a predictor of the risk of hip and spine fractures in Asian men and women. However, whether aBMD is similarly predictive in Asian men and women is uncertain. There are no data available concerning the

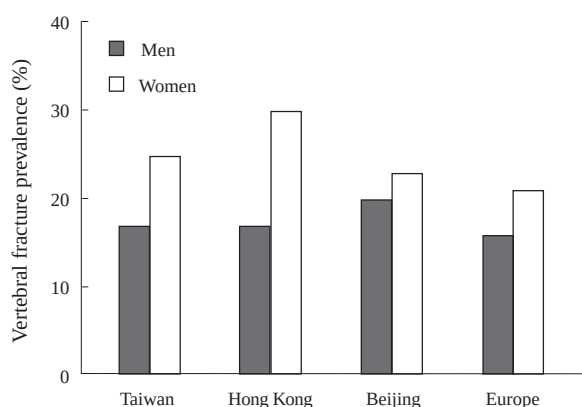


Fig. 4. The prevalence of vertebral fractures is similar in Chinese men and women aged 70 to 79 years in different regions, and similar to European Caucasians. Adapted from Tsai et al,²⁴ Lau et al,²⁵ Nevitt et al²⁶ and O'Neil et al.¹⁹

predictive strength of aBMD for hip fracture in Asian men. In women, Lau et al¹² reported that Chinese women with hip aBMD in the lowest quartile had a 4.5-fold higher relative risk of hip fracture, which is similar to reports in Caucasians. In contrast, spinal aBMD is a better predictor for risk of vertebral fracture in Chinese women than Chinese men;^{26,28} a 1 SD reduction of lumbar spine aBMD was associated with a 2.4-fold increase in vertebral fracture risk in women and a 1.5-fold increase in men.^{26,28}

The reason aBMD predicts a similar fracture risk in Caucasian men and women, but may not in Asian men and women, is uncertain. Several factors may influence the ability of aBMD to predict the risk of fractures.⁵⁰⁻⁵³ Although the young mean aBMD value is lower in Chinese, Chinese have a higher SD compared to Caucasians; hence, fewer Chinese will be below the cut-off value of -2.5 SD using the Caucasian criterion.⁵³ aBMD is higher in men than women with vertebral and hip fractures because men have larger bones.⁵⁴⁻⁵⁸ Volumetric BMD (vBMD) is the same in men and women with fractures.⁵⁶⁻⁵⁸ This may explain why a given level of aBMD or 1 SD reduction of aBMD predicts the same absolute risk of fractures in Caucasian men and women.

If the fracture threshold is similar in both men and women, and a given aBMD or vBMD predicts the risk of fracture similarly in both men and women, why is the incidence of fractures lower in men?

Men are taller and heavier than women; hence, they impose a higher absolute load on the bones. However, their bones are also larger so that the load per unit area (stress) is the same in young men and women.⁵⁷ Thus, the gender difference in peak bone size is not the explanation for the gender difference in fracture rate in old age. The reason men fracture less commonly than women resides in the age-related changes that occur. Men adapt their skeleton better to a falling bone strength than women during ageing.

The adaptation is the greater periosteal apposition that occurs in men rather than in women during ageing. This is discussed below in brief. The greater periosteal apposition increases bone cross-sectional area and offsets endosteal bone loss. Thus, the loss of bone strength during ageing is less in men than in women for these two reasons. Parallels may occur both in Asian men and women.

Based on engineering principles, fracture is likely to occur when the loads imposed on the bone exceed the bone strength. We have developed a fracture risk index (FRI) at the spine which reflects this relationship.⁵⁷ The FRI is the ratio of vertebral body compressive load to its strength. Loads are determined by upper body weight, height and the spinal muscle moment arm, while strength is estimated from the vertebral body cross-sectional area (CSA) and vBMD. Fracture is likely to occur when loads imposed on

the bone is greater than strength, that is when the FRI is >1. Changes in bone size, vBMD and loading (weight, height) are captured by the FRI. The FRI increases by only 21% in men but by 102% in women during ageing; hence, only 9% of men but 26% of women have a FRI of >1.⁵⁷ The lower incidence of fractures in men reflects the lower proportion of the male population at high risk with a FRI greater than unity. There may be parallels explaining why fewer Asian men than Asian women have fractures.

Pathogenesis of Bone Fragility

Proximal Femur

The structural basis responsible for the lower bone fragility at the proximal femur in Caucasian men than Caucasian women is partly understood. Peak femoral neck size, not peak vBMD, is greater in men than women.^{59,60} Beck et al⁵⁹ reported that peak femoral neck width was about 20% higher, while peak cortical thickness was only 5% higher in men than women. The larger femoral neck size was associated with greater bone strength in men than women. After adjustment for the gender differences in body size, men still have greater bone size and bone strength.⁶¹ Thus, the gender differences in femoral neck size are greater than the gender differences in bone mass or cortical thickness.

Net femoral neck bone loss is less in men than women during ageing.^{59,62} The lesser diminution of femoral neck/shaft aBMD in men than women is largely due to *greater* periosteal apposition rather than *lesser* endosteal bone resorption in men than women during ageing.⁶³⁻⁶⁶ Beck et al⁶³ reported that periosteal expansion at the femoral neck increased with age in men but not in women. Ruff and Hayes⁶⁴ reported that periosteal expansion was greater while endosteal bone loss was similar at the femur and tibia in both men and women. Greater increase in femoral neck width in men than women has been reported in Caucasians in Australia (Duan and Seeman, unpublished data). In contrast, the NHANES III study suggests that the age-related increase in periosteal apposition at the femoral neck is similar in both men and women (both ~10%).⁵⁹

Increased periosteal apposition offsets the endosteal bone loss, maintaining bone strength. Bone formed on the periosteal surface is biomechanically advantageous because it increases cross-sectional moment of inertia and bending strength of the long bone.⁶⁷ A greater reduction of femoral neck section modulus was reported in elderly women than men.⁵⁹ Thus, bone strength at the femoral neck is better maintained in Caucasian men than Caucasian women during ageing because periosteal apposition with ageing is greater in men.

There are limited data in Asia comparing gender differences in bone size and structural elements at the

proximal femur during growth and ageing. Peak aBMD at the femoral neck is higher in Asian men than women because bone size is greater in men. Tsai et al⁶⁸ reported that the femoral neck area was about 13% higher in Chinese men compared to women in Taiwan. Whether peak femoral neck vBMD and peak cortical thickness are the same in Asian men and women is unknown.

During ageing, femoral neck aBMD declines less in Asian men than Asian women.⁶⁸⁻⁷⁰ Periosteal apposition at the femoral neck increased with age in Chinese men but not in women,⁶⁸ and this most likely explained the lower net bone loss in Asian men than Asian women. The absolute amount of bone loss on the endosteal surface of femoral neck is probably accelerated in very elderly Chinese men. Ho et al⁷¹ reported that femoral neck aBMD decreased by 16% in Chinese men and by 22% in elderly Chinese women in the age group of >85 years relative to the age group of <75 years.

The lower hip fracture rate in Asians is unlikely to be explained by racial differences in aBMD, as Asians have lower aBMD than Caucasians, largely because their bone size is smaller.⁶⁰ Peak femoral neck width is about 7% larger in Caucasian men than Asian men, and 6% higher in Caucasian women than Asian women (Duan and Seeman, unpublished data). Peak femoral neck vBMD derived from dual-energy X-ray absorptiometry (DXA) shows no difference in Asians and Caucasians of either gender.⁶⁰ If femoral neck vBMD is lower in older Caucasian than Asian men, then Caucasian men have a greater net bone loss than Asian men.²⁶

If Caucasian men lose more bone during ageing than Asian men, this may be due to Asian men having greater

periosteal apposition or losing less endosteal bone than Caucasian men. The latter may be due to Asians having a lower endosteal remodelling rate (activation frequency), less resorption or greater bone formation in the basic multicellular unit (BMU). Available data suggest that periosteal apposition is greater in Caucasian than Asian men. Beck et al⁶³ reported that femoral neck expansion increased by 1% per decade in Caucasian men, while Tsai et al⁶⁸ reported that femoral neck expansion increased by 0.6% per decade in Chinese men.

Both lesser and greater net bone loss in Asian than Caucasian men are reported in cross-sectional studies.^{59,69,70,72} Relative to peak, aBMD decreases by 20% in Caucasian men and by 10% in Asian men in Hong Kong.^{59,69} In another study, femoral neck aBMD decreased more greatly in Asian than Caucasian men⁷² (Fig. 5). However, expressing the changes in percentage terms may be misleading if the initial value and variance (SD) is different between racial groups.

As with our studies of the FRI at the spine, Tsai et al reported that the factor of risk (load/strength) at the femoral neck did not increase with age in Chinese men but increased with age in elderly women after the age of 65 years. Older women have higher factor of risk for hip fractures than elderly men.⁷³

The biomechanical basis of the racial differences in hip fracture rates has not been studied in men. In women, Nakamura et al⁷⁴ compared 57 Japanese and 119 American Caucasians. Height and weight were greater, and femoral neck bone mineral content (BMC) and cross-sectional moment of inertia (CSMI) were greater in Caucasian women compared to Japanese women, suggesting that

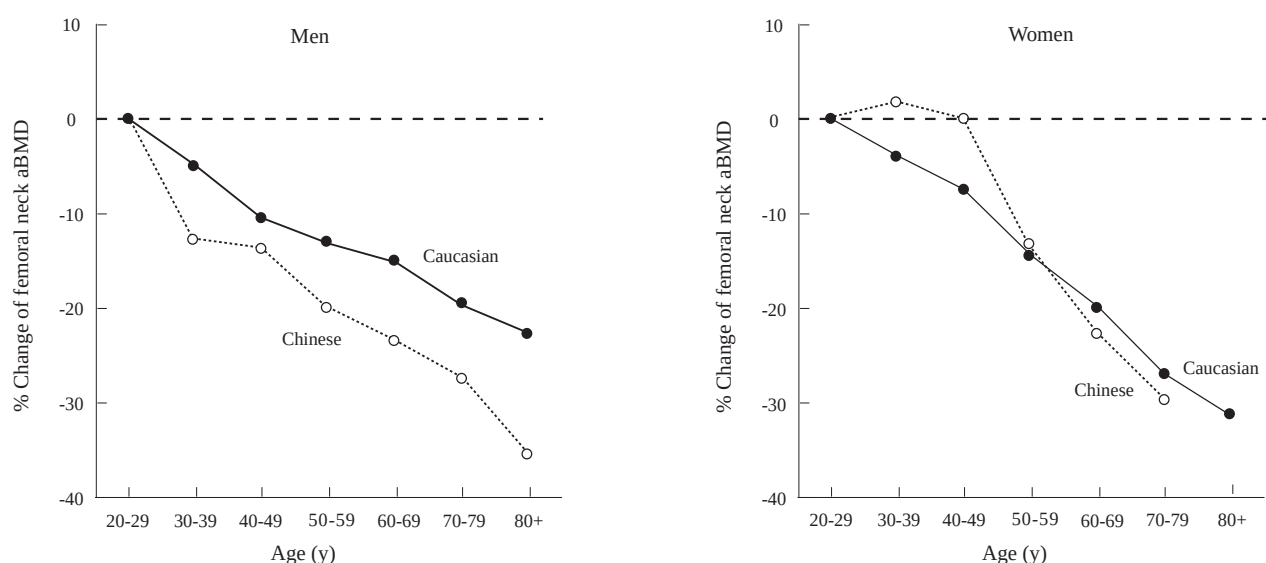


Fig. 5. The age-related diminution of femoral neck aBMD relative to peak is greater in Chinese men compared to Caucasian men but is similar in Chinese women compared to Caucasian women. Adapted from Beck et al⁶⁹ and Liu et al.⁷²

absolute bone strength is greater in Caucasians. However, the safety factor was about 35% less in Caucasians than Asians. The authors suggest that the shorter femoral neck length is a major contributor to the higher femoral neck safety factor in Asians.

Shorter hip axis length (HAL) in Asians than Caucasians may partly account for the lower hip fracture risk in Asians.⁷⁵ However, shorter leg length may account for the differences in HAL. Men have a longer HAL than women, but have a lower incidence of hip fractures. No prospective studies have been done examining whether fracture rates are less in persons with a shorter HAL. Asians have similar trunk length but shorter leg length than Caucasians.^{76,77} This may protect against hip fracture because the relative shorter distance of the proximal femur to the ground may produce less force on the hip when falls occur. The shorter leg length may also increase the bending strength during falls.⁷⁴

Vertebral Skeleton

Peak vertebral size is greater in Caucasian men compared to Caucasian women, while peak vertebral vBMD is no different.^{78,79} From the age of 7 to 17 years, vertebral vBMD increased by 30% to 40% while vertebral size and BMC increased by 200% to 300% in boys.⁸⁰ Trabecular number and thickness are also similar in young men and women.⁸¹ Thus, the greater amount of bone gained during growth builds wider but not more dense vertebrae in boys than girls. The larger vertebrae in men than women are mainly due to men having greater cross-sectional area but not vertebral body height.^{78,79}

Similarly, at peak, vertebral size is greater in Asian men than women. However, in contrast to Caucasians, Yu et al⁸² reported that peak vertebral vBMD was 7% to 11% lower in Asian men compared to Asian women. Our preliminary data show that the estimated peak vertebral vBMD derived from DXA in postero-anterior view is 10% lower in Chinese men than Chinese women aged 18 to 45 years, while vertebral body width is 13% greater in Chinese men than Chinese women (Duan and Seeman, unpublished data). Tsai et al⁸³ reported that peak vertebral vBMD derived from DXA was 16% lower in men compared to women, while vertebral size was 16% greater in men.

Premenopausal Chinese women have more bone mineral in the posterior processes than men (61% vs 50%, respectively), so the higher vertebral vBMD derived by DXA postero-anterior scanning may be an artifact because the greater amount of bone in the posterior elements in women is not corrected for bone size in the vBMD measurement.⁸⁴ Moreover, as the vertebral body volume is overestimated by DXA, it may cause a greater error in men than in women because men have larger vertebral size.^{85,86}

This of course does not explain the findings by Yu et al using quantitative computed tomography (QCT).

Thus, whether peak vertebral vBMD is different in Asian men compared to Asian women remains unsettled. If vBMD is lower in Chinese men than women, is this due to thinner cortices, fewer trabeculae or thinner trabeculae. What factors regulate gender and racial differences in vertebral size and structural elements? The onset of puberty is 2 years later in Chinese boys compared to girls, and the pubertal growth is 2 years longer in boys.^{87,88} Whether differences in pubertal progression are responsible is uncertain.

Most studies report that vertebral aBMD measured by DXA decreases less in Caucasian men than women.^{62,89,90} However, by using QCT, histomorphometry and ashing, the absolute amount of trabecular bone loss on the endosteal surface of vertebrae is similar in men and in women.^{81,91-93} The reason men lose less net bone loss and have less fragility fractures than women is most likely due to greater periosteal apposition in men compared to women rather than less endosteal bone loss. As with the femur, the greater periosteal apposition increases cross-sectional area, diminishing the load per unit area (stress) on the spine. Greater periosteal apposition in men also offsets the (similar) loss of bone from the endosteal surface more in men than women so vBMD and vertebral strength is better maintained in men than women.⁷⁹ Some evidence exists for supporting similar processes in Asian men and women;^{83,94} vertebral trabecular vBMD measured by QCT declined similarly in Japanese men and women,⁹⁴ while greater periosteal apposition is reported in Asian men compared to Asian women at the vertebra.⁸³

The incidence of fractures in Caucasian men is lower than Caucasian women for the above reasons. If the loss of trabecular bone is similar in Asian men and women and periosteal apposition is greater in Asian men than women, then the incidence of fractures should also be lower in Asian men than Asian women.

The similar prevalence of vertebral fractures in Asians and Caucasians may reflect a parallel load to strength relationship in the spine in these races. Although smaller vertebral body size is an independent risk factor for vertebral fractures in men and women,⁹⁵⁻⁹⁷ the smaller bone is probably loaded by a proportionally smaller load (weight, muscle mass). The load per unit cross-sectional area may then be no different between Asians and Caucasians.

If periosteal apposition is greater in Asians than Caucasians, and if bone loss is less in Asians than Caucasians, then fewer Asians will be at risk for fracture because fewer develop structural abnormalities that predispose to structural failure when loading occurs. There are no studies comparing these surface specific effects by

ethnic groups and it is unknown whether the absolute amount of bone lost during ageing is similar by race or whether it is less in Asians compared to Caucasians. If it is less, is this because remodelling rates are lower or is it because BMU balance is less negative? What are the relative changes in the periosteal apposition across age? Do Asians have greater periosteal apposition than Caucasians? Is this sex specific or site specific? Answers to these questions are unavailable.

Whether vertebral trabecular vBMD is different between Asians and Caucasians is also uncertain. One study reported that vertebral trabecular vBMD measured by QCT was lower in Japanese men compared to Caucasian men.⁹⁴ However, the small sample size and the use of different QCT machines made the data difficult to interpret.⁹⁴ Many studies have confirmed that after accounting for racial differences in body size, most of the differences in aBMD disappear.^{60,98-100}

Reduced Bone Formation in Asian and Caucasian Men

Increased bone resorption due to oestrogen deficiency contributes to bone loss in postmenopausal women. There is no midlife acceleration of bone loss in men. Reduced bone formation rather than increased bone resorption is likely to contribute to bone loss in men. Most of the histomorphometric studies report that trabecular bone loss occurs mainly by thinning, while the trabecular connectivity is largely preserved in elderly men.^{81,101-103} These data favour reduced bone formation as the cause of trabecular thinning.

Francis et al¹⁰² reported that advancing age was associated with decreased osteoid surfaces and osteoid seam width while eroded surfaces was unchanged with age. These suggest bone formation was reduced with no change in bone resorption. Clarke et al¹⁰⁴ studied 43 healthy men between the ages of 20 to 80 years; cancellous bone volume and osteoblast-osteoid interface decreased by 40.0% and 19.2%, respectively. Double and single-labelled osteoid also decreased by 18.6% and 18.0%, respectively, suggesting that the osteoblastic activity declines with age while osteoclast surfaces remain unchanged. These data imply that the age-related bone loss in men may be the result of reduced bone formation with ageing.

Increased bone resorption markers with age have been reported in several studies.^{105,106} However, most investigators report no age-related increase in bone resorption markers while bone formation markers decreased with age in healthy men.^{104,107-109} Serum osteocalcin declined with advancing age in a cross-sectional study of healthy men aged 20 to 85 years, while total and free deoxypyridinoline, a specific marker of bone resorption, did not change with age.¹⁰⁴ In a cross-sectional study of 147 healthy men aged 20 to 83

years, bone formation and resorption markers decreased with age.¹⁰⁷ Orwoll et al¹⁰⁸ reported that N-telopeptide excretion (NTX) was not increased in healthy men aged 21 to 86 years. Fatayerji and Eastell¹⁰⁹ reported that markers of bone formation and resorption were the highest in young men, with no increase in older men.

Reduced bone formation rather than increased bone resorption may also be largely responsible for the bone loss in Asian men. Cross-sectional studies on biochemical markers suggest that bone formation markers were reduced while bone resorption markers were not increased in men.¹¹⁰⁻¹¹² Tsai et al¹¹⁰ reported that both bone formation and resorption markers decreased with age in healthy Chinese men. Sone et al¹¹¹ measured urinary NTX in 238 men and 214 women between the ages of 20 to 79 years from a healthy Japanese population, and reported no change with age in men but an increase in women. Yoshimura et al¹¹² reported that markers for bone formation and resorption were unchanged with ageing in men, but increased with age in older women (Fig. 6). Whether the reduced bone formation is associated with trabecular thinning rather than the loss of connectivity in Asian men during ageing is unknown.

Both increased or decreased bone remodelling is reported in Caucasian men with vertebral or hip fractures.¹¹³⁻¹¹⁵ No studies have been done in Asia using histomorphometric or biochemical measurements of bone remodelling in Asian men with spine or hip fractures.

Sex Hormones and Ageing

Androgens

Declining gonadal function with ageing is widely reported in men and is caused by primary gonadal failure due to the decreased numbers and volume of the Leydig cells and impaired hypothalamic-pituitary function.¹¹⁶ Both serum testosterone (T) and free (bioavailable) T decline with age.^{105,117} As serum sex-hormone-binding globulin (SHBG) increases with age, serum free T declines more greatly than total T.¹⁰⁵ Khosla et al¹⁰⁵ reported that serum total T decreased by 30% and bioavailable T decreased by 64% in a cross-sectional analysis of 346 healthy men. Using total T criteria, the incidence of hypogonadal T increased to about 20% in men over 60, 30% in men over 70, and 50% in men over 80 years of age, and even greater percentages were reported using free T index.¹¹⁸

Several studies suggest a positive relationship between serum T and aBMD,^{107,119-121} whereas others have not shown this association.^{105,122,123} There are no prospective studies showing a positive relationship between T and the rate of bone loss in men, and no studies showing that men with low T have rapid bone loss. Hypogonadal men have lower aBMD and increased risk of fracture.^{124,125} Men with spine

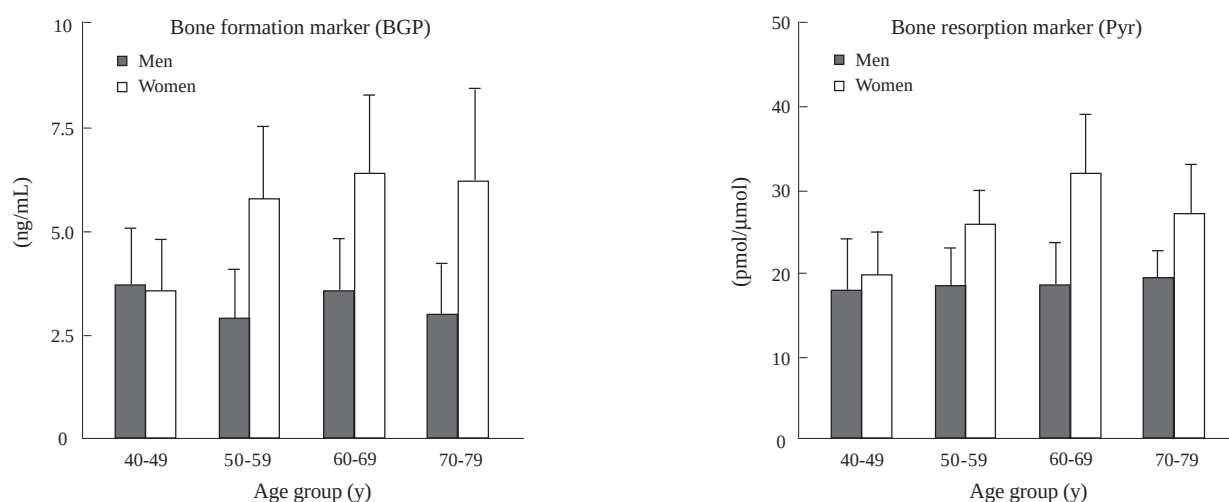


Fig. 6. Biochemical markers of bone formation and resorption did not increase with age in men but increased in postmenopausal women in Japan. Adapted from Yoshimura et al.¹¹²

or hip fractures also have a higher prevalence of hypogonadism.^{126,127} Boonen et al¹¹⁵ reported that men with recent hip fractures have reduced T compared to age-matched controls (164.3 ± 88.3 vs 447.5 ± 181.4 ng/dL, $P < 0.001$). Our preliminary data show that among the 120 randomly sampled elderly healthy men aged 60 years or over, 20% have serum T below 10 nM, the lower limit of the young normal range. About 43% of men with hip fractures have T level below the low normal range (10 nM/L).¹²⁸

In Thailand, Ongphiphadhanakul et al¹²⁹ reported that free T but not estradiol decreased with age in healthy men. No association between T and aBMD was detected. No association between total T and aBMD was reported in a smaller group of healthy elderly Japanese men, with a mean age of 74 years, despite the lower T.¹³⁰

There are many unresolved issues. Is hypogonadism more prevalent in Asian men with vertebral or hip fractures? Is reduced bone formation reported in Asian men due to reduced T? What factors regulate the gender difference in periosteal apposition during ageing in Asians? At what level of T or oestrogen (E2) below a critical threshold value causes increased remodelling and a negative BMU balance? What are the structural abnormalities caused by hypogonadism? Is the low T associated with greater loss of cortical thickness, trabecular thinning or trabecular disruption?

Oestrogens

Recent studies suggest that E2 deficiency plays a role for achievement of peak bone mass and age-related bone loss in men. Serum E2 decreases with age in elderly men.^{105,106} Khosla et al¹⁰⁵ reported that serum bioavailable E2 decreased by 47% in the elderly men. Low E2 but not T level is associated with low aBMD in elderly men.^{105,123}

The age-related fall in bioavailable E2 may contribute to

bone loss in men by increasing bone remodelling and worsening BMU balance. In the study by Khosla et al,¹⁰⁵ bioavailable E2 correlated inversely with serum osteocalcin ($r = -0.26$, $P < 0.001$) and urinary NTx ($r = -0.12$, $P < 0.05$). Szulc and colleagues¹⁰⁶ reported that bioavailable E2 correlated inversely with bone resorption markers, adjusting for age and weight (β CTX: $r = -0.20$, Dpyr: $r = -0.14$, both $P < 0.01$). Bone markers were about 11% and 35% higher in men with lowest quartile of bioavailable E2 compared with those in the highest quartile. These data suggest that low bioavailable E2 is associated with high bone turnover and rapid bone loss in elderly men.

There is only one study done in Asians reporting that E2 was independently associated with aBMD at the spine, femoral neck, trochanter, and Ward's triangle ($r = 0.22$ to 0.26).¹²⁹ However, the data in that paper were difficult to interpret because total E2 did not decrease with age. Whether serum free E2 decreased with age was not reported.

E2 deficiency may be more prevalent in men with vertebral fractures.¹³¹⁻¹³⁴ Carlsen et al¹³¹ reported 42 men with primary osteoporosis with either vertebral fractures or aBMD below -2.5 SD, 33% of the patients E2 were in the low or undetectable range, while only 3% had T below the normal range. Barrett-Connor et al¹³² reported that low E2 was associated with higher prevalence of vertebral fracture in men but not in women. However, no association between E2 and vertebral fracture in men has not been detected in several studies.^{95,102,113,135} There is also no evidence showing men with hip fracture have low E2 compared to age-matched controls without fracture.¹¹⁵

Relative Contribution of Oestrogen and Androgen

Oestrogen may be important for trabecular bone while

androgen may be important for cortical bone. Androgen receptors are more prevalent in cortical bone than in trabecular bone, suggesting that trabecular bone may be less of the androgen target region.¹²⁵ The lower E2 may explain why men with vertebral fractures have lower vertebral trabecular BMD and architectural disruption, while the lower androgen may explain why men with hip fracture have reduced femoral neck width and reduced cortical thickness as androgen may regulate periosteal bone formation.^{96,135}

Oestrogen may regulate remodelling rate and bone resorption, whereas both oestrogen and testosterone are important in maintaining bone formation in ageing men.¹³⁶ The imbalance of bone remodelling caused by reduced bone formation may be mediated by androgen deficiency. Androgens are likely to account for the larger peak bone width in men than women during growth. Whether androgens account for greater periosteal expansion with ageing in men is unknown. Animal data suggest that androgen deficiency during growth and ageing is associated with smaller bone size due to the reduced periosteal apposition.¹³⁷⁻¹³⁹ Oestrogen inhibits periosteal apposition during growth. The slowing periosteal expansion and endocortical bone formation during puberty in girls may be mediated by oestrogen.⁴³ Oestrogen may also regulate long bone length during growth as oestrogen deficiency caused by oestrogen receptor mutations and aromatase deficiency in young man is associated with epiphyseal patency and increased leg length.^{140,141}

Summary and Conclusion

The incidence of hip fractures is lower in men than women in most countries. The incidence of hip fractures is lower in Asian than Caucasian men (and lower in Asian than Caucasian women). For vertebral fractures, data are sparse and less reliable because the information is largely based on prevalence rather than incidence figures with insufficient attention to defining 'fracture'. Vertebral fracture prevalence data are difficult to interpret as traumatic fractures in youth are more common in men than in women and will be falsely assumed to be due to bone fragility. This may be partly why many prevalence studies report similar or higher prevalence of vertebral fractures in men than in women for both Caucasian and Asian communities, while incidence studies in Caucasians report that vertebral fractures occur less commonly in men than in women. There are no vertebral fracture incidence data in Asians.

Within a racial/ethnic group, the reason peak aBMD is higher in men than women is mainly the result of gender differences in bone size. Likewise, within a gender, the higher aBMD in Caucasian than Asian males is largely the result of differences in bone size, not density. Peak femoral

neck and vertebral vBMD is no different in male and female Caucasians but there is some evidence that vBMD at the spine, but not hip, is lower in female than male Asians. This needs verification. If correct, whether this is due to differences in trabecular number or thickness or both should be determined. Whether peak vBMD at the hip or spine differs in Asian and Caucasian men (or Asian and Caucasian women) is uncertain.

Net bone loss is less in Caucasian men than in Caucasian women due to greater periosteal apposition in men. Whether this is so in Asians needs to be studied. Asians have shorter leg length and hip axis length (HAL) than Caucasians, which may contribute to the lower risk of hip fractures in Asians compared to Caucasians. Reduced bone formation as well as increased bone resorption is responsible for the age-related bone loss in Asian and Caucasian men. No study has been done using histomorphometric and biochemical measurements to determine whether there is a parallel change in remodelling between gender or racial groups.

Caucasian men and women with vertebral or hip fractures have similar vBMD at the fracture site. Whether Asian men and women with fractures have similar vBMD to each other, and to the corresponding Caucasian gender with fractures, is not known. The prevalence of hypogonadism is unknown in Asian men. Studies of anti-fracture efficacy using drugs are needed in Asian men.

Comparative studies are needed in almost every aspect of the skeletal metabolism: the epidemiology of fractures, the pathophysiology of skeletal growth and ageing, the hormonal regulation of growth and ageing and the effects of drug therapy. However, these studies require careful design and attention to methodological issues so that endpoints observed in one country, gender or racial group can be validly compared with endpoints in another region. Until these studies are done, it will not be possible to make credible causal inferences regarding observed gender and racial differences in skeletal mass, size and architecture, the hormonal regulators of these structures, and corresponding gender and racial differences in fracture rates.

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