

## What is needed to advance the treatment of osteoporosis in the UK?

Osteoporosis is a condition associated with a very significant personal and public health burden. Worldwide, osteoporotic fractures account for 0.83% of the global burden of noncommunicable disease. Despite recent huge advances, adherence to osteoporosis therapy is often poor. There has been a recent growing awareness of rare, but potentially serious, side effects that appear more common in patients who taken therapy for several years. This perspective considers the very significant advances we have made in management of this common condition in recent years, and more particularly highlights the areas where we remain uncertain about how best to advise our patients – and how to ensure that those individuals at highest risk are identified and treated.

**Keywords:** • adherence • algorithm • duration • fracture • osteoporosis • side effect • therapy

Osteoporosis is a condition that carries with it a very significant personal and public health burden. There are an estimated 1.5 million fragility fractures each year [1]. It has been reported that 10 million Americans over 50 years old have osteoporosis and a further 34 million are at risk of the disease. Health economists estimate that osteoporosis-related costs will double over the time period 2010–2050 in Europe; this means an increase in osteoporosis-related costs from 40 billion Euro in 2000 to almost 80 billion Euro in 2050 [2]. The condition is very common in older adults; studies from North America have estimated the remaining lifetime risk of common fragility fractures to be 17.5% for hip fracture, 15.6% for clinically diagnosed spine fracture and 16% for wrist forearm fracture in white women aged 50 years. Corresponding risks among men are 6, 5 and 2.5%. Data from the General Practice Research Database in the UK have indicated that the risk is similar in the UK [3]. Thus, one in two women and one in five men that are 50 years of age will have an osteoporotic fracture in their remaining lifetime. To put

these figures in context, the estimated lifetime risk of endometrial carcinoma for a 50 year old woman is 2.6%; for breast cancer 10%; for coronary heart disease 46% and for stroke 20% [4]. As the number of individuals who live to an age when fragility fracture becomes common increases worldwide, these figures seem set to rise exponentially, and with it the societal and personal costs. Regarding the latter, it is commonly reported that all osteoporotic fractures are associated with significant morbidity, but both hip and vertebral fractures are also associated with excess mortality. Osteoporotic fractures are responsible for 0.83% of the global burden of noncommunicable disease and 1.75% of the European burden, where osteoporotic fractures account for more disability adjusted life years than many other chronic noncommunicable diseases [5]. These figures may shock many people who have traditionally considered osteoporosis to be an inevitable (but not serious) consequence of aging.

Of course, we now have available to us diagnostic criteria for osteoporosis; fracture prediction algorithms that allow us to esti-

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mate the risk of a fracture over a ten year period, and effective therapies that have been proven in randomized controlled trial settings to increase bone density, and reduce fracture risk. Unfortunately we are also aware that, in common with many medications taken for silent, long term conditions, adherence is often poor. Clinicians and patients have also struggled with a growing awareness in recent years of rare, but potentially serious, side effects that appear more common in patients who have taken therapy for several years. This perspective considers the very significant advances we have made in management of this common condition in recent years, and more particularly highlights the areas where we remain uncertain about how best to advise our patients – and how to ensure that those individuals at highest risk are identified and treated.

### Treatment options currently available in the UK

Most patients require pharmacological therapy to reduce the risk of fracture, and we have at our disposal a plethora of current and future therapeutic agents. Treatment decisions should be based upon fracture risk; bisphosphonates remain the primary treatment of osteoporosis, with alternative agents including the RANK ligand inhibitor, denosumab, strontium ranelate (in some circumstances) and raloxifene. Teriparatide is the only anabolic agent currently available and improves bone architecture and decreases both vertebral and nonvertebral fractures, but is currently only available in those patients with severe osteoporosis who at highest risk of fracture.

The role of potentially modifiable lifestyle risk factors for osteoporosis should not be underestimated. Epidemiological data suggest that a sedentary lifestyle, tobacco smoking and a diet deficient in calcium can all potentially reduce bone density. All patients should be offered the opportunity to engage in a discussion about modify these risk factors as early as possible in their treatment pathway. Any potentially modifiable risk factor should be addressed where at all possible. It might be remarked upon, however, that although most clinicians would consider this good practice, and would certainly seem sensible, we have little in the way of trial evidence to confirm our practice [6]. For example, exercise intervention programs have on occasion increased fracture rates through an increased fall rate [7].

In the UK population it cannot be assumed that the adult population is receiving recommended amounts of calcium and vitamin D, especially elderly patients. This is likely to become a more prevalent problem as the population becomes more elderly. There have been numerous studies demonstrating that with opti-

mal calcium and vitamin D levels can increase bone density and also reduce fracture incidence. From one meta-analysis in postmenopausal women, an intake of elemental calcium of 1000 mg/day reduced fracture risk by approximately 30% [8]. Some other studies have also noted remarkable improvements in rates of hip and nonvertebral fractures being reduced by 43 and 32%, respectively, with an elemental calcium intake of 1200 mg/day and vitamin D 800 units/day [9]. However, the precise and absolute benefit of calcium and vitamin D in isolation and the potential extrapolation of any increase on bone mineral density (BMD) may not be completely clear; a meta-analysis of over 1806 participants in over 18 trials demonstrated that supplemental calcium alone increased mean total body bone density by 2.05% from baseline. This is encouraging, but a pivotal point from this meta-analysis is that nonvertebral fracture risk was not definitively reduced (relative risk [RR]: 0.86 [95% CI: 0.43–1.72]), even though the vertebral fracture risk was seemingly reduced (RR = 0.79 [95% CI: 0.54–1.09]) [10]. Recent reports that have linked calcium supplementation to an increased risk of cardiovascular disease have proved concerning [11], although more recent analyses have provided some reassurance [12]. Vitamin D deficiency has been reviewed in some depth over recent years and often strongly linked to risk of osteoporosis and fracture – particularly in postmenopausal women [8,13,14]. It is important to note that not all studies regarding vitamin D optimization necessarily translated to RR reduction in fracture, and that guidance about intakes varies very significantly internationally [15]. In general, further reassurance about the safety or otherwise of calcium supplementation would certainly be helpful for clinicians and patients alike, as would a clear strategy about how best to link vitamin D supplementation with a reduced fracture risk.

Of course, all notable randomized-controlled trials for other osteoporosis treatments were undertaken after calcium and vitamin D levels were optimized, and in highly selected patient populations – very different from the ‘real world’ in which we operate. Adherence to treatment with calcium and vitamin D supplementation remains an inherent problem of treatment and an ongoing challenge that we will discuss later.

As discussed previously, treatment with bisphosphonates forms the mainstay of drug treatment for osteoporosis in the UK. Commonly used bisphosphonates include alendronate, risedronate and zoledronate. As effective inhibitors of osteoclast action they reduce bone turnover, increase BMD and hence reduce fracture risk. There is good evidence for bisphosphonate use in cases of osteoporosis. Meta-analysis data (pooled for both alendronate and risedronate studies) resulted

in: RR of vertebral fracture of 0.58 (95% CI: 0.51–0.67, seven randomized controlled trials [RCTs],  $n = 9340$ ), a RR of hip fracture of 0.71 (95% CI: 0.58–0.87, six RCTs,  $n = 19,233$ ), a RR of wrist fracture of 0.69 (95% CI: 0.45–1.05, six RCTs,  $n = 1037$ ) and a RR for other nonvertebral fractures of 0.78 (95% CI: 0.69–0.88, eleven RCTs,  $n = 22372$ ) [16]. However, the major issues related to bisphosphonate use are essentially threefold: side effects, tolerability and adherence to therapy. Patients' reported side effects are mainly related to the gastrointestinal system and include nausea, dyspepsia, abdominal pain and gastro-oesophageal reflux disease. There is uncertainty as to whether the aforementioned side effects can be truly attributed to bisphosphonate therapy. Oesophageal erosion, ulcer or stricture formation is the more serious adverse feature that can largely be avoided with thorough counseling regarding the correct way in which the drug should be taken. As to whether bisphosphonate use can contribute to or cause oesophageal cancer is a point which remains unclear [17,18]. Furthermore, there is now a growing awareness of two other potentially serious side effects, one very uncommon (osteonecrosis of the jaw) and the other still rare (atypical femoral fracture) [19]. The emergence of concerns about the link between osteoporosis therapy and these conditions has heightened awareness of one of our very significant knowledge gaps – how long to treat patients for, as will be discussed later.

In recent years, we have seen the advent of a newer therapy, denosumab a fully monoclonal antibody with a different mechanism of action compared with the bisphosphonates. Denosumab has an affinity for the cytokine RANKL. By binding to RANKL the overall result is inhibition of osteoclast activation and thus a reduction in bone turnover. Denosumab is given as a subcutaneous injection once every 6 months. The FREEDOM trial demonstrated a statistically significant 68% reduction in RR of radiographically diagnosed vertebral fractures (over a period of 36 months on 6-monthly denosumab treatment). The nonvertebral fracture and hip fracture risks were also significantly reduced with a RR reduction of 20% (HR: 0.80; 95% CI: 0.67–0.95) and 40% (HR: 0.60; 95% CI: 0.37–0.97), respectively. Denosumab is hence clearly effective in reducing fracture risk [20] and because denosumab treatment is given as an injection, we have certainty around who has received treatment and when, another factor that will be discussed in greater detail later.

Until recently, there was a greater prominence of strontium ranelate in the therapeutic armamentarium. Although the mechanism of strontium ranelate action is not fully understood, several studies have demon-

strated that strontium ranelate acts as both an antiresorptive and a bone-forming agent. Strontium ranelate has been shown to be beneficial for patients with osteoporosis [21]. The evidence base is particularly related to postmenopausal women with reference to early and sustained reduction in rate of vertebral fracture. As well as this benefit, it has been postulated that strontium ranelate also decreases risk of nonvertebral fractures and increases bone mineral in postmenopausal women without osteoporosis.

However, there have been concerns raised over the safety of strontium ranelate with particular reference to an increased risk of cardiovascular disorders including myocardial infarction (RR compared with placebo 1.6, (95% CI: 1.07–2.38) [22]. In light of this potential increased risk, strontium is now reserved as an option for treatment in postmenopausal women with a high risk of fracture who are not suitable for bisphosphonate therapy and alternatively for men at an increased risk of fracture or when other modalities are deemed not appropriate or safe. The current recommendation for use of strontium ranelate includes monitoring for signs of evolving cardiovascular disease (including ischemic heart disease, peripheral vascular disease, cerebrovascular disease and uncontrolled hypertension). If any of the features arise, it is recommended that strontium ranelate is stopped. Prior to these concerns emerging, strontium was unusual because it had good randomized controlled trial data in elderly patients – a group often excluded and in whom these data are invaluable. As the proportion of the oldest old who will require treatment increases, it is increasingly important that we consider this in trial designs to ensure they are properly represented.

To consider a different agent, raloxifene is a second generation selective estrogen receptor modulator that works by acting as an antiresorptive agent. Raloxifene improves BMD when compared with a lesser degree as compared with other agents [23]. Interestingly, despite a lesser improvement in BMD as compared with other agents, raloxifene does demonstrate a similar effect in terms of a reduction in the rate of vertebral fractures, but no effect on the frequency of nonvertebral fractures.

Trials with fracture end points are very expensive because they require large numbers of patients. However, BMD is an imperfect surrogate as while highly correlated with fracture risk, there have been instances of very significant increase in BMD with unchanged, or even increased, fracture risk – the fluoride experience [24]. The ideal intermediate that we could adopt for use in cost effective trials would be easy to measure, responsive to drug therapy and a very good surrogate for fracture risk.

Finally, the therapies considered above are all antiresorptive agents. We have currently available to us only one anabolic agent – teriparatide – a recombinant fragment of human parathyroid hormone. Treatment normally lasts for a maximum duration of 2 years, carrying with it the question of when best to give the treatment, and what to follow it with. As with the other agents, teriparatide has been proven to be beneficial in osteoporosis in randomized controlled trials. One of the larger placebo-controlled trials found RR reduction of 0.35 (95% CI: 0.22–0.55) and 0.65 (95% CI: 0.43–0.98), for vertebral and nonvertebral fractures, respectively, with the use of teriparatide [25]. In the UK only patients with severe osteoporosis who have failed or are unable to take conventional antiresorptive drugs are considered to be eligible for teriparatide treatment according to NICE guidance, restricting their use considerably. It should be noted that the cost of teriparatide is also significantly greater than the previously mentioned treatments, which will inevitably limit its use.

### Who to treat?

Of course, any decision to embark on a chosen treatment needs to be taken carefully and in conjunction with discussion with the patient, particularly as many of the treatments are medium-long term and require patients' adherence in order to optimize the chances of improving BMD and improving fracture risk. Patient education and improving patients' understanding is vital to improving adherence and thus reducing risk of fracture.

Traditionally, decision to treat was based on BMD measurements, with individuals with a T score of  $-2.5$  below typically receiving treatment. However, in recent years there has been a significant advance through the advent of fracture prediction algorithms such as FRAX. While not without its limitations in terms of its mixed performance in different populations [26], this is a tool which is now commonly utilized in clinical practice in the UK, and allows the clinician to calculate the 10-year risk of a major osteoporotic or hip fracture, and to share this information with the patient. The hope is that this information is more intuitive than a T score. The primary parameters included in the FRAX tool assessment include clinical risk factors for osteoporosis that are easy to enter in primary care, information on personal and family prior fracture in addition to the (optional) BMD at the femoral neck. Many clinicians will link a calculated risk with NOGG guidance regarding treatment decisions. While the intervention threshold rises with age (30% fracture probability at age 80 compared with 7.5% at age 50), the proportion of women eligible for treatment rises from 20 to 40% with age, highlight-

ing the prevalence of osteoporotic fracture in the oldest old. While there is no doubt that these developments have very significantly advanced how we manage osteoporosis therapy in the UK, much work is still ongoing regarding how the FRAX tool might be further refined – should falls risk be included, or some other measure of functional performance, given studies suggesting that this may predict fracture independent of BMD [27,28], for example, or more information about comorbidities [29,30]? Most recent discussions have centered upon the incorporation of trabecular bone score, a recently derived analytical tool derived from lumbar spine DXA images [31].

Epidemiological studies have consistently shown that one of the strongest risk factors for future fracture is prior fracture [32]. However, despite this, numerous studies have shown that few patients leaving hospital after a fragility fracture have been initiated on osteoporosis treatment [33]. In response to this, fracture liaison services (FLS) have been successfully implemented across many parts of the UK. The concept of these services is to specifically identify and target those patients with a new fracture – one FLS reported that 80% of subsequent fractures happened in the first year post-index fracture, with 50% of these occurring during the first 6–8 months; dependent on whether the incident fracture was hip (6 months) or nonhip (8 months) [34]. In addition to identifying individuals requiring treatment, the FLS also aims to improve outcomes post fracture, by aiming to restore physical mobility and independence as well as promoting good bone health and lifestyle modification. Despite the limitations and requirements of a FLS (the expense and the need for a dedicated coordinator, or at least a coordinated strategy with integration of care across several care settings) the ability to identify individuals at high risk of fracture and initiate treatment that will be continued is clearly critical to our goal of successfully reducing the burden of osteoporotic fracture. The International Osteoporosis Foundation initiative 'Capture the Fracture' that allows services to apply for recognition and benchmarking of themselves against 13 standards that include patient identification and evaluation; falls prevention services and recording of fragility fracture patients in a database that feeds into a central national database has allowed us to begin to map provision of such services – and current trials will establish how effective such services are.

While secondary promotion (and ways of charting success in our efforts) is clearly very important, an effective primary prevention strategy is also paramount; the challenge is identifying an effective (and cost-effective) way to achieve this.

### How to encourage good adherence & compliance

Suboptimal adherence to prescribed medication is a common and well-recognized problem in chronic diseases, including osteoporosis, where persistence with medication such as bisphosphonates is known to be as low as 35% at 1 year [35]. Lack of adherence results in lack of protection from fragility fracture, and reasons for lack of compliance include lack of appreciation of risk, side effects experienced and concerns about side effects. A woman's perception of her own risk of fracture may reflect many things, including her personal or family experience of prior fracture. It may also reflect her awareness of health issues, a phenomenon well recognized in healthier, more educated women, often termed 'the worried well.' Previous work using the GLOW cohort has found that while a woman may accurately rank her own fracture risk relative to her peers, this tends to be an underestimate of her actual fracture risk [36], and may reflect her awareness of her personal risk factors that are captured in fracture prediction algorithms, such as prior fracture, family history, cigarette smoking and prednisolone use, or it may reflect other lifestyle factors that currently remain uncaptured in these commonly used clinical tools. The value of patient education programs in drug adherence and compliance was recently the focus of a systematic review [37]. Although patient education improved adherence to medication in four studies, two large randomized studies reported no benefit. The authors reported wide variation in quality of studies in the osteoporosis area. The efficacy of patient education was variable across studies, and might usefully be the subject of future study if we are to identify therapies to inform this important area.

### How to agree duration of therapy

Several studies have shown that short term use of existing osteoporosis therapies is effective treatment for reducing fracture risk, as has been discussed in some detail above. However, more uncertain is how best to manage some patients' long term, particularly given the highly variable pharmacodynamics of the agents currently available, ranging from those with very slow off-set, such as zoledronic acid, to those with shorter off-set such as risedronate, to those with almost immediate termination of effect upon cessation of therapy such as denosumab and risedronate. While limited evidence suggests that in postmenopausal women, long term use sustains increased bone mineral density, with bisphosphonates also maintaining a reduced incidence of vertebral and nonvertebral fragility fractures, the effects of discontinuing therapy have not been fully evaluated, although in the cases of alendronate

and zoledronate residual fracture benefits appear to extend another 3–5 years after discontinuing an initial 3–5 year treatment period [38,39], with more recent data suggesting that patients who have received six zoledronate infusions can stop treatment for 3 years with apparent maintenance of benefits [40]. We are increasingly aware that there are some risks associated with treatment; there is limited evidence that long-term treatment with bisphosphonates may be associated with increased risk of some side effects. However, to date trials have been underpowered to detect these rare events and thus the risks of long-term treatments remain unclear, particularly given recent data to suggest that 10 years of alendronate therapy was associated with minimal, transient bone tissue composition changes [41], and a recent systematic review suggesting that patients with low bone density who remain at high risk of fracture should remain on therapy for long term given the persisting benefits of therapy and low risk of side effects [42]. Given the paucity of well-designed randomized controlled trials to substantiate the long-term benefits and risks of bisphosphonates and denosumab for osteoporosis in postmenopausal women, future trials are warranted.

### Personalized medicine: the right drug for the right patient

Tailoring treatments to our patients are something which is not a new concept, but it is one which is evolving and becoming more important over time. There is now far more emphasis on creating a balanced two-way dialogue from the outset of any management pathway/medical decision making process (between patient and clinician). This approach is generally regarded as good medical practice and furthermore, it may serve to improve patient engagement and enhance adherence to treatment. However, beyond this layer of personalized care there currently appears to be a growing movement toward a far more sophisticated model of personalized medicine. Much of the work being undertaken in the area of personalized medicine now involves aiming to make management/treatment decisions based on information acquired from genetic and epidemiological studies.

The very essence that a single uniform treatment (and dose) will be equally effective for individuals of different nationalities, risk profile and medical backgrounds seem both improbable and potentially flawed. With particular reference to osteoporosis, studies have certainly demonstrated genetic associations [43] but it is not entirely certain whether these associations confer any additional clinical risk of fracture or morbidity. Moreover, whether these associations can be utilized to predict future morbidity or even response to pharmacological therapy is unclear.



Better understanding of the genetic and environmental associations and interactions that might be relevant in osteoporosis treatment are pivotal in developing a fully tailored and targeted approach to treating osteoporosis.

### New therapies

Treatments for osteoporosis over the last few decades have largely been comprised of antiresorptive agents designed to prevent bone loss. Teriparatide and PTH 1–84 are the only currently approved anabolic agents that primarily build new bone density. With the better understanding of the pathophysiology of the disease, various new drug targets have been identified. The new emerging treatments for osteoporosis include c-src kinase inhibitors,  $\alpha V\beta 3$  integrin antagonists, C1CN7 inhibitors and nitrates, calcilytics, antibodies against Dkk-1, statins, MEPE fragments, activin inhibitors and endocannabinoid agonists are present in various stages of clinical drug development. Odanacatib, cathepsin K inhibitor and romosozumab, a humanized monoclonal antisclerostin antibody, are emerging treatments furthest in development and in advanced clinical studies. These exciting therapies provide hope that we will continue to augment our drug armamentarium.

### Conclusion

In conclusion, osteoporosis is a condition that carries with it a very significant personal and public health burden. In recent years, we have seen huge advances in our knowledge of how to diagnose the condition, to allow randomized controlled trials of therapy; we have seen the emergence of fracture prediction algorithms that allow us to calculate fracture probability and we have at our disposal a growing armamentarium of therapies. The challenges that remain and carry the

most weight in terms of the impact they might have, are first to ensure that we identify those individuals at high risk of osteoporotic fracture and second that we intervene with a treatment with which we will see good adherence and compliance. A particular need is a good evidence base for therapies in the oldest adults. Behind this however, there also sits a public health agenda about ensuring optimization of peak bone mass in adolescents through adequate calcium intake and weight bearing activity – lifestyle measures that will pay dividends to bone health throughout the lifecourse.

### Future perspective

Over the next 5–10 years, while the choice of drugs to treat osteoporosis seems set to increase still further, the most significant advances may well be improved targeting of the correct therapy to individuals at specific points in the lifecourse. It is to be hoped that as our skills in this area increase, the burden of osteoporotic fracture will decrease. This will include public health measures to ensure optimal peak bone mass, and strategies to retard age-related bone loss in later years. With the growing research area of sarcopenia, and an acute awareness of the interplay between muscle and bone health, it seems likely that much attention will be centered around prevention of age-related muscle loss, and associated falls risk.

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### Executive summary

#### The size of the problem

- Osteoporosis is a major personal and public health burden through its association with fragility fracture.
- Osteoporotic fractures are responsible for 0.83% of the global burden of noncommunicable disease and 1.75% in Europe, where osteoporotic fractures account for more disability adjusted life years than many other chronic noncommunicable diseases.

#### Current therapies

- There have been very significant advances in recent years around diagnosis and therapy, but also emerging concerns about possible side effects of some treatments.
- Current therapies include bisphosphonates, denosumab, raloxifene and teriparatide.

#### The challenges ahead

- The challenges that are faced, and the issues that if tackled will significantly advance osteoporosis therapy in the UK include advances in patient identification, personalized medicine, adherence to therapy in addition to a stronger evidence base regarding duration of treatment.

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