

# Epidemiology and management of osteoporosis in the People's Republic of China: current perspectives

Xiao Lin<sup>1</sup>  
Dan Xiong<sup>1</sup>  
Yi-Qun Peng<sup>1</sup>  
Zhi-Feng Sheng<sup>1</sup>  
Xi-Yu Wu<sup>1</sup>  
Xian-Ping Wu<sup>1</sup>  
Feng Wu<sup>2</sup>  
Ling-Qing Yuan<sup>1</sup>  
Er-Yuan Liao<sup>1</sup>

<sup>1</sup>Institute of Metabolism and Endocrinology, <sup>2</sup>Department of Pathology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

**Abstract:** With the progressive aging of the population, osteoporosis has gradually grown into a global health problem for men and women aged 50 years and older because of its consequences in terms of disabilities and fragility fractures. This is especially true in the People's Republic of China, which has the largest population and an increasing proportion of elderly people, as osteoporosis has become a serious challenge to the Chinese government, society, and family. Apart from the fact that all osteoporotic fractures can increase the patient's morbidity, they can also result in fractures of the hip and vertebrae, which are associated with a significantly higher mortality. The cost of osteoporotic fractures, moreover, is a heavy burden on families, society, and even the country, which is likely to increase in the future due, in part, to the improvement in average life expectancy. Therefore, understanding the epidemiology of osteoporosis is essential and is significant for developing strategies to help reduce this problem. In this review, we will summarize the epidemiology of osteoporosis in the People's Republic of China, including the epidemiology of osteoporotic fractures, focusing on preventive methods and the management of osteoporosis, which consist of basic measures and pharmacological treatments.

**Keywords:** osteoporosis, fracture, epidemiology, management

## Introduction

Osteoporosis (OP) can be defined as a systematic skeletal disorder characterized by low bone mass and the microarchitectural deterioration of bone tissue, with a consequent increase in the fragility of bone and susceptibility to fracture. OP can be classified into two main categories: primary OP and secondary OP. The former can occur in both males and females of all ages, but it often occurs in postmenopausal women; it also happens later in life in men. By contrast, secondary OP is the result of medication use (glucocorticoid, immunosuppressant), disease (Cushing's syndrome, hyperparathyroidism), other conditions (vitamin D deficiency and hypogonadism), and so on.<sup>1</sup> Nowadays, OP has become a serious problem throughout the world.<sup>2</sup> In developed countries, for example, the prevalence rate of OP in older adults was about 13%–18% and 21.2% in the United States and Sweden, respectively.<sup>3,4</sup> In the People's Republic of China, however, the mean prevalence of OP in older adults is estimated at 15.7%, and it is considered to be increasing gradually with the increasing age of the total population, which is associated with the improvement of the average life expectancy. Since there were about 202.43 million people aged 60 years and older in the People's Republic of China at the end of 2013,<sup>5</sup> the People's Republic of China will carry a large proportion of the financial burden of OP. Moreover, because of the family planning policy in the People's Republic of China, the ratio of older people is likely to increase significantly in the coming years.

Correspondence: Ling-Qing Yuan; Er-Yuan Liao  
Institute of Metabolism and Endocrinology, The Second Xiangya Hospital, Central South University, No 139 Middle Renmin Road, Changsha, Hunan 410011, People's Republic of China  
Email allenylq@hotmail.com; eyliao@21cn.com

Osteoporotic fracture related to OP is also a huge global problem. The main categories of osteoporotic fracture are: hip fracture, vertebral fracture, and distal forearm fracture. There are also other bone sites where osteoporotic fractures appear (tibia, ribs, pelvis, humerus, clavicle, fibula, etc). The cost of osteoporotic fracture, especially hip fracture, is so huge that it will have an impact on many families. Therefore, OP has received much attention in many countries of the world.<sup>6,7</sup>

For the management of OP, there are two types of methods. One includes basic measures such as physical exercise, changing to a healthy lifestyle, quitting smoking, supplementation of calcium and vitamin D, and so on. The other type is pharmacological treatment, and the two main categories available so far for treating OP are antiresorptives and anabolic drugs.<sup>8,9</sup> However, Chinese herbal medicine is an alternative choice that is very popular in the People's Republic of China. Therefore, this review will summarize the epidemiology and treatment of OP in the People's Republic of China.

## Definition of OP

The definition of OP can be defined in three different ways. The medical definition is that OP is a skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue with an increase in fragility of bone, and a tendency to fracture easily. The most widely used method is the clinical definition proposed by the World Health Organization (WHO) in 1994, which is defined as bone mineral density (BMD) measurements in women that have fallen by more than 2.5 standard deviations (SDs) below the young average value.<sup>10</sup> In addition, pain, kyphosis, loss of height, and a history of fragility fracture are used as operational definitions of OP.<sup>11</sup> Therefore, in defining OP, it is important to consider both the strength of the bone and risk of fractures.

## Diagnosis of OP

A clinical diagnosis should be made of individuals who sustain a low-trauma or fragility fracture. Currently in the

People's Republic of China, the most commonly used method for the diagnosis of OP is established by measuring BMD by dual-energy X-ray absorptiometry (DEXA) according to WHO diagnostic criteria.<sup>12,13</sup> Based on the T-scores derived from BMD measurements of the total hip or neck of femur, the diagnosis is classified as normal, osteopenia, or OP (Table 1).<sup>10,14</sup> However, for economic reasons, only the big hospitals in large cities such as Beijing, Shanghai, and some provincial capitals are equipped with DEXA equipment, which hinders the diagnosis, prevention, and treatment of OP. Research conducted in Beijing validated the OP Self-assessment Tool for Asians (OSTA) as a simple and effective tool for identifying primary OP in postmenopausal Han Chinese women. It is a calculator based on the age and body weight using the following formula:

$$[\text{body weight (kg)} - \text{age (year)}] \times 0.2.^{15}$$

## Epidemiology of OP in the People's Republic of China

The People's Republic of China has a population of more than 1.398 billion, which is 18.84% of the world's population.<sup>16</sup> Though the annual rate of growth has dropped from 1.69% in 1996 to 1.20% at present,<sup>17</sup> the population will continue to increase gradually with the improvement of residents' living conditions, increased average life expectancy, and the development of a social health care system. People older than 60 years accounted for 6.10% of the population in 1964 and 10.97% (about 130 million people) at the end of the 20th century; according to the Sixth National Population Census of the People's Republic of China, it was 13.26% (about 177 million) in 2010, with those older than 65 years accounting for 8.87% of the population. Recently published data indicates that 15% (202.43 million) are older than 60 years in 2013.<sup>18</sup> Furthermore, this percentage is anticipated to reach 25% (about 400 million) by 2050.<sup>19</sup> Because of this, it has been estimated that the population with OP will increase sharply from 83.9 million in 1997 to 212 million by 2050.<sup>19</sup>

**Table 1** World Health Organization criteria for the diagnosis of osteoporosis

Diagnosis categories	Definitions
Normal	BMD within 1 SD of the young adult mean value (T-score $\geq -1.0$ )
Osteopenia	BMD $> 1$ SD below the young adult mean, but $< 2.5$ SD below this value ( $-2.5 < \text{T-score} < -1.0$ )
Osteoporosis	BMD $\geq 2.5$ SD below the young adult mean value (T-score $\leq -2.5$ )
Severe (established) osteoporosis	BMD $\geq 2.5$ SD below the young adult mean value (T-score $\leq -2.5$ ) and in the presence of $\geq 1$ fragility fractures

**Note:** Data from World Health Organization Study Group,<sup>10</sup> and Kanis et al.<sup>14</sup>

**Abbreviations:** BMD, bone mineral density; SD, standard deviation.

All of this makes OP a major public health problem in the People's Republic of China.

There are regional differences in the distribution of OP in the People's Republic of China. A survey by Li et al<sup>20</sup> was conducted in five areas of the People's Republic of China including the north (Jilin), south (Guangdong), east (Shanghai), northeast (Beijing), and southwest (Chengdu), which involved 5,593 Chinese of Han nationality selected by the stratified multistep cluster sampling method in 2002. BMD was measured and questionnaires were taken among people aged over 40 years and it was found that the prevalence rates of OP (in descending order) are as follows: Jilin (15.1%); Shanghai (14.2%); Chengdu (11.3%); Guangdong (10.2%); and Beijing (5.2%). The differences might be due to environmental, nutritional, and genetic factors. In our previous study, the relationship between body composition and fracture risk using the Fracture Risk Assessment (FRAX) model in an urban sample of central south Chinese postmenopausal women showed that 37.5% suffered from OP.<sup>21</sup>

OP is mainly found in females. Epidemiologic studies have indicated that the incidence of OP in females aged 50–59 years have increased by 50%.<sup>22</sup> A large-scale study in Europe showed that OP affected only 3%–6% of men over 50 years old, but over 30% of women.<sup>2</sup> What is more, the gradient with which prevalence increases with age is steeper for females.<sup>2</sup> This phenomenon can also be seen in the People's Republic of China. A survey conducted in Hefei in the People's Republic of China showed that the ratio of females to males with OP is 1.61:1.0.<sup>23</sup> Most cases of OP occur in postmenopausal women, and the incidence increases with age.<sup>24,25</sup> The main reasons why women are at a higher risk of OP are as follows: 1) the speed of bone loss in women after menopause is much more rapid than in men because of a significant decrease in estrogen; and 2) women have a longer life expectancy than men.<sup>19</sup> In recent years, however, the prevalence and effects of OP in men has aroused the attention of researchers and health care professionals as the population ages, and up to 25% of men aged over 50 years will experience OP. Moreover, men had less knowledge of OP than women.<sup>26,27</sup> One study that investigated Chinese male's knowledge of OP in Macau observed that the group of men aged over 55 years scored significantly lower than women, according to the Osteoporosis Knowledge Assessment Tool (OKAT).<sup>28</sup> This result is in accordance with a study conducted in Hong Kong.<sup>29</sup> Supposedly, the situation in Mainland China should be similar. Unfortunately, suffering any osteoporotic fracture leads to a higher mortality rate in men than in women.<sup>30,31</sup> Therefore, it is time to highlight

the care of men's health; in connection with this, our team has established BMD reference databases for the diagnosis and evaluation of OP in the men of central southern China, which is important and useful for the detection of OP in men.<sup>32</sup> There have been few large-scale studies or surveys on male OP sufferers in Mainland China, and it is necessary and urgent to attach importance to men's bone health as well as women's.

## Importance of osteopenia

Osteopenia occurs as the precursor of OP when BMD T-scores are between  $-2.5$  and  $-1.0$ , according to the WHO diagnostic standard.<sup>14</sup> About 64.6% (~11.35 million) of women and 57.6% (10.04 million) of men aged 50 years or older experienced osteopenia according to statistical data from the National Health and Nutrition Examination Survey for the years 2005–2006.<sup>18</sup> Unlike the prevalence of OP in men, over 30% of men aged 50 years or older have osteopenia, which is just a little lower compared to the prevalence of OP in women. The prevalence of osteopenia, however, increases more quickly with age among elderly men compared to women.<sup>33</sup> Furthermore, it often takes several years for osteopenia to transition to OP, sometimes just 1 year for individuals with rapid severe bone loss osteopenia, and it can also lead to fragility fractures causing physical limitations, substantial morbidity, mortality, hospital care, and so on.<sup>34</sup> In the People's Republic of China, there has been hardly any research studying the prevalence of osteopenia and its influence on populations. There was a survey about the prevalence of osteopenia in elderly patients with psychiatric disorders in Huzhou, People's Republic of China, which showed that the prevalence of osteopenia was 33.3% and that male patients had a higher rate of osteopenia than females (42.1% versus 28.1%, respectively).<sup>35</sup> The reason for this phenomenon may be that most females developed OP (53.1% versus 5%), whereas a substantial proportion of males suffered from osteopenia. It is necessary and important to discover and even predict the risks of osteopenia, since the majority of fractures actually take place in osteopenic subjects. Because of that, the patients may be treated and preventive steps can be taken earlier to greatly decrease the rate of morbidity and mortality related to osteoporotic fractures.

## Epidemiology of osteoporotic fracture

Osteoporotic fracture, one of the most severe complications of OP, is prevalent among the elderly population with OP. It is considered to be a fracture from low-energy trauma

that is defined as a fall from a standing height or less, or a trauma that would not give rise to fracture in a healthy individual.<sup>36</sup> OP causes more than 8.9 million fractures annually worldwide – approximately 1,000 cases per hour.<sup>37</sup> In the People's Republic of China, the risk of osteoporotic fractures (40%) in women is higher than the sum of the incidence of breast cancer, endometrial cancer, and ovarian cancer, while in men (at 13%), it is higher than the risk of prostate cancer.<sup>38</sup> A cross-sectional and population-based study conducted in Shanghai showed that the prevalence of osteoporotic fractures in the elderly was 15.9% in females and 14.3% in males.<sup>39</sup> A large national study in Beijing found that the prevalence of fractures was 26.6%.<sup>40</sup> In rural areas, the total prevalence rate of OP among the population over 60 years old was 8.83%,<sup>18</sup> and a rate of 14% was reported in a local study of Chongqing City.<sup>41</sup> In addition, there have been two studies related to fracture rates in Hong Kong: one reported that 30.4% of old men had at least one low-trauma fracture,<sup>42</sup> while the other reported that the rate of a history of fractures among those over 50 years old was just 6.6%.<sup>43</sup> The differences in the study samples and data collection methods may explain the huge discrepancy. The BMD measured by DEXA is the gold criterion for OP diagnosis, and it is the most available predictor of fracture in clinical practice. The risk of osteoporotic fracture increases constantly, as BMD T-scores decline from  $-1.5$  to  $-3$  SD;<sup>44</sup> that is to say, the lower the BMD, the higher risk of fracture will be.

BMD, however, is not the only risk factor in fracture, since fracture can also happen in the absence of OP,<sup>45</sup> maybe because of deterioration of bone quality. It is well known that bone strength is measured by both BMD and bone quality. Also, fall risk and other clinical risk factors are important in fracture prediction. Another tool for predicting the risk of fracture is the FRAX model, developed from the data of nine cohorts around the world, which uses clinical risk factors, with or without BMD, to compute the 10-year probability of hip fracture or a major osteoporotic fracture.<sup>46</sup> In Asia, there are different intervention thresholds within FRAX algorithms for some Asian countries and regions. Hong Kong researchers recommend using the Caucasian risk profile to calculate the absolute fracture risk for Hong Kong subjects.<sup>47</sup> However, when we use FRAX to estimate the 10-year risk of hip fracture in Chinese mainland women, the predicted fracture probability in Chinese mainland women was much lower than that for United Kingdom or Hong Kong Chinese women. Based on our previous study,<sup>48</sup> we have suggested that intervention in terms of both BMD testing and treatment should be recommended for individuals with a 10-year

probability of major osteoporotic fracture that exceeded 4.0% or a 10-year probability of hip fracture that exceeded 1.3%. Since osteoporotic fractures characteristically occur in the areas of the skeleton with high amounts of trabeculae, the most common types of osteoporotic fractures are vertebra fractures. The other two common types of osteoporotic fractures are hip and distal forearm fractures, all of which have their own respective characteristics. Other sites for osteoporotic fractures, including the tibia, pelvis, clavicle, ribs, and so on, have also received special attention in recent years.<sup>6,7</sup> The financial and health burden of osteoporotic fractures, especially hip fractures, is enormous in the People's Republic of China because of the size of the population. One study examined the health care costs of osteoporotic fractures in a hospital in Shanghai during 2002–2004 and found that the average hospital stay was almost 1 month, and the average total cost was around RMB 12,000 (about USD 1,929).<sup>49</sup> A similar phenomenon had been found in the Chinese capital, Beijing.<sup>50</sup> In fact, these data just reflect the cost and burden of osteoporotic fracture 10 years earlier. With the aging population and changes in people's lifestyle, both the number of OP cases and its complications (in terms of osteoporotic fracture) are coupled with a rapid increase in the total costs.<sup>51</sup> Next, we will discuss the epidemiology and characteristics of the three main categories of osteoporotic fracture.

## Hip fracture

Hip fracture is most likely to be a fatal result of OP, with devastating and expensive consequences because it causes both significant morbidity and excess mortality. The total annual number of hip fractures is expected to rise from 1.3 million in 1990 to 2.6 million by 2025, and 4.5 million by 2050 worldwide.<sup>52</sup> Asia accounted for almost half of this number, most notably in the People's Republic of China.<sup>53,54</sup> Surveys conducted in Beijing,<sup>55</sup> Shenyang,<sup>56</sup> and Tangshan<sup>57</sup> 20 years ago showed that the rates of hip fracture were 88.0, 67.2, and 12 cases per 100,000 women and 97.0, 80.8, and 25 cases per 100,000 men, respectively. The results of all three researches are very interesting, revealing that in the age range from 50 to 55 years, the incidence of hip fracture is higher in men than in women. This probably indicates that males of that age group mainly suffer from severe force fractures related to trauma.

The incidence of hip fractures, however, increases in both males and females with increasing age, especially in females. For instance, there was a dramatic increase in the incidence of hip fractures in the population of Tangshan by 85% in men and 306% in women from that in 1994, based on

the data from the Sixth National Population Census (2010).<sup>57</sup> The female to male ratio reversed to 1.03:1.0.<sup>58</sup> Analogously, the average annual number of hip fractures in people older than 50 years, according to the Beijing Ministry of Health, increased from 479 to 2,423 in women and from 441 to 1,586 in men between 1990 and 2004. In other words, the rates for those aged 50 years or older increased by 58% in women and 49% in men.<sup>59</sup> Similar trends can also be seen in other areas of the People's Republic of China including Taiwan,<sup>60</sup> Chongqing,<sup>41</sup> and Hefei.<sup>23</sup> The growth rate of osteoporotic fractures in urban women and men was 3.34% and 3.85%, respectively, and the same rates were 3.36% and 1.00% for rural areas between 2002 and 2006. It is expected on this basis to reach 626 per 100,000 men and 1,444 per 100,000 women by 2050. That is to say, there will be 5.91 million hip fractures in 2050 in the People's Republic of China.<sup>18</sup> In fact, the number of hip fractures is more than that in the People's Republic of China since hip fractures in rural areas, the vast majority of patients with hip fracture choose to rest at home instead of receiving surgical treatment due to economic reasons, which leads to the underreporting of hip fractures.<sup>18</sup> These results may relate to the fact that there is a larger number of women with OP than men, and that women have a rapid loss of bone after menopause. Furthermore, the number of hip fractures and its incidence will keep on increasing with the aging population, the development of urbanization, and the changing lifestyle of people who are less likely to walk and engage in outdoor exercise and instead rely more on cars and buses.<sup>38</sup> Though severe trauma accounted for a high proportion of total hip fractures, the vast majority, however, followed a fall from standing height or less in both men and women who have low bone strength.<sup>61</sup> But in Hong Kong, the age-adjusted incidence rate of hip fracture among people aged 65 years or older decreased from 381.6 per 100,000 men and 853.3 per 100,000 women in 2001 to 341.7 and 703.1 by 2009, respectively,<sup>62</sup> a trend that has also been observed in Western countries.<sup>63</sup> This trend might be replicated in Mainland China in the future, with increased awareness and knowledge of OP, the development of the economy, and improvements of the medical insurance system.

Osteoporotic hip fractures have numerous adverse outcomes and result in high mortality among the elderly population. A person who has survived hip fracture usually exhibits decreased mobility, impaired quality of life, more dependence on family, and increased demand for medical caregivers and social services, as well as a substantial physical, mental, and financial burden.<sup>64-66</sup> The rate of disability is up to 50% and the mortality is as high as 15%–33% in the

1st year after hip fracture.<sup>18,67</sup> What is worse is that about 28% of females and 37.5% of males die by the 2nd year.<sup>68</sup>

Among all types of osteoporotic fractures in the People's Republic of China, the cost of hip fractures is the highest. A prospective study of the economic burden of osteoporotic fractures in Western China showed that the annual total costs of hip fracture was RMB 27,283 (or USD 4,386) per person-year, followed by vertebral fracture (RMB 21,474, or USD 3,452). The annual rate of increase in cost is about 6%, and it is estimated that it will be five times of that by 2050, when the total cost for the whole country will reach RMB 1,800 billion (USD 288 billion).<sup>18</sup> Yet, the patients' average self-declared family income was only RMB 2,307±548 (or USD 371±88) per month.<sup>51</sup> The majority of the cost is associated with direct medical care costs because the average hospital stay for hip fracture is about 22–24 days. However, the nonmedical direct costs and indirect costs also cannot be ignored. The long hospitalization makes patients prone to develop acute complications including bronchopneumonia and urinary tract infections, which occupy more medical resources.<sup>69</sup> Therefore, an osteoporotic fracture is a considerable burden, not only on the individual and family, but also on the health service system and on the whole society in the People's Republic of China. Hence, understanding the etiology and risk factors for OP is important and significant in the prevention of hip fracture. Further research is needed to find new prevention methods and new therapies for hip fractures.

## Vertebral fracture

Despite being the most common complication of OP, accounting for almost 50% of all osteoporotic fractures, vertebral fractures have received less attention compared to hip fractures.<sup>70</sup> The transition site between the more rigid and more flexible part of the spine and the mid part of the kyphotic region of the thoracic spine are the common sites of vertebral fractures.<sup>71</sup> Although vertebral fractures are often coupled with back pain, height loss, and kyphosis, a large number of vertebral fractures are asymptomatic, and the difficulty in distinguishing the causes of these physical symptoms means that only 30%–40% vertebral fractures come to medical attention.<sup>72</sup> The wedge fracture is the most common type of vertebral fracture.<sup>73</sup> Nowadays, plain radiograph, computed tomography, and magnetic resonance imaging are the most common techniques for detecting vertebral fractures.<sup>74</sup>

Increasing age, increasing number of clinical risk factors, and decreasing BMD are related to the prevalence of vertebral fracture. Besides, the prevalence of vertebral

fracture is increasing in association with aging. The prevalence of vertebral fractures is lower than 20% for people aged 50–69 years in Beijing, Chengdu, and Shanghai, and that of people aged 70–79 years is 19%, 25.1%, and 25.42%, respectively. For people aged over 80 years, however, the prevalence of vertebral fractures is above 36% in all three cities.<sup>18</sup> Approximately 18.1 million new vertebral fractures occur every year in the People's Republic of China, and it is estimated that the total number of vertebral fractures will reach 367.5 million in 2020 and 485.0 million by 2050.<sup>18</sup> Research on the prevalence of vertebral fractures in Beijing indicated an incidence of about 15% among postmenopausal women, reaching 40% in women aged 80 years or older.<sup>75</sup> About 22% of subjects aged over 45 years were found to have vertebral fractures in Hong Kong, South China.<sup>76</sup> The incidence of vertebral fractures among Chinese women older than 65 years from Taiwan is 20%.<sup>77</sup> This incidence is similar to that found in Caucasian women.<sup>78</sup> For Chinese men aged over 50 years, the prevalence of vertebral fractures was about 14%. Generally, the incidence of vertebral fractures is similar to, or slightly higher, in Chinese women than in men in all age groups.<sup>20</sup>

The clinical consequences of vertebral fracture include chronic disabling pain, spinal deformity with round kyphosis, pulmonary dysfunction, loss of mobility, gross impairment in activities of daily life, psychosocial disturbance (notably depression), and excess long-term mortality.<sup>79</sup> The heavy financial burden brought about by vertebral fractures is another issue. The annual cost is USD 13.8 billion in the US,<sup>80</sup> and SEK 4.6 billion (USD 0.71 billion) in Sweden.<sup>81</sup> However, there is a lack of data on the cost of vertebral fractures in the People's Republic of China, but it is likely that the amounts involved would draw attention. Besides this, vertebral fracture is a risk factor for both future vertebral and nonvertebral fractures, such as hip fractures.<sup>82,83</sup> Therefore, understanding the prevalence of vertebral deformities and the risk factors for vertebral fractures would help doctors to make appropriate decisions and focus their attention on the diagnosis and prevention of OP, since the majority of vertebral fractures are independent of falls and are clinically silent.

## Distal forearm fracture

Distal forearm fracture has a different age distribution from vertebral or hip fractures. The incidence increases linearly from ages 40 to 65 years.<sup>84</sup> This may be related to the patterns of falling with advancing age. In general, about one-half of cases are due to tripping or slipping; these may be the most

frequent causes of falls among elderly patients. Another one-fifth are due to syncope, one-fifth to one-third are due to a loss of balance, and the remainder are the result of miscellaneous factors.<sup>85</sup> In men, however, the incidence rates stay relatively constant between the ages of 20 years and 80 years. The female to male ratio is about 4:1. The most common type of distal forearm fractures is the Colles' fracture, mainly caused by falling outdoors. The peak incidence of distal forearm fractures often occurs in winter, particularly during periods of icy weather.<sup>86</sup> Though less than 20% of distal forearm fracture patients are hospitalized, it does not appear to cause significant mortality compared with hip fractures;<sup>37</sup> the influence of this should not be neglected. In women with a distal forearm fracture, the functions related to the upper extremity (meal preparation, heavy housekeeping, shopping) and social roles will be limited in the early period after injury, and their psychological health will also be impaired.<sup>87</sup> In addition, the average cost of the 1st year after distal forearm fracture was approximately RMB 8,828 (or USD 1,419) per person in the People's Republic of China between 2010 and 2012,<sup>51</sup> and about 40% of the cost was for hospitalization. This characteristic is similar to that found in some developed countries.<sup>81,88,89</sup> Nevertheless, very few studies have been published so far on the incidence of distal forearm fracture in the People's Republic of China, and it needs much more technical and financial resources to conduct a comprehensive and complete epidemiological survey due to the large population involved.

## Risk factors for OP

Understanding the risk factors for OP is significant for several reasons: 1) it can help us to understand the pathophysiology of the disorder; 2) it can help in the treatment of individual patients; 3) it is available to support preventive strategies against OP and fractures; and 4) it can be helpful in decreasing the incidence of OP and fractures.

The risk factors for OP can be classified into different categories: general factors; body composition; lifestyle; dietary factors; genetic factors; and secondary factors (Table 2).

### General factors

Females are more likely to have OP, since estrogen loss takes place rapidly after menopause. As age is the absolute risk factor for OP, with advancing age, the incidence of OP obviously increases. Some studies have indicated that weight is a protective factor for OP, since it can protect against fracture by cushioning and absorbing the impact of a fall, and given that it reduces the likelihood of hip fracture due to falls.<sup>90,91,92</sup>

**Table 2** Risk factors for osteoporosis

Categories	Risk factors
General factors	Female Age Height Body mass index History of fragility fracture
Body composition	Fat mass Lean mass
Dietary factors	Vitamin D Calcium
Lifestyle	Sedentary or lack of exercise Cigarette smoking Alcohol drinking Caffeine
Genetic factors	<i>OPG, RANK, RANKL</i> <i>ESR1, LRP4, LRP5, BTB40, SOST</i> A family history of fracture
Medications	Glucocorticoids Immunosuppressants Heparin Anticonvulsants Thiazolidenediones Proton pump inhibitors
Diseases	Endocrine disorders Gastrointestinal diseases Hematologic diseases Other disorders

Our study, and another previous study, also showed that postmenopausal nonobese women with type 2 diabetes have a lower BMD and higher OP rate,<sup>93,94</sup> but now, more surveys are confirming that high body mass index (BMI) is also a risk factor for OP, especially for the overweight population. Another risk factor is height: tall people have a greater risk of OP than shorter individuals.<sup>95</sup>

## Body composition

Traditionally, body composition comprises fat mass and lean mass. Lean mass has been found to be positively associated with BMD at all bone sites, and it is a protective factor for OP.<sup>96</sup> But the relationship between fat mass and OP is, however, controversial.<sup>97,98</sup> There are different opinions about the different BMI levels and the distinct value criteria.<sup>99</sup>

## Dietary factors

Vitamin D deficiency status has been defined as having serum 25-hydroxyvitamin D (25[OH]D) levels <50 nmol/L (20 ng/mL).<sup>100</sup> The People's Republic of China covers a large area, and regions at different latitudes receive different amounts of sunlight, but in almost every city, the phenomenon of insufficient vitamin D status is found, including in Beijing,<sup>101</sup> Shanghai,<sup>102</sup> Shenyang,<sup>103</sup> Lanzhou,<sup>104</sup> and

even Hong Kong.<sup>105</sup> Our recent nationwide cross-sectional multicenter study of serum 25(OH)D levels among postmenopausal women in the People's Republic of China demonstrated that vitamin D deficiency and insufficiency are common among postmenopausal women in the People's Republic of China, especially during the winter and among those living in urban areas. Our study recruited 1,688 women with a mean age of 65.4 years, and our results showed that 61.4% of these postmenopausal women had a serum 25(OH)D level <20 ng/mL. The overall prevalence was 91.2% for 25(OH)D <30 ng/mL and 37.6% for 25(OH)D <15 ng/mL.<sup>106</sup> Many studies have shown that low vitamin D levels are associated with increased OP and fracture incidence.<sup>107–109</sup>

The main reasons for vitamin D deficiency are twofold: a lack of adequate exposure to sunlight; and shortage of a dietary vitamin D source. A Chinese diet based on plant proteins, apart from being low in calcium content, also lacks high vitamin D content.<sup>110</sup>

## Lifestyle

It is well known that physical activity is beneficial to the skeleton, and that the restriction of physical activity and immobility lead to bone loss.<sup>111</sup> However, with the economic development and improvement of people's living standards, a sedentary lifestyle that depends much more on cars and buses is popular among the Chinese, which is harmful to BMD. Moreover, mahjong is a very popular entertainment activity in the People's Republic of China, which results in long periods of sitting, even causing mahjong-related deep vein thrombosis.<sup>112</sup> In addition, cigarette smoking, alcohol drinking, and high levels of caffeine intake can decrease BMD in women and men, thus increasing the risk of OP.<sup>113,114</sup>

## Genetic factors

OP is a polygenetic disorder disease, and gene–gene interactions may play a key role in determining the risk of the disease. What is more, BMD is a highly heritable trait, with heritability estimated at 50%–80%.<sup>115</sup> Several susceptibility genes for OP, including *OPG, RANK, RANKL, ZBTB40, ESR1, LRP4, LRP5, MARK3, MHC, SPTBN1*, and *SOST*, have been revealed.<sup>116,117</sup> Moreover, six OP susceptibility genes (*ESR1, LRP5, OPG, RANK, ZBTB40*, and *SOST*) have been found to be associated with BMDs in a Han Chinese population,<sup>118</sup> and Li et al<sup>119</sup> found that *GALNT3* plays a role in the genetic susceptibility to OP among Chinese postmenopausal women. Besides, a family history of fracture is also associated with an increased risk of OP and fracture in an older population, particularly in older women.<sup>120</sup>

## Secondary factors

Factors causing secondary OP can be grouped into two categories: medications and diseases. Glucocorticoids are one of the most common medications to induce OP.<sup>121</sup> Other medications consist of immunosuppressants, heparin, anticonvulsants, thiazolidinediones, proton pump inhibitors, and so on.<sup>122</sup> Numerous diseases are known to cause bone loss and OP, including endocrine disorders (malnutrition, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hypogonadism), gastrointestinal diseases (primary biliary cirrhosis, Crohn's disease, hemochromatosis, inflammatory bowel disease, pancreatic diseases), hematologic diseases (multiple myeloma, systemic mastocytosis, leukemia, thalassemia, lymphoma), and other disorders (such as rheumatoid arthritis, stroke, depression).<sup>75,114</sup>

## Management of OP

OP is a condition that is often asymptomatic or even "silent" until a fracture occurs. Fracture, consequently, is always associated with significant morbidity, mortality, and a heavy economic burden. Therefore, attaching more importance to preventing and detecting younger patients and selecting appropriate treatment for those who are already affected is important in the prevention of OP-related fractures. Two kinds of methods are used in the People's Republic of China to decrease the risk of OP and its related effects: basic measurements and pharmacologic treatments.<sup>38,123</sup>

### Basic measurements

Basic measurements are indispensable for the prevention of OP and for decreasing the incidence of osteoporotic fractures. Basic measurements are not only suitable for the primary and secondary prevention of OP, but they can also be used during periods of drug treatment or rehabilitation therapy for OP for the entire population. The main basic measurements for preventing OP are as follows.

### Lifestyle adjustment

Lifestyle and patients' behavior are associated with OP and fractures. Tai Ji Quan or square dancing are popular among the Chinese people. Patients should generally avoid cigarette smoking, and the excessive consumption of alcohol and caffeine.<sup>113,114</sup> Moreover, tea is very popular with Chinese people, and previous studies have demonstrated that tea consumption is a protective factor in maintaining BMD.<sup>124</sup> However, the relationship between tea intake and the risk of OP and fracture is inconsistent.<sup>125–127</sup> A sedentary lifestyle

or inactivity, which accelerate bone loss, should be avoided among elderly people as much as possible.

## Nutrition counseling

To maintain bone health, adults should maintain a balanced diet that is rich in calcium, has adequate vitamin D, low salt, and appropriate amounts of protein. The Chinese Society of Nutrition recommends that 800 mg per day of calcium for adults is beneficial for obtaining peak bone mass in young people, and at least 1,000 mg per day for postmenopausal women and the older population.<sup>38</sup> Moreover, vitamin D is essential for the absorption of calcium, and there is increasing recognition of its critical role in bone health, so the supplementing of calcium must be coupled with vitamin D. Adequate exposure to sunlight is beneficial for the synthesis of vitamin D through the skin. A daily intake of 600–800 IU should be recommended for the older population and 800–1,200 IU for OP patients,<sup>38</sup> which is in accordance with the National Osteoporosis Foundation's recommendations.<sup>128</sup> The International Osteoporosis Foundation suggests that the level of 25(OH)D should not be below 30 ng/mL (75 nmol/L) in order to decrease the risk of falls and fractures.

Central obesity is a negative factor for bone metabolism. An inverse relationship has been found between the ratio of visceral adipose tissue/subcutaneous adipose tissue and BMD, which might be the result of obesity-induced chronic inflammation. However, weight reduction might not have a negative effect on bone metabolism when there is adequate calcium intake.<sup>129,130</sup>

### Physical exercise

Exercise plays an important role in the management of osteoporotic patients and can result in a myriad of positive benefits, such as the achievement of peak bone mass, a reduction in the risk of OP, and the building or maintenance of bone strength.<sup>131</sup> Weight-bearing, muscle-strengthening, and balance-training exercises are particularly helpful for improving agility, strength, posture, coordination, and balance, thus reducing the risk of a fall. Recommended activities include walking, jogging, aerobics, stair climbing, field or racquet sports, dancing, and Tai Ji Quan, a traditional Chinese martial art.<sup>79</sup> However, the severity and progression of the patient's bone loss, as well as the location of any previous fractures, should be taken into account. Hence, OP patients should avoid flexion-biased exercises such as abdominal crunches, lifting heavy weights, and excessive twisting or bending.<sup>132</sup>



### Reducing fall risk

Falling plays a critical role in most osteoporotic fractures, and fall prevention is important for patients with OP.<sup>133</sup> Fall prevention strategies involve checking and correcting vision problems related to age as quickly as possible, evaluating neuromuscular coordination and cognitive function, improving proprioceptive and vestibular systems, reviewing adverse effects of medications (dizziness, hypoglycemia, orthostatic hypotension) and promoting exercise.<sup>134,135</sup> Another factor that should be given more attention is environmental modification consisting of minimizing safety hazards in the home (installing grab bars/handrails near toilets, providing adequate lighting, providing appropriate shoes, altering slippery and wet surfaces, and eliminating obstructions).<sup>136</sup> In addition, some assistive devices, such as properly-fitted canes and walkers, and certain types of joint protectors are also useful to facilitate a steadier gait and reduce the risk of a fall.<sup>137</sup>

### Reasonable application of glucocorticoid and bone loss prevention

By using the equivalent of prednisone 5 mg/day for 3–6 months, BMD has been shown to decrease rapidly, and the risk of fracture has increased dramatically (relative ratio [RR] value: any fracture, 1.33–1.91; hip fracture, 1.61–2.01; vertebral fracture, 2.60–2.86; and forearm fracture, 1.09–1.13). Fractures induced by glucocorticoids have three characteristics:<sup>138,139</sup> first, the risk of fracture has nothing to do with age, sex, and basic diseases; second, hip or rib fracture can still occur even with the normal BMD, therefore, there seems to be no safe dose of glucocorticoid to avoid bone loss and fractures; and third, muscle weakness and myopathy can reduce the ability to balance, which leads to falling and fracturing easily.

The guidelines for the diagnosis and treatment of glucocorticoid-induced OP (GIOP) in the People's Republic of China point out that patients who require the long-term use of glucocorticoids should be measured for BMD every 6–12 months.<sup>140</sup> Glucocorticoid treatment is defined as less than 3 months for the short term, 3–6 months for the short-to-medium term, and more than 6 months for the long term.<sup>141</sup> The American College of Rheumatology recommended that patients treated with glucocorticoids (the equivalent dose to prednisone >5 mg/day) for more than 3 months should take the following treatment measures:<sup>142</sup> first, they should make improvements to their lifestyle (no smoking and drinking less); second, they should engage in appropriate weight-bearing exercise; third, they should take supplements of calcium and vitamin D; and fourth, they should take

bisphosphonates (however, premenopausal women should be careful). If patients require the long-term use of glucocorticoids, and there is an already existing risk for developing OP, preventive measures should be taken more imminently. Apart from improving lifestyle, engaging in appropriate weight-bearing exercise, and supplementing calcium and vitamin D, hormone replacement therapy (HRT) should be adopted in a timely way (when there is gonadal dysfunction or other clinical indications), and lumbar spine or hip BMD should be measured regularly.<sup>138</sup> When the BMD T-score is <–1, bisphosphonates should be given, and if the patients are contraindicated for or intolerant to bisphosphonates, we recommended teriparatide or denosumab as an alternative choice, but considering the price and convenience of the two drugs in the People's Republic of China, calcitonin becomes the second choice for most patients. If the BMD is normal, patients should be followed up every 1–2 years, coupled with a measurement of BMD.<sup>143</sup>

At present, agreement has not yet been reached in every country with respect to the prevention and treatment of GIOP, but all the guidelines point out that steps should be taken to measure BMD where there is long-term use of glucocorticoids.<sup>144–146</sup> Most opinions suggest that bisphosphonates should be taken as the first-line treatment with supplements of calcium and vitamin D, which are the basic drugs for primary and secondary prevention. In 2010, the American College of Rheumatology updated its guidelines for the prevention and treatment of GIOP, focusing on the following points:<sup>142</sup> first, when planning to use a glucocorticoid, measurements should be taken to prevent and treat GIOP, especially the timely supplementation of calcium and vitamin D; second, bisphosphonates, such as zoledronic acid, are the first choice of treatment; and third, common vitamin D is useful for decreasing the bone loss induced by low and medium doses of glucocorticoid, but it has no protective effect on OP induced by a high dose of glucocorticoid.

There are five aspects to the prevention of GIOP, which are set out as follows:<sup>138,143,147</sup> first, avoid the abuse of glucocorticoids as much as possible, and nonglucocorticoid medication should be taken as the first choice by patients. Second, choose the best dosage, usage, and course of treatment. Patients who are used to glucocorticoids should take topical remedies as much as possible in order to reduce the dosage and side effects of glucocorticoids. In addition, oral treatment should be taken as an alternative day therapy, so as to keep the feedback function of the hypothalamic–pituitary–adrenal axis. Third, treatment with the agents should be reduced, or even terminated, as soon as the disease is controlled, and

if patients need the long-term use of glucocorticoids, the lowest effective dose is recommended. In the past, a daily dose of 7.5 mg of prednisone (5 mg in the morning, 2.5 mg in the afternoon) was regarded as the “physiological” requirement, but many of these patients have also suffered from GIOP.<sup>148</sup> Multifactorial analysis has shown that 24-hour urinary cortisol/creatinine excretion is a good index to judge whether the cortisol is excessive or not, and it is a predictor of BMD. Fourth, a combination using antiosteoporotic drugs (for example, using bisphosphonates first, and then activated vitamin D or sex hormones) should be used to prevent GIOP. Last, BMD should be measured regularly.

### Suggestions for solving the problems faced by the People’s Republic of China concerning OP

In order to solve the problems that exist in the People’s Republic of China about OP, we proposed a number of suggestions, as follows: first, continue to increase the basis for and clinical study investment of preventing OP and improve the quality of research pertaining to the epidemiology of OP by governmental and nongovernmental methods. Second, strengthen the professional teaching of OP, have doctors engage in OP education as on-the-job continuing education training content (so as to improve the understanding of OP), and encourage medical staff to pay more attention to OP. Third, improve the ability to diagnose and treat OP by setting up specialized OP outpatient services, and offer different equipment (DEXA or ultrasonic instruments) according to different levels of hospitals and economic situations; if this is done, patients with back pain or osteoporotic fractures can be diagnosed and treated earlier. Fourth, enhance popular science education and improve the awareness of OP among people, especially those at high risk for OP. Most importantly, establish a healthy lifestyle of drinking more milk, engaging in more exercise, and increasing sun exposure, which is the key to increasing adolescent peak bone mass and maintaining young bone health.<sup>18</sup> Therefore, everyone should understand that no one is immune to OP, and that it is a silent disease that is present before a fragility fracture occurs, which people can do much to prevent.

### Pharmacologic treatment

The guidelines for the prevention and treatment of OP proposed by the Chinese Society of Osteoporosis and Bone Mineral Research (CSOBMR) in the People’s Republic of China<sup>38</sup> recommends pharmacological treatment for the following indications: 1) postmenopausal women and men aged 50 years or older (they should be considered for treatment if they have a hip or vertebral fracture, including a fragility fracture);

2) a Dual Energy X-ray Absorptiometry (DEXA) T-score below  $-2.5$  at the femoral neck or spine after excluding other secondary causes; 3) an osteopenic patient with a T-score of  $-1.0$  to  $-2.5$ , and with at least one risk factor for OP with or without fracture; and 4) an Osteoporosis Self-assessment Tool for Asians (OSAT) screening for high risk and a 10-year probability of a major osteoporotic fracture of at least 20%, or a hip fracture risk of at least 3% (based on FRAX).

The drugs approved by the State Food and Drug Administration for the treatment and prevention of OP can be classified into two categories: antiresorptive agents and anabolic agents. Antiresorptive agents include bisphosphonates, calcitonin, HRT, selective estrogen receptor modulators, and denosumab. Anabolic agents consist of teriparatide and intact parathyroid hormone (PTH), while another mixed bone-forming and anti-resorptive drug is strontium ranelate. Their specific effects on the prevention and treatment of OP are shown in Table 3. Besides, Chinese herbal medicine is a popular alternative treatment in the People’s Republic of China. The goal of all treatment is to build bone and reduce the risk of fracture.

### Traditional Chinese medicine

In the People’s Republic of China, people are looking for complementary or alternative medicines to treat OP. Traditional Chinese medicines have been used to treat bone-related diseases for thousands of years in the People’s Republic of China.<sup>149,150</sup> A study of their mechanisms has shown that some Chinese herbal medicines have an estrogen-like effect, which was considered to be due to phytoestrogens,<sup>151</sup> and they may induce osteoblast differentiation and osteogenesis.<sup>152</sup> It has been demonstrated that some Chinese herbal medicines have therapeutic anti-OP effects in animal models<sup>153,154</sup> or in postmenopausal women.<sup>155</sup> However, due to the lack of large multicenter samples and rigorous control studies to identify the anti-OP effect of Chinese herbal medicines, they have only been recommended as alternative or supplementary medications for OP treatment at the present stage. It is well known that there are plenty of natural resources with an osteogenesis effect, either in the form of medicinal herbs or bioactive components. Further work should therefore be done to investigate their mechanisms and adverse effects by means of clinical investigations in a strict multicenter, randomized control study before their clinical use.

### Combination therapies

The combined application of antiosteoporotic drugs is more complex, bearing in mind the interaction between drugs. By combining bisphosphonates and HRT, BMD increased

**Table 3** Medications for the prevention/treatment of OP

Categories	Agents	Indications	Dosage and method	Effects on BMD	Effects on risk of fractures	Side effects	Prevention or treatment
Antibiosorptive	Alendronate	PMOP, men's OP, and GIOP <sup>38,156</sup>	Oral 10 mg/day, 70 mg/week <sup>157</sup>	↑Lumbar spine and hip <sup>158</sup>	↓Vertebral, nonvertebral, and hip <sup>159</sup>	Bone, joint or muscle pain, inflammation of the eye, dyspepsia, esophagitis, and osteonecrosis of the jaw. <sup>160</sup>	Prevention and treatment <sup>38,156</sup>
	Residronate	PMOP, men's OP, and GIOP <sup>38,156</sup>	Oral 5 mg/day, 35 mg/week <sup>161</sup>				
	Zoledronic acid	PMOP <sup>38</sup>	IV 5 mg/year, <sup>162</sup>	↑Spine <sup>38</sup>	↓Vertebral <sup>163</sup>	Facial or hand flushing, rash, nausea, urinary frequency, rhinitis, epistaxis, headache, and back or joint pain <sup>79</sup>	Treatment, but not prevention
	Ibandronate	PMOP <sup>38</sup>	IV 3 mg/3 months <sup>163</sup>		↓Vertebral, nonvertebral <sup>38</sup>	Increasing fracture risk, cardiovascular, uterine cancer, breast cancer, stroke, and thromboembolic event risk <sup>165,166</sup>	Prevention and treatment
	Calcitonin	PMOP <sup>38</sup>	Nasal 200 IU/day or IM 50 IU/day <sup>164</sup>	↑Spine and hip <sup>38</sup>	↓Vertebral, nonvertebral <sup>38</sup>		
	HRT	PMOP <sup>38</sup>	Individualized dose				
	SERMs	PMOP	60 mg/day <sup>167</sup>	↑Spine and femoral neck	↓Vertebral <sup>168</sup>	Hot flushes, leg cramps, swelling, a flu-like syndrome, peripheral edema and vasomotor symptoms, and deep vein thrombosis <sup>169</sup>	Prevention and treatment
	Denosumab	PMOP	Subcutaneous injection 60 mg/6 months <sup>170</sup>	↑Lumbar spine and hip <sup>170</sup>	↓Vertebral, nonvertebral, and hip <sup>171</sup>	Hypocalcemia, skin infections, osteonecrosis of the jaw, and atypical femoral fractures <sup>172</sup>	Treatment
Anabolic	PTH and teriparatide	PMOP and men's OP	Subcutaneous injection 20 µg/day, less than 2 years <sup>172</sup>	↑Spine and hip <sup>173</sup>	↓Vertebral, nonvertebral <sup>173</sup>	Leg cramps, vertigo, pain, nausea, orthostatic hypotension, and a modest rise in serum and urine calcium <sup>174</sup>	Treatment
Combined Antiresorption with stimulated bone formation	Strontium ranelate	PMOP	Oral 2 g/day <sup>38</sup>	↑Lumbar spine, femoral neck, and total hip <sup>175</sup>	↓Vertebral, nonvertebral <sup>176</sup>	Headache, nausea, diarrhea and skin reaction syndrome, Stevens–Johnson syndrome, and toxic epidermal necrolysis <sup>79</sup>	Prevention

**Abbreviations:** OP, osteoporosis; BMD, bone mineral density; PMOP, postmenopausal osteoporosis; GIOP, glucocorticoid-induced osteoporosis; IV, intravenous; IM, intramuscular; HRT, hormone replacement therapy; SERMs, selective estrogen receptor modulators; PTH, parathyroid hormone.

more in the lumbar spine and hip when compared with either agent alone.<sup>177</sup> But several noted studies showed that the concurrent use of bisphosphonates and PTH attenuated the anabolic effects of PTH on BMD, rather than obtaining addictive effects in vivo and in vitro.<sup>178–180</sup> However, starting the drugs sequentially rather than simultaneously – that is to say, treatment with PTH several months before adding bisphosphonates – was associated with a greater and more rapid increase in BMD at the lumbar spine and hip.<sup>181</sup> Nevertheless, the combination of denosumab and teriparatide improved BMD at the spine and hip more than with either denosumab or teriparatide alone in patients with severe OP.<sup>182,183</sup> Further research is still needed to determine whether these combinations result in improved fracture protection, and their long-term safety implications should be considered.

## Future prospects

With an increase in life expectancy and the aging of the population in the People's Republic of China, the number of people with OP will increase greatly in future generations. This is coupled with a mounting number of osteoporotic fractures, which will have a far-reaching and devastating impact on the individuals themselves, and also on the health service, economy, and population as a whole because of the high rates of morbidity and mortality, and the heavy economic burden. Fortunately, many of the risk factors for this disease are well recognized, and models for predicting the probability of OP are currently being developed, making OP preventable. Moreover, measurements should be taken to prevent OP and enable therapy for OP to be provided. Other than the common drugs mentioned earlier, there are also some other osteoporotic drugs, such as novel selective estrogen receptor modulators (bazedoxifene),<sup>184</sup> antisclerostin antibodies (sclerostin),<sup>185</sup> cathepsin K inhibitors (odanacatib),<sup>186</sup> and stem cell therapy,<sup>187</sup> which act more directly on bone-forming pathways to enhance bone formation without provoking an osteoclast-mediated bone-resorptive response. It will take several years for these to be applied in clinical practice, however, before Phase III trials are finished. In fact, weighing the data on side effects, the cost of the drugs, the effects compared with the already available drugs, the risk rate of osteoporotic fractures, and the patients' perspectives are critical when making decisions about the treatment of OP. Of course, nonpharmacological interventions (adequate calcium and vitamin D supply, regular exercise, the prevention of falls, smoking cessation, limited alcohol intake, etc) are also important. Therefore, a good understanding of the

epidemiology of OP and osteoporotic fractures can help identify those at greatest risk and permit the appropriate targeting of treatment for the prevention of fractures. As with other chronic diseases, each patient should make a lifelong plan for OP prevention and treatment.

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## Disclosure

The authors report no conflicts of interest in this work.

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